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Acute Behavioral Effects of Phencyclidine on Rhesus Monkey Performance in an Operant Test Battery

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FREDERICK, D. L., M. P. GILLAM, R. R. ALLEN AND M. G. PAULE. *Acute behavioral effects of phencyclidine on rhesus monkey performance in an operant test battery.* PHARMACOL BIOCHEM BEHAV **52**(4) 789–797, 1995.—The effects of phencyclidine (PCP; a noncompetitive NMDA antagonist) were assessed in rhesus monkeys using performance in an operant test battery (OTB) consisting of five food-reinforced tasks thought to engender responses dependent upon aspects of time estimation, short-term memory, motivation, learning, and color and position discrimination. End-points included percent task completed (PTC), response rate or latency, and response accuracy. Testing occurred 15 min after IV injections of PCP (0.00, 0.003, 0.01, 0.03, 0.1, 0.13, 0.18, and 0.3 mg/kg). PCP disrupted performance of all tasks at 0.30 mg/kg. PTC was significantly decreased in the time estimation, motivation, and learning tasks at doses ≥ 0.13 mg/kg. PTC for the short-term memory and color and position discrimination tasks was significantly decreased at 0.18 mg/kg and above. Response rate was significantly decreased at 0.13 mg/kg and above in the motivation and learning tasks and at 0.18 mg/kg and above in the time estimation, short-term memory, and color and position discrimination tasks. Response accuracy was significantly decreased in the time estimation, short-term memory, and learning tasks at doses ≥ 0.13 mg/kg, while accuracy in the color and position discrimination task was decreased only at 0.30 mg/kg. PCP's effects on OTB performance were generally nonspecific, in that the time estimation, short-term memory, learning, and motivation tasks were all equally sensitive, with the color and position discrimination task being the least sensitive. These results are different than those obtained from earlier studies on the effects of MK-801, a more selective noncompetitive NMDA antagonist.

Monkeys Phencyclidine MK-801 NMDA antagonist 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

1-(1-PHENYLCYCLOHEXYL) piperidine hydrochloride (phencyclidine; PCP) is a noncompetitive *N*-methyl-D-aspartate (NMDA) antagonist that also interacts at sigma-opiate receptor sites and blocks the reuptake of dopamine [see (33) for review]. The NMDA subtype of the excitatory amino acid receptor complex is critical for the initiation (and is also thought to contribute to the preservation) of long-term potentiation (LTP; a form of synaptic enhancement), which occurs when afferent projections to CA1 cells in the rat hippocampus are electrically stimulated in close temporal proximity (1,6). NMDA antagonists such as PCP, MK-801 and 7-chlorokynurenate block LTP by altering processes that are critical to its initiation [see (7) for review]. It has been speculated that the mechanisms responsible for the initiation and preservation of LTP may also be critical to more complex learning (7) and short-term memory processes (3); hence, we hypothesized that

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behaviors thought to depend on learning and short-term memory processes may be more sensitive to disruption by NMDA antagonists than are other behaviors.

PCP has been shown to induce stereotypic behaviors, disrupt locomotor activity, and differentially affect learning and memory processes in a number of species (10,16,29,30), including humans (15). Low doses of PCP have been shown to increase response rates (4,32) while higher doses generally decrease responding and increase latency to respond in a dose dependent fashion (5,11,27,28,32). PCP has also been shown to disrupt acquisition (14,28) and performance (28) of complex operant tasks at doses that only minimally affect short-term memory (12,13).

The present experiment assessed the acute effects of PCP on rhesus monkey performance in an operant test battery (OTB) developed at the National Center for Toxicological Research (NCTR). The OTB was devised to permit the simultaneous assessment of multiple behaviors, each believed to model different brain functions. The tasks and the brain functions they were designed to model include: temporal response differentiation (time estimation), delayed matching-to-sample (short-term memory and attention), progressive ratio (motivation to work for food), incremental repeated acquisition (learning), and conditioned position responding (color and position discrimination). Previous studies from this laboratory have shown these tasks to be differentially sensitive to a variety of prototypic psychotropic agents [see (20) for an overview], and that OTB performance of well-trained rhesus monkeys is generally indistinguishable from that of children (21).

PCP was chosen for this experiment because of its relatively well characterized mechanism of action at NMDA and sigma-opiate receptor sites and to compliment the results of recent experiments from this laboratory with MK-801 (2), a noncompetitive NMDA antagonist that is about 60 times more potent than PCP at the PCP receptor site and about one-half as potent at the sigma-opiate receptor site (17). PCP 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 most OTB endpoints monitored. It was hypothesized that if processes involved in LTP are critical to learning and short-term memory, then the OTB tasks that model aspects of learning and short-term memory would be the most sensitive to PCP's acute effects by virtue of its ability to block LTP. Also, the similarity in OTB performance between monkeys and children may prove valuable with regard to extrapolating to humans the impact of the behavioral effects of acute PCP exposure in primates.

METHOD

Subjects

Nine male rhesus monkeys (*Macaca mulatta*) between 3 and 6 years of age and weighing up to 7 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 (9,23–26). During this experiment, six monkeys exhibited stable baselines for the motivation and learning tasks, five for the short-term memory and color and position discrimination tasks, and four for the time estimation task. Animal housing, feeding, etc., were as previously described (23). Briefly, each monkey was individually housed and fed its daily allotment of food immediately after each 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 approved by the NCTR Institutional Animal Care and Use Committee.

Apparatus

The apparatus has been previously described in detail (23) 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) delivery was centered below the levers.

Operant Schedules

A brief description of the operant tasks contained in the OTB follows. The use and description of which have also been reported in detail (20,23) and a diagram of the behavioral test panel is shown in Paule et al. (22).

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 minimum 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 subjects could immediately start another trial.

Short-term memory 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 (of the five animals showing stable performance in this task, two were presented time delays of 2, 8, 16, 32, 48, and 64 s, another two were presented delays of 2, 4, 8, 16, 32, and 48 s, and one was presented delays of 1, 2, 4, 8, and 16 s). After the time delay, all three plates were illuminated, each with a different geometric symbol, only one of which matched the sample. A response to the match 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.

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 upon 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, 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.

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.

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.

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 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 task (30 min) were presented the next test day.

Drugs and Dosing Procedure

Phencyclidine hydrochloride (National Institute on Drug Abuse, Rockville, MD) was dissolved in bacteriostatic (0.9% benzyl alcohol) saline for a final injection volume of 0.1 ml/kg. The purity was determined to be 99.5% by an in house high-performance liquid chromatographic analysis. Doses of PCP (0.00, 0.003, 0.01, 0.03, 0.1, 0.13, 0.18, and 0.3 mg/kg; IV) were administered in a randomized order. PCP injections were given on Tuesdays and/or Fridays, while 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 PCP 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 Endpoints

The endpoints measured in each task have been described in detail elsewhere (23). Three fundamental measures were monitored for most tasks: percent task completed (PTC), response rate or latency, and response accuracy.

PTC. The PTC data are measures of a predetermined performance criteria and are functions of both response rate and response 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 upon the length and difficulty of the task. The PTC endpoint is a convenient and comprehensive measure showing intraanimal 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 for the learning task (collapsed across components), 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 responses 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. For the time estimation task, mean duration of lever hold, and for the motivation task, the breakpoint (the magnitude of the last ratio completed for which the monkey earned a reinforcer) were also calculated. Interresponse times (from press to press) were recorded for the motivation and color and position discrimination tasks. For the learning task, within-sequence errors and between-sequence 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 ev-

TABLE 1

DOSE OF PHENCYCLIDINE IN mg/kg

Task	End Point	SAL.	0.003	0.01	0.03	0.1	0.13	0.18	0.3
Time estimation	PTC	38.1 ± 3.9	30.6 ± 11.5	29 ± 9.2	39 ± 4.3	34.8 ± 4.5	0*	0*	0.28 ± 0.2*
(TRD; n = 4)	RR	0.15 ± 0.04	0.15 ± 0.07	0.13 ± 0.06	0.17 ± 0.06	0.17 ± 0.06	0.05 ± 0.01	0.005 ± 0.004	0.01 ± 0.003
	ACC	33.6 ± 7.2	35 ± 15.6	23.7 ± 8.3	33.9 ± 9.9	34.9 ± 8.4	0*	†	1.4 ± 1.2* (3)
	Avg. hold	6 ± 1.1	7.8 ± 2.1	5.4 ± 1.3	6.2 ± 1.4	6.2 ± 1.4	0.57 ± 0.24*	0.79 ± 0.34*	2 ± 0.81*
Short-term memory	PTC	45 ± 5.9	43.8 ± 11.4	47.7 ± 7.3	50.8 ± 8.9	53.7 ± 9.5	32.2 ± 5.4	11.2 ± 8.6*	1.9 ± 1.6*
and attention	Overall RR	0.7 ± 0.11	0.75 ± 0.15	0.68 ± 0.13	0.73 ± 0.17	0.89 ± 0.17	0.38 ± 0.07	0.11 ± 0.09*	0.01 ± 0.007
(DMTS; n = 5)	Observ. RL	3.6 ± 1.1	2.1 ± 0.72	2.2 ± 0.57	2.1 ± 0.5	1.5 ± 0.34	4.2 ± 1	183 ± 71*	170 ± 52*
	Choice. RL	1.5 ± 0.18	1.1 ± 0.16	1.3 ± 0.16	1.3 ± 0.2	1.1 ± 0.17	1.8 ± 0.21	2.2 ± 0.9	9.8 ± 0.4*
	Overall ACC	72.2 ± 6.7	75 ± 10.4	71 ± 5.6	74.4 ± 7.2	74.2 ± 6.9	56.2 ± 4.6*	46.8 ± 10.9* (2)	21.2 ± 10.4* (2)
Motivation	PTC	18.5 ± 2.8	19.3 ± 3.7	19.4 ± 3.7	17.6 ± 4.2	18.3 ± 4.4	7.5 ± 5.2*	0.21 ± 0.13*	0.17 ± 0.14*
(PR; n = 6)	BP	97.1 ± 13.8	96.5 ± 14.4	97.7 ± 14.5	84.8 ± 13.3	90.1 ± 18.6	21.6 ± 12.2*	0.75 ± 0.35*	0.4 ± 0.3*
	RR	2.2 ± 0.45	2.2 ± 0.5	2.2 ± 0.5	1.8 ± 0.5	2.1 ± 0.6	0.5 ± 0.4*	0.003 ± 0.001*	0.003*
Learning	PTC	65.7 ± 8.1	55.7 ± 14.8	71.8 ± 10.3	52.4 ± 10.4	65.3 ± 12	32.6 ± 2.2*	4.8 ± 3*	5 ± 1.4*
(IRA; n = 6)	Overall RR	1.3 ± 0.26	1.4 ± 0.45	1.7 ± 0.31	0.84 ± 0.25	1.3 ± 0.37	0.41 ± 0.09*	0.03 ± 0.02*	0.01 ± 0.004*
	Overall RR	1.3 ± 0.26	1.4 ± 0.45	1.7 ± 0.31	0.84 ± 0.25	1.3 ± 0.37	0.41 ± 0.09*	0.03 ± 0.02*	0.01 ± 0.004*
	Overall ACC	60.6 ± 5.5	62.5 ± 9	63.2 ± 7.2	51 ± 9	60 ± 8.7	30 ± 3.6*	†	†
Color and position	PTC	93.4 ± 3	84 ± 16	100	84 ± 16	94.3 ± 5.7	81 ± 11.5	10.4 ± 3.8*	10.8 ± 3.6
discrimination	RR	1.4 ± 0.27	1.4 ± 0.27	1.5 ± 0.34	1.4 ± 0.45	1.7 ± 0.33	1 ± 0.24	0.13 ± 0.06*	0.15 ± 0.05*
(CPR; n = 5)	Observ. RL	4.7 ± 3	5.4 ± 4.3	1.3 ± 0.26	2.7 ± 1.5	1.1 ± 0.3	2.1 ± 0.45	225 ± 74*	81 ± 72*
	Choice. RL	0.28 ± 0.03	0.26 ± 0.02	0.22 ± 0.01	0.32 ± 0.08	0.24 ± 0.02	0.35 ± 0.08	0.31 ± 0.07	2 ± 0.58*
	ACC	95.5 ± 1.5	97.9 ± 2.1	99.3 ± 0.4	90.5 ± 8.4	91 ± 6.9	83.2 ± 6.3	67.6 ± 5.7* (4)	48.3 ± 3.2* (4)

PTC = percent task completed; RR = response rate; RL = response latency; BP = breakpoint.

*Denotes significant difference from vehicle (saline) performance ($p < 0.05$). All ns as indicated unless otherwise noted ( ).

†Indicates insufficient number of observations for analysis.

ery time an incorrect lever is pressed prior to reinforcer delivery (i.e., completion of the chain). A within-sequence error cannot occur during the one-lever sequence. 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 saline (vehicle) sessions. For a subject's data to be included in the time estimation and color and position discrimination accuracy analyses, a minimum of three trials must have been completed. For inclusion in the short-term memory and learning task 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% percent 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 to vehicle control performance by Bonferroni's (BON) multiple *t*-tests (19).

RESULTS

Results from the five OTB tasks are summarized in Table 1. Baseline (noninjection) data were not significantly different from those for saline vehicle injections for any of the behavioral end points monitored (not shown). In Table 1 and for all subsequent references, overall refers to data collapsed across all time delays in the short-term memory task and across all levels in the learning task. To emphasize the disruptive effects of PCP on complex brain functions thought to be modeled in the OTB, figures generally present data from endpoints specific to individual OTB tasks.

Time Estimation

PCP significantly decreased accuracy and PTC in the time estimation task at 0.13 mg/kg and above, whereas response rates were significantly decreased at doses ≥ 0.18 mg/kg. The frequency of lever holds that were 2 s or longer in duration are shown in Fig. 1. Response bursts (lever holds < 2 s), common in this task, appear in Fig. 2. Mean duration of lever hold (all presses included) was significantly decreased at PCP doses ≥ 0.13 mg/kg.

Short-Term Memory

PCP significantly decreased overall response rates and PTC at 0.18 and 0.30 mg/kg in the short-term memory task. Observing response latencies were significantly increased at 0.18 and 0.30 mg/kg of PCP, while choice response latencies were increased only at 0.30 mg/kg. Overall accuracy was significantly decreased at PCP doses ≥ 0.13 mg/kg. Note that decreased accuracy appeared to be primarily a function of dose and not the length of delay (see Fig. 3).

Motivation

PCP significantly decreased break point, PTC, and response rates at 0.13 mg/kg and above in the motivation task.

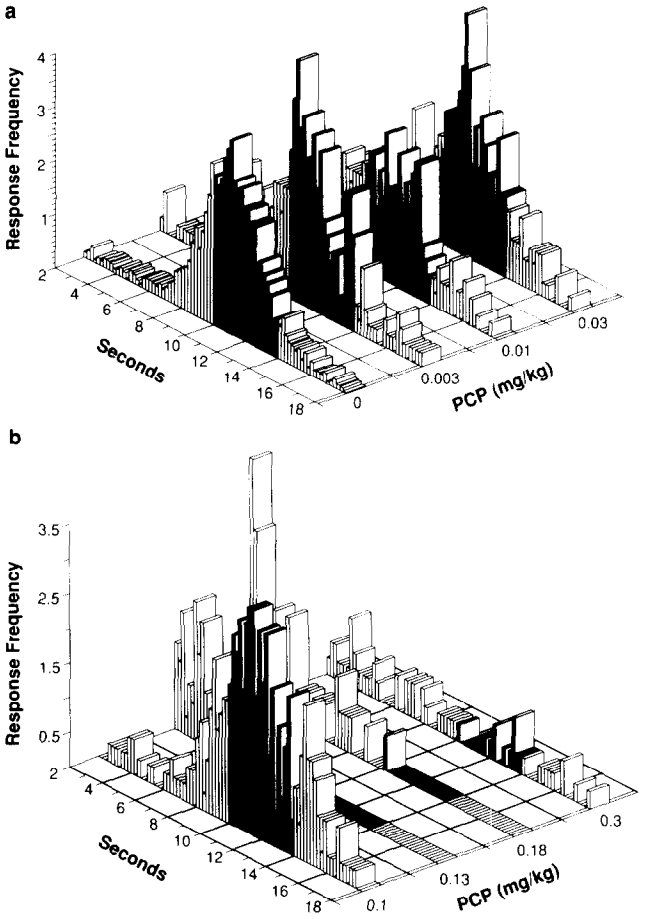

FIG. 1. (a,b) Effect of PCP on duration of lever hold in the time estimation task for holds ≥ 2 s in duration. Data are means for all four subjects. Bars represent 0.2-s intervals (i.e., the first bar represents the frequency of lever holds with a duration of 2.00–2.20 s). The shaded area represents correct (lever holds > 10 s but < 14 s) responses.

Figure 4 shows average interresponse time (IRT) distributions obtained for the motivation task.

Learning

PCP significantly decreased accuracy, PTC, and overall response rates at 0.13 mg/kg and above in the learning task. No subject was able to complete the 20 errorless sequences necessary to advance beyond IRA1 at the highest dose tested (0.30 mg/kg). Figures 5a and b, show the effects of PCP on within- and between-sequence errors for the learning task at the two lever (IRA2) sequence.

Color and Position Discrimination

PCP significantly decreased response rates and PTC at 0.18 and 0.30 mg/kg in the color and position discrimination task. Response accuracy was significantly decreased only at 0.30 mg/kg. Observing response latencies were increased at 0.18 mg/kg of PCP, but not at 0.30 mg/kg. Choice response latencies were increased only at 0.30 mg/kg. Figure 6 shows

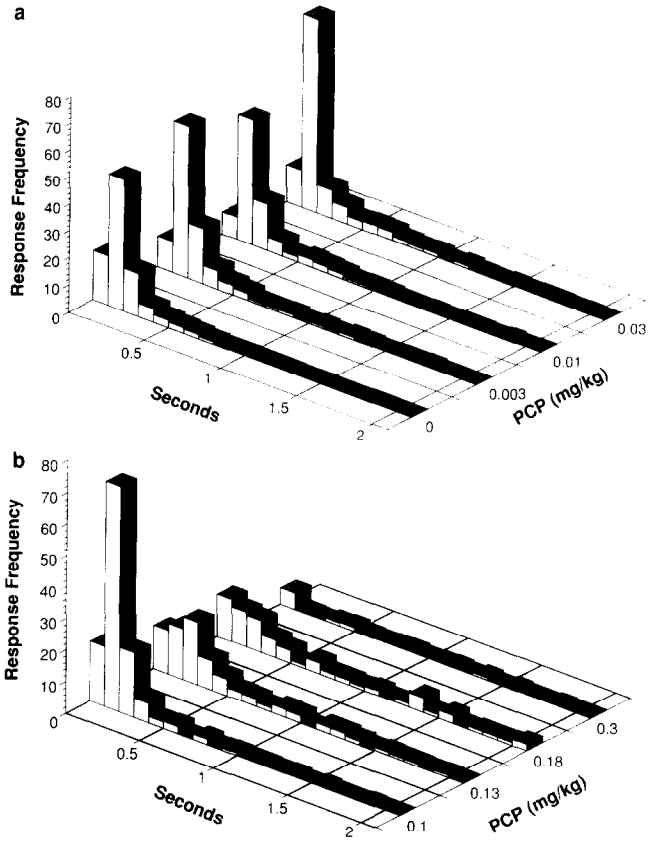

FIG. 2. (a,b) Effect of PCP on duration of lever hold in the time estimation task for holds less than 2 s in duration. Data as described in Fig. 1 except that bars represent 0.1-s intervals. (i.e., the first bar represents the number of lever holds with a duration of 0.00–0.09 s).

average interresponse time distributions obtained for the color and position discrimination task.

DISCUSSION

The present data do not support the hypothesis that the learning and short-term memory tasks would be more sensitive to disruption by PCP than would the other OTB tasks; the present findings are contrary to what would have been expected if processes involved in long-term potentiation (LTP) were selective for both of these functions. Using the occurrence of a significant disruption in task performance at doses lower than those affecting other tasks as a criteria for determining relative task sensitivity, those designed to model time estimation, short-term memory, motivation, and learning were all equally sensitive to the acute effects of PCP; color and position discrimination was the least sensitive. This suggests that PCP's acute effects on OTB performance were relatively nonspecific. This order of task sensitivity to PCP is, however, distinguishable from all other drugs tested in this laboratory under similar conditions [e.g., (9,23–26)], including the more selective noncompetitive NMDA antagonist MK-801 (2).

The NMDA receptor is thought to be critical for the induction (and to some degree preservation) of long-term potentiation (7), and the processes involved in LTP are also thought to be essential for more complex forms of learning and memory (3,7). In the present experiment, PCP disrupted aspects of learning task performance (i.e., response rate, PTC) at doses that did not significantly affect behavior in a short-term memory task. This greater sensitivity of learning behavior over short-term memory was evidenced by the greater number of acquisition (between-sequence) errors than recall (within-sequence) errors in the learning task. Moreover, acquisition errors in the learning task occurred at doses of PCP that had relatively nonspecific effects on performance of the short-term memory task (e.g., disrupted performance accuracy, but did not affect recall in any delay-dependent manner). This observation that learning (or acquisition) is more sensitive to PCP's acute effects than is short-term memory (or retention) is also consistent with previous reports in monkeys and other species (12,13,28) and suggests that processes involved in LTP may be more essential for acquiring new information than retaining it.

As mentioned earlier, previous studies have reported that PCP differentially affects response rate, depending on dose and behavioral schedule (4,5,28,32). In the present experiment, PCP increased the frequency of short interresponse times (IRTs), which generally reflects an increased rate of responding, in the motivation and color and position discrimination tasks, but these effects were not systematic or statistically significant (see Figs. 4 and 6, respectively). In both the time estimation and short-term memory tasks, PCP decreased response accuracy at a dose that did not affect response rate. In the learning task, response rate was decreased at the same dose that decreased accuracy. If one considers only the effects

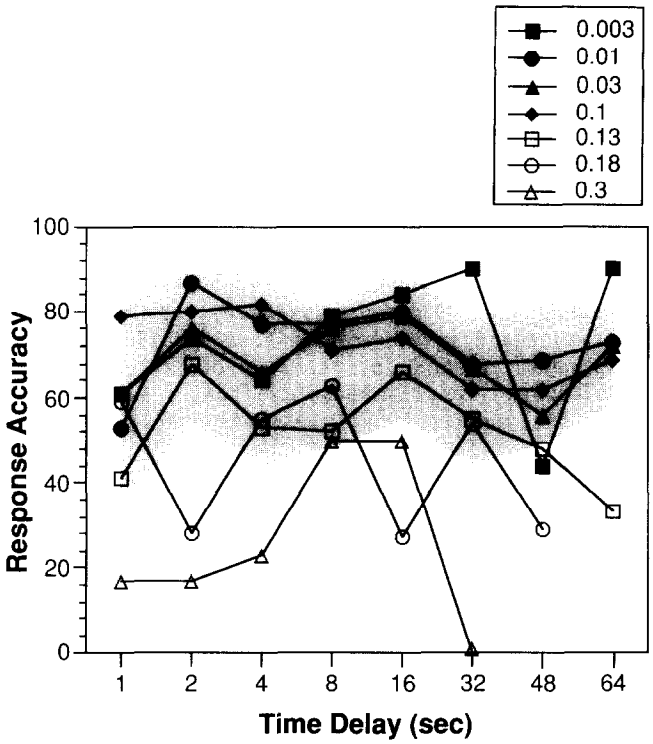

FIG. 3. Effect of PCP on response accuracy in the short-term memory task. The shaded area represents the 95% confidence interval constructed from data for vehicle control sessions. Note that when accuracy was disrupted (0.18 and 0.30 mg/kg) the effect was nonspecific and not a function of the length of time delay.

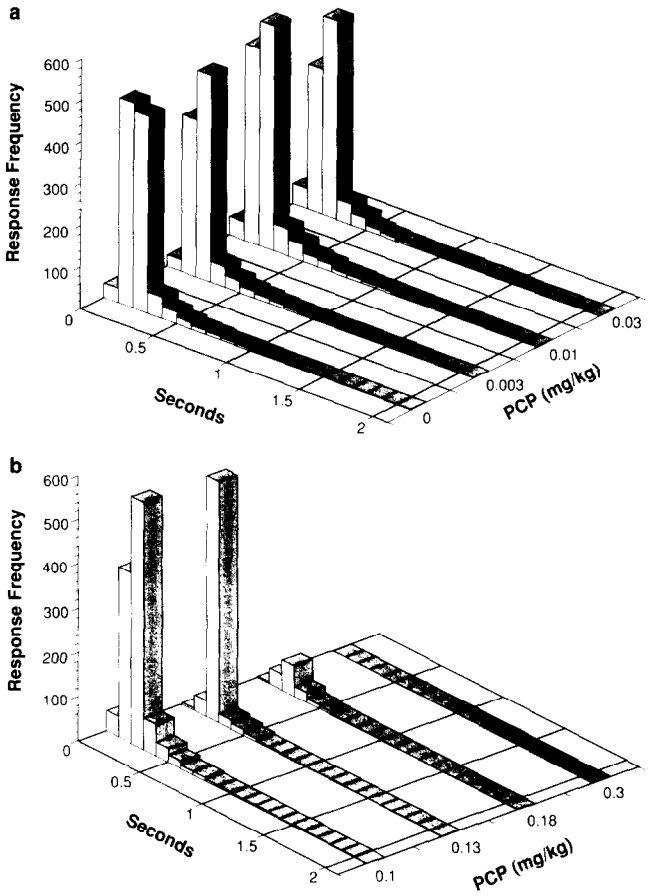

FIG. 4. (a,b) Interresponse time distributions (IRTs) for the motivation task. Data are means for all six subjects. PCP increased the frequency of short IRTs at 0.003 and 0.10 mg/kg. Responding was abolished at the highest dose tested (0.30 mg/kg).

of PCP on OTB task response rates, the order of task sensitivity becomes motivation = learning > time estimation = short-term memory > color and position discrimination. This order of sensitivity still does not support the hypothesis that PCP would selectively disrupt the performance of the learning and short-term memory tasks more than the other OTB tasks.

Previous experiments from this laboratory have been conducted on the effects of MK-801 on OTB performance under similar experimental conditions [see (2) for details]. Although both MK-801 and PCP are noncompetitive NMDA receptor antagonists, PCP is less potent than MK-801 at the PCP receptor site, has greater affinity for sigma opiate receptors, and is a more potent blocker of dopamine reuptake than MK-801 (17). In general, the effects of PCP and MK-801 on OTB performance differed in two primary ways. First, MK-801 was about two to three times more potent than PCP in disrupting OTB behavior in monkeys, a finding that is consistent with published literature in other species [see (17,18,31)]. Second, when comparing relative task sensitivities, the effects of MK-801 were more selective than were those of PCP. Using the criteria of significant drug effect on any measure of task performance to determine relative sensitivities, the learning and time estimation tasks were much more sensitive to the acute effects of MK-801 than were the short-term memory, motivation, and color and position discrimination tasks. In contrast, the learning, motivation, time estimation, and short-term memory tasks were equally sensitive to PCP's acute effects. Whether these differential effects are the result of the differential receptor specificities for each drug remains to be determined.

Although PCP and MK-801 differed with respect to their potencies and selectivity of effects, their qualitative effects on the short-term memory task were very similar, while they differentially affected the motivation and learning tasks [see (2)]. For example, both drugs disrupted aspects of learning task performance at doses that had little effect on measures of short-term memory. PCP, however, increased acquisition (between-sequence) errors in the learning task at doses that did not affect recall (within-sequence) errors, whereas MK-801 increased both acquisition and recall errors in the learning task at the same doses (see Fig. 7). Such data suggest that MK-801 differs from PCP in its effects on disruption of learning task performance. Given that MK-801 is more potent

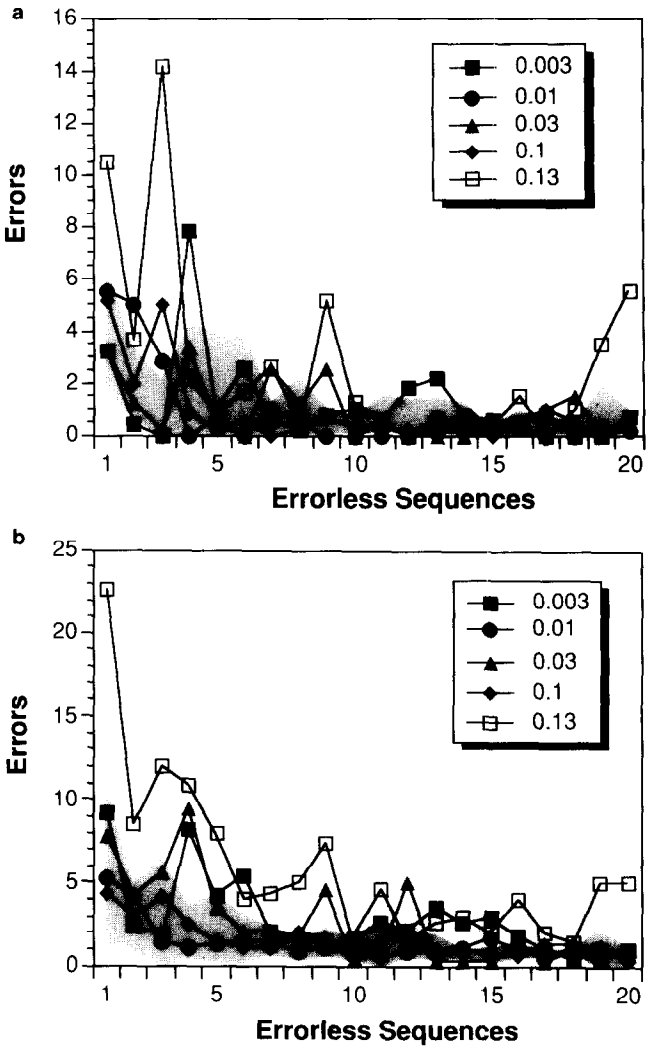

FIG. 5. (a,b) Effect of PCP on within-sequence (recall) errors (a) and between-sequence (acquisition) errors (b) in the learning task at the two-lever sequence. Data are means for six subjects. The shaded area represents the 95% confidence interval constructed from data for vehicle control sessions.

NMDA antagonist than PCP (17), such an effect could be interpreted as supporting the hypothesis that NMDA antagonists disrupt learning and short-term memory by affecting LTP. Alternatively, it could be argued that MK-801 simply disrupted stimulus control over behavior, because it disrupted performance of the short-term memory task in a nonspecific fashion, irrespective of time delay. The greater relative sensitivity of the motivation task to PCP than to MK-801 may be due to PCP's higher affinity for sigma opiate receptors, its greater ability to block dopamine reuptake, or a combination of both factors.

In summary, PCP produced a relatively nonspecific, dose-dependent disruption across OTB tasks that was distinguishable from the more selective NMDA antagonist MK-801 (2). The data do not support the hypothesis that OTB tasks modeling learning and short-term memory would be the most sensitive to PCP's acute effects because of its ability to block induction of LTP. Whether the disruption of learning behavior reported here can be explained by PCP's interference with processes involved in the induction and preservation of LTP is equivocal.

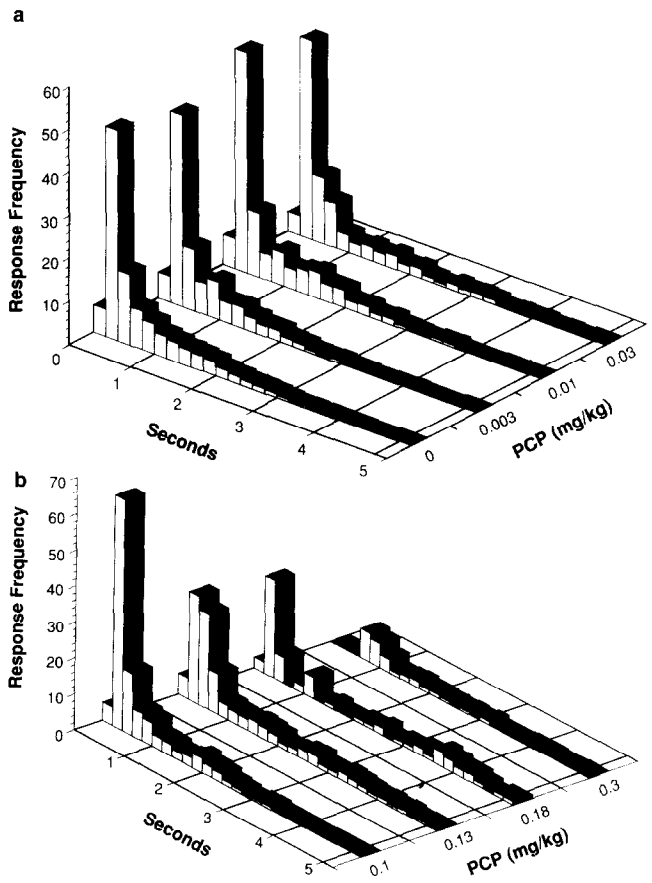

FIG. 6. (a,b) Interresponse time distributions (IRTs) for the color and position discrimination task. Data are means for all five subjects. PCP produced a small increase in the frequency of short IRTs at 0.01 and 0.10 mg/kg.

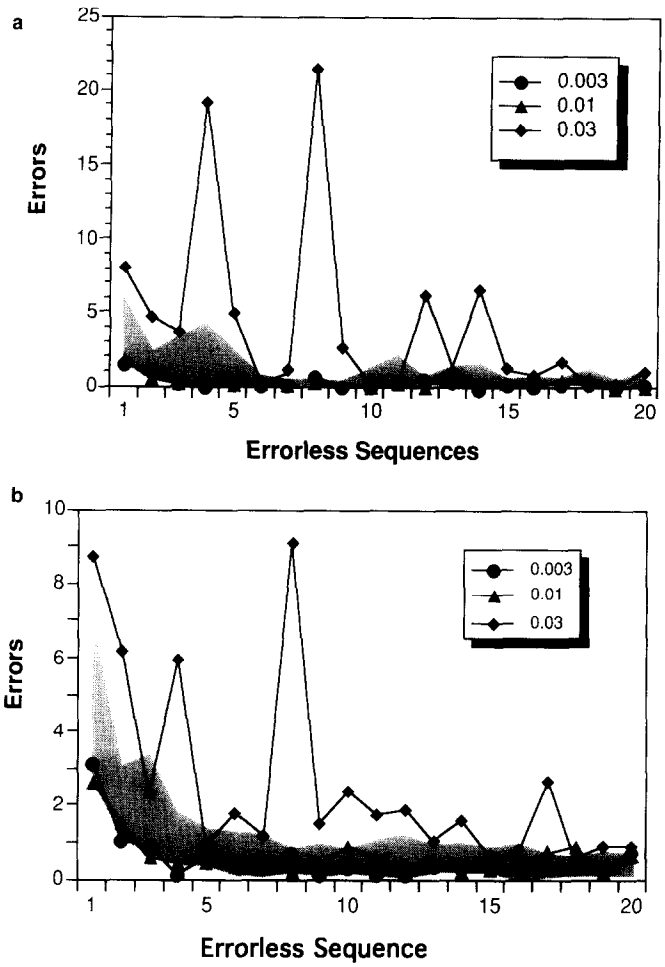

FIG. 7. (a,b) Effect of MK-801 on within (a) and between-sequence (b) errors in the learning task at the two-lever sequence. Data are means for seven subjects unless otherwise indicated and as described in Fig. 5a and b [adapted from (2)].

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