

Effects of Phencyclidine, Pentobarbital, and *d*-Amphetamine on the Acquisition and Performance of Conditional Discriminations in Monkeys¹

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MOERSCHBAECHER, J. M. AND D. M. THOMPSON. *Effects of phencyclidine, pentobarbital, and d-amphetamine on the acquisition and performance of conditional discriminations in monkeys.* PHARMAC. BIOCHEM. BEHAV. 13(6) 887-894, 1980.—In each of two components of a multiple schedule, monkeys were required to respond on a right or left lever depending upon the stimulus combination (a color and a geometric form) presented. Reinforcement of a response in the presence of one stimulus (the form) was therefore conditional upon the other stimulus (the color). The completion of a two-member chain of discriminations produced a food pellet. Errors produced a brief timeout. One component of the multiple schedule was a repeated-acquisition task where the discriminative stimuli for left- and right-lever responses changed each session (learning). In the other component, the discriminative stimuli for left- or right-lever responses were the same each session (performance). Phencyclidine, pentobarbital, and *d*-amphetamine each produced dose-related decreases in the overall rate of responding in both components of the multiple schedule. At high doses each drug increased the percent errors in each component. At lower doses, however, the three drugs produced selective effects on accuracy. Errors were increased in the learning component at lower doses than those required to disrupt the discrimination in the performance component. A signal detection analysis of the data revealed that none of the drugs tested increased errors by selectively affecting either discriminability or bias.

Repeated acquisition	Multiple schedule	Conditional discrimination	Signal detection analysis
Phencyclidine	Pentobarbital	<i>d</i> -Amphetamine	Lever press Monkeys

THE effects of phencyclidine on simple schedule-controlled behavior have been investigated in pigeons [25], mice [2,26], rats [20,27], and monkeys [3, 4, 5, 7, 9, 10, 11]. Though phencyclidine has been described as having both amphetamine- and barbiturate-like effects [5], there have been only a few studies in which the behavioral effects of these drugs have been directly compared. For example, in a multiple fixed-ratio (FR) fixed-interval (FI) schedule of food presentation, phencyclidine produced effects which were qualitatively similar to those of *d*-amphetamine in both the pigeon [25] and mouse [26]. Generally, with increasing doses, phencyclidine increased and then decreased overall response rates in the FI component, while producing only a dose-related decrease in response rate in the FR component. This effect in the FR schedule differs from that of pentobarbital, which has been reported to increase and then decrease response rates with increasing doses in both components of a multiple FR FI schedule [26]. In monkeys the effects of phencyclidine also appear to differ from those of pentobarbital. For example, in squirrel monkeys responding under a variable-interval (VI) schedule of food presentation, pen-

tobarbital produced only a dose-dependent decrease in responding, while phencyclidine has been reported to produce small increase in response rate at low doses and decreases at higher doses [9,11].

In comparison to *d*-amphetamine and pentobarbital, relatively little is known concerning the effects of phencyclidine on complex behavior. The effects of *d*-amphetamine on complex behavior have been studied using a variety of repeated-acquisition procedures [24]. For example, Moerschbaecher *et al.* [18] used a multiple schedule to investigate the effects of *d*-amphetamine on the repeated acquisition and performance of conditional discriminations in pigeons. In this procedure the reinforcement of a response in the presence of one stimulus (a geometric form) was conditional upon another stimulus (a color). In one component of the multiple schedule the behavioral task consisted of the same conditional discrimination each session (performance). In the other component, the conditional discrimination was changed each session (acquisition). *d*-Amphetamine was found to increase errors in each component of the multiple schedule. Responding in the acquisition component, how-

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ever, was generally disrupted (i.e., errors increased) at lower doses than those that affected responding in the performance component. Similar results have been obtained in patas monkeys responding under a multiple schedule of repeated acquisition and performance of response chains [23]. In one component of the multiple schedule, the monkey acquired a different four-response chain each session by responding sequentially on three keys in the presence of four geometric forms (acquisition). In the other component, the four-response chain was the same each session (performance). It was found that *d*-amphetamine selectively disrupted acquisition at doses that had no effect on performance. In a related study [19], the effects of *d*-amphetamine on the acquisition and performance of four-response sequences in monkeys were directly compared to those of phencyclidine. In this study different discriminative stimuli were not, however, associated with each response in the sequence; that is, a tandem schedule was used (cf. [22]). Across the range of doses tested (0.01 to 0.24 mg/kg), phencyclidine generally had less of a selective error-increasing effect on the acquisition baseline than did *d*-amphetamine. That is, phencyclidine tended to disrupt accuracy in each component of the multiple schedule.

The purpose of the present study was to further characterize the effects of phencyclidine on behavior involving complex discriminations. The repeated acquisition and performance of conditional discriminations was used as the baseline procedure. Unlike the tandem procedure [19], this baseline permits the evaluation of a drug's effect on the acquisition and performance of discriminations which are under the control of external discriminative stimuli. An advantage of this particular procedure is that the accuracy data are readily amenable to a signal detection analysis. Such an analysis may be useful in determining differential drug effects which otherwise may not be readily apparent from measures involving overall accuracy [1]. As comparison drugs, *d*-amphetamine and pentobarbital were also studied.

METHOD

Subjects

Two adult male patas monkeys (*Erythrocebus patas*) were used. Both subjects had experimental histories involving the repeated acquisition and performance of conditional discriminations. *d*-Amphetamine had previously been administered to both subjects approximately 2 months prior to the start of the present study. Each subject was maintained at about 85% of its free-feeding weight (13.5 and 11.5 kg) on a diet consisting of banana-flavored food pellets, monkey chow, fruit, and vitamins. The pellets were either earned during the experimental session or, when necessary, provided after the session. Monkey chow, fruit, and vitamins were given to each subject after the daily session. Water was continuously available.

Apparatus

Each subject was housed in a primate cage (Research Equipment Co., model LC-1103) measuring 83.6×98.2×87.4 cm. The bars were removed from one side of the cage and replaced with an aluminum panel. An array of four recessed levers (Automatic Electric, model PK369-D6B) was aligned horizontally to the left of the vertical midline of the panel. The levers were spaced 4 cm apart, center to center, and were 45 cm above the cage floor. A fifth identical recessed

lever was centered 12 cm above this array. Of these five levers, only the upper center and the extreme lower left and right levers were used during the present study. Each lever required a minimum force of 0.98 N for activation. An in-line projector (Industrial Electronic Engineers), mounted 4 cm above each lever, was used to project the different stimuli (colors and geometric forms). An additional lever, which operated the pellet dispenser, was mounted 11 cm to the right and 6 cm up from the center of the right-hand lever. A green pilot lamp (No. 1820) was mounted 6 cm below the food lever. A pellet dispenser (R. Gerbrands, model A) delivered 500-mg banana-flavored food pellets (P.J. Noyes Co.) into an aperture (8×8 cm) which was located 3 cm to the right from the center of the food lever. Solid-state scheduling and recording equipment was located in an adjacent room.

Baseline Procedure

A multiple schedule of repeated acquisition and performance of conditional discriminations served as the baseline procedure (cf. [17,18]). In each component of the multiple schedule, the monkey's task was to respond on either the right or left lever depending upon the stimulus displayed above the center lever. Completion of a two-member chain of these discriminations was required to produce a food pellet.

In the *performance* component of the multiple schedule, the discriminative stimuli for left- or right-lever responses were the same from session to session. One of four white geometric forms (a vertical bar, circle, square, or a figure eight) superimposed on a colored (green or red) background was displayed above the center lever. A response on the center lever produced a stimulus (white) over the left and right levers; the stimulus remained on until a response was made on either lever. In the first member of the chain, a vertical bar on a green background was the discriminative stimulus for a left-lever response. In the second member of the chain, a circle on a red background was the discriminative stimulus for a left-lever response. All other stimulus combinations (e.g., circle-green, vertical bar-red, square-red, etc.) were discriminative stimuli for a right-lever response. The occurrence of each geometric form was equiprobable following either a left- or right-lever response (noncorrection). Correct right-lever responses had no consequences other than the production of another stimulus above the center lever. A correct left-lever response in the first member of the chain changed the background color (from green to red); a correct left-lever response in the second member of the chain illuminated the pilot lamp under the food lever. A press on the food lever then operated the pellet dispenser and reset the chain. Errors (e.g., responding on the left lever when right was correct) produced a 10-sec timeout, during which time all the stimuli were off and responses had no programmed consequences. Errors did not reset the chain. Since there were eight possible stimulus combinations (each appearing with equal probability), two of which were stimuli for a left-lever response (i.e., first and second members of the chain), the actual number of correct responses in each chain varied (an average of 8 with a minimum of two left-lever responses).

In the *acquisition* component of the multiple schedule, four different white geometric forms (a horizontal bar, triangle, cross, and an "X") and two colors (green and red) served as stimuli. Unlike the performance component, however, the discriminative stimuli for left- and right-lever re-

sponses changed each session. For example, during one session the stimuli for a left-lever response might be triangle-green and cross-red, while in the next session they might be horizontal bar-green and "X"-red. In all other aspects, the procedure was identical to the performance component. Since all combinations of forms and colors were used during the study, a session would occasionally occur in which only one stimulus for a left-lever response would differ from that of the previous session (e.g., cross-green, circle-red followed by triangle-green, circle-red). During such sessions neither drug nor saline was tested.

In summary, during each session, the monkey acquired a different chain of conditional discriminations in one component of a multiple schedule (learning), while in the other component the chain of conditional discriminations was the same each session (performance). The components alternated after 50 reinforcers or 25 min (excluding time spent in timeout), whichever occurred first. A 10-sec blackout (during which all stimuli were off and responses had no programmed consequences) separated the component changes. Each session terminated after 200 reinforcers or 4 hr, whichever occurred first. Sessions were conducted daily with few exceptions and always began in the acquisition component.

Drug Testing

The drugs used and the order in which they were tested were *d*-amphetamine sulfate, phencyclidine hydrochloride and pentobarbital sodium. *d*-Amphetamine sulfate and phencyclidine hydrochloride were dissolved in saline. Pentobarbital sodium was dissolved in a vehicle containing propylene glycol (40% v/v), alcohol (10% v/v), and sterile water (q.s. ad). The drugs were injected IM (*gluteus m.*) 5 min presession. The volume of each injection was 0.05 ml/kg body weight. The doses (expressed as the salt) of each drug were tested in a mixed order. Drug sessions were separated by at least five days, during which time there were baseline sessions and a control session (saline or vehicle alone injected IM 5 min presession).

Data Analysis

The data for each session were analyzed in terms of (a) the overall response rate (total responses/min, excluding timeouts) in each component and (b) the overall accuracy or percent errors ($[\text{errors}/\text{total responses}] \times 100$) in each component. The data for each subject were analyzed by comparing a given drug session with the control range of variability (saline or vehicle sessions). A drug was considered to have an effect to the extent that the dose data fell outside of the control range. The data were also subjected to a signal detection analysis. For both saline and drug sessions the probability of a correct left-lever response (total correct left-lever responses/total correct left-lever responses + total incorrect right-lever responses) was plotted as a function of the probability of an incorrect left-lever response (total incorrect left-lever responses/total incorrect left-lever responses + total correct right-lever responses). In addition to these measures based on session totals, within-session changes in responding were monitored by a cumulative recorder.

RESULTS

The effects of phencyclidine on rate of responding and percent errors in each component of the multiple schedule

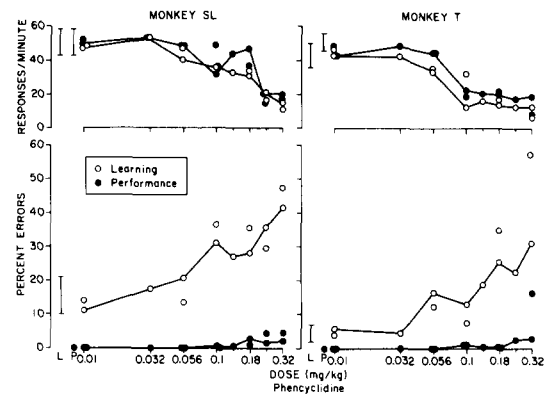


FIG. 1. Effects of varying doses of phencyclidine on the overall response rate and percent errors in each component of the multiple schedule for each subject. The range of 15 saline sessions is indicated by the brackets or data point for the learning (L) and performance (P) components. Connected data points represent the first determinations and unconnected points represent second determinations.

are shown for each subject in the dose-effect curves of Fig. 1. The range of 15 saline control sessions are shown at the left of each curve for the learning (L) and performance (P) components. At any given dose, phencyclidine generally had the same effect on rate of responding in both components. For monkey SL, response rate in each component tended to decrease with increasing doses of phencyclidine. Though more asymptotic at the higher doses, the data for monkey T were similar in that phencyclidine produced only decreases in the rates of responding. In both subjects, percent errors in the learning component increased as a function of increasing doses of phencyclidine. Large error-increasing effects occurred in the learning component at doses which had little or no effect on errors in the performance component (e.g., monkey SL, 0.1 and 0.13 mg/kg; monkey T, 0.056–0.18 mg/kg). At higher doses (e.g., 0.24 and 0.32 mg/kg) errors were increased in both components of the multiple schedule. With a single exception (monkey SL, 0.056 mg/kg), each dose of phencyclidine which decreased response rate in the learning component also increased errors in the learning component. In the performance component, however, certain doses of phencyclidine produced substantial decreases in response rate without increasing errors (e.g., monkey T, 0.13 and 0.18 mg/kg).

The accuracy data shown in Fig. 1 are based on session totals (overall percent errors). These data do not provide evidence that acquisition (i.e., a decrease in errors within the session) occurred under control conditions or that phencyclidine affected acquisition. Such evidence is illustrated in the cumulative response records shown for monkey SL in Fig. 2. The response pen stepped with each correct response and was deflected downward each time a chain was completed. Errors are indicated by the event pen, which was held down during each timeout. The event pen was also deflected and the response pen reset with each component change. As is shown in the saline record, the session began in the learning component (L) and then changed to the performance component (P). Errors (event pen) decreased in the learning component as the session progressed (within-session error reduction). Note that errors were much more frequent in the first learning component than in the second. In comparison

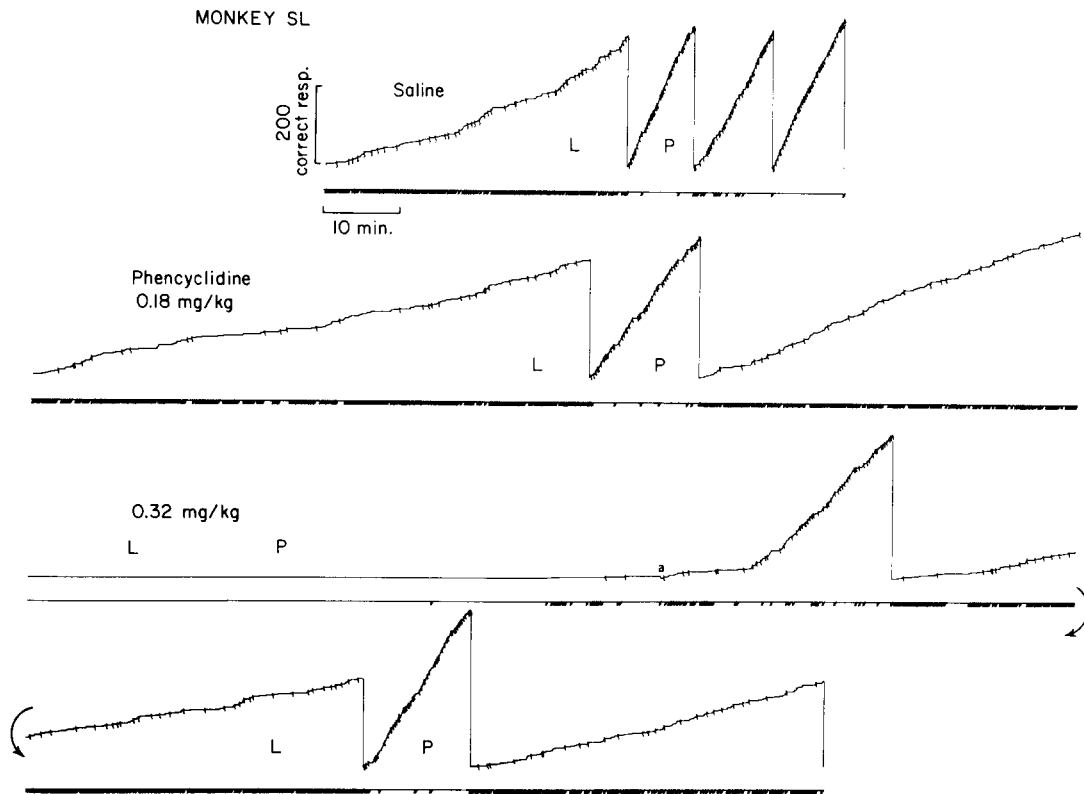


FIG. 2. Effects of two doses of phencyclidine on the within-session responding of monkey SL under the multiple schedule with learning (L) and performance (P) components. The response pen stepped with each correct response and was deflected downward each time food was presented. Errors are indicated on the event pen, which was held down during each timeout. The event pen was also deflected and the response pen reset each time the components changed. The last performance component is omitted from the record at the 0.18 mg/kg dose.

to saline, the major effect of the 0.18 mg/kg dose was to increase errors in the learning component throughout the session (see first and third excursions of the cumulative record). Note that acquisition was virtually eliminated at this dose. At a higher dose (0.32 mg/kg) no responses were made during the first cycle of the multiple schedule. During the second cycle, few responses were made in the learning component, while errors were markedly increased in performance, especially at the beginning of the component (point *a* in Fig. 2). During the remainder of the session, behavior recovered in the performance component and few additional errors were made. In the learning component, however, errors persisted and the discrimination was not acquired.

Pentobarbital dose-effect curves are shown for each subject in Fig. 3. The range of 9 vehicle control sessions are shown at the left of each curve. Doses ranging from 1 to 3.2 mg/kg had little or no effect on rate of responding in either component, while at higher doses (5.6–13.3 mg/kg) response rate was decreased. In addition, the rate-decreasing effects produced at doses of 5.6 and 10 mg/kg were somewhat greater in the learning component than in the performance component. The magnitude of this difference between the rate-decreasing effects produced in each component tended to be greater for pentobarbital than for phencyclidine. The effects of pentobarbital on accuracy (i.e., percent errors) were similar to those observed with phencyclidine. Doses ranging from 1 to 3.2 mg/kg had no effect on errors while at higher doses, selective error-increasing effects occurred. In

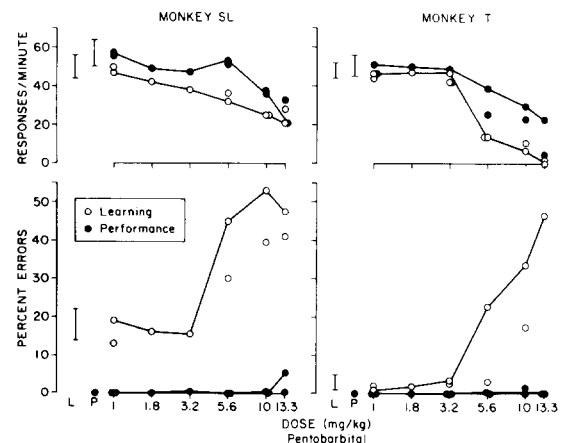


FIG. 3. Effects of varying doses of pentobarbital on the overall response rate and percent errors in each component of the multiple schedule for each subject. The range of 9 vehicle control sessions is indicated by the brackets or data point for the learning (L) and performance (P) components. Connected data points represent the first determinations and unconnected points the second determinations. For monkey T, percent errors in the learning component for the second determination at the 13.3 mg/kg dose is not shown since the response rate was virtually zero.

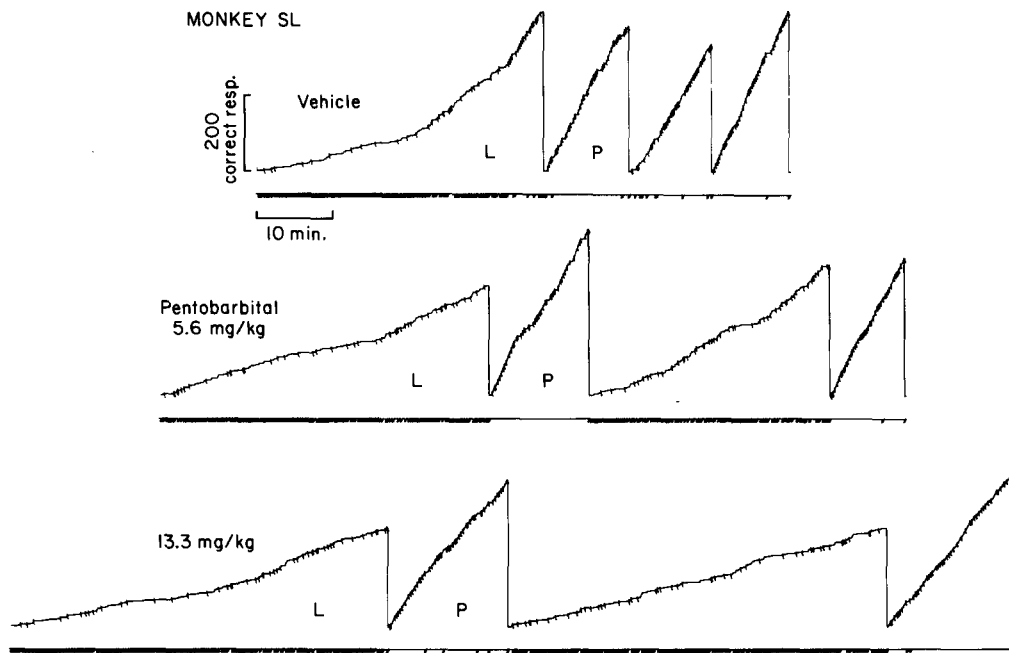


FIG. 4. Effects of two doses of pentobarbital on the within-session responding of monkey SL under the multiple schedule with learning (L) and performance (P) components. The recording details are the same as in Fig. 2.

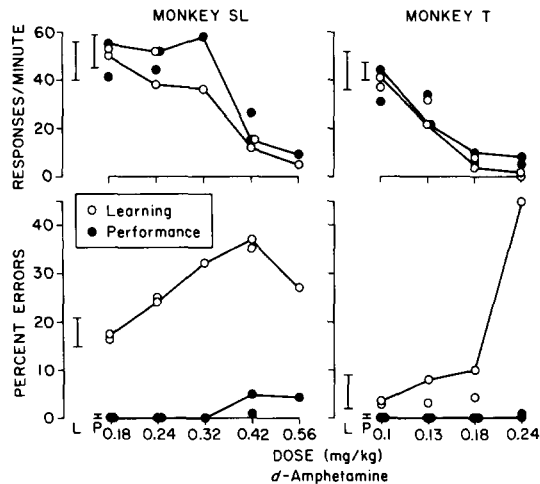


FIG. 5. Effects of varying doses of *d*-amphetamine on the overall response rate and percent errors in each component of the multiple schedule for each subject. The range of 9 saline sessions is indicated by the brackets for the learning (L) and performance (P) components. Connected data points represent the first determinations and unconnected points the second determinations. For monkey T, percent errors in the learning component for the second determination at the 0.24 mg/kg dose is not shown since the response rate was virtually zero.

monkey SL, doses of 5.6 and 10 mg/kg (both determinations) selectively increased errors in the learning component. In monkey T, these same doses (first determination) had the same selective effect. In both subjects, however, at each effective dose, the error-increasing effects produced by pentobarbital in the learning component were attenuated in the

second determination (unconnected data points) in comparison to the first.

Effects of pentobarbital on the within-session responding of monkey SL are shown in Fig. 4. Note that in comparison to the vehicle control record, the 5.6 mg/kg dose disrupted acquisition without affecting responding in the performance component. At the 13.3 mg/kg dose, even greater disruption of acquisition is apparent in the cumulative record. In addition, though response rates were decreased in both components, pentobarbital did not produce prolonged periods of pausing in this subject as was observed with phencyclidine (cf., Fig. 2).

d-Amphetamine dose-effect curves are shown for each subject in Fig. 5. The range of 9 saline control sessions are shown at the left of each curve. In monkey SL, doses ranging from 0.18 to 0.32 mg/kg had little or no effect on rate in either component. At the higher doses, however, response rates were decreased in both components. Monkey T was considerably more sensitive, on a mg/kg basis, to the rate-decreasing effects of *d*-amphetamine. In this subject, substantial decreases in response rate occurred in both components at doses as low as 0.13 mg/kg. Percent errors in the learning component were selectively increased in monkey SL at doses of 0.24 and 0.32 mg/kg, while higher doses increased errors in both components. For monkey T, errors were increased in the learning component only at the 0.24 mg/kg dose (first determination).

Effects of *d*-amphetamine on the within-session responding of monkey SL are shown in Fig. 6. Though errors in the learning component were increased at the 0.24 mg/kg dose, the discrimination was acquired late in the session towards the end of the second learning component. As can be seen in the lower records of Fig. 6, the 0.42 mg/kg dose increased errors in both components. At this dose, however, no acquisition occurred during the entire session. Unlike the higher

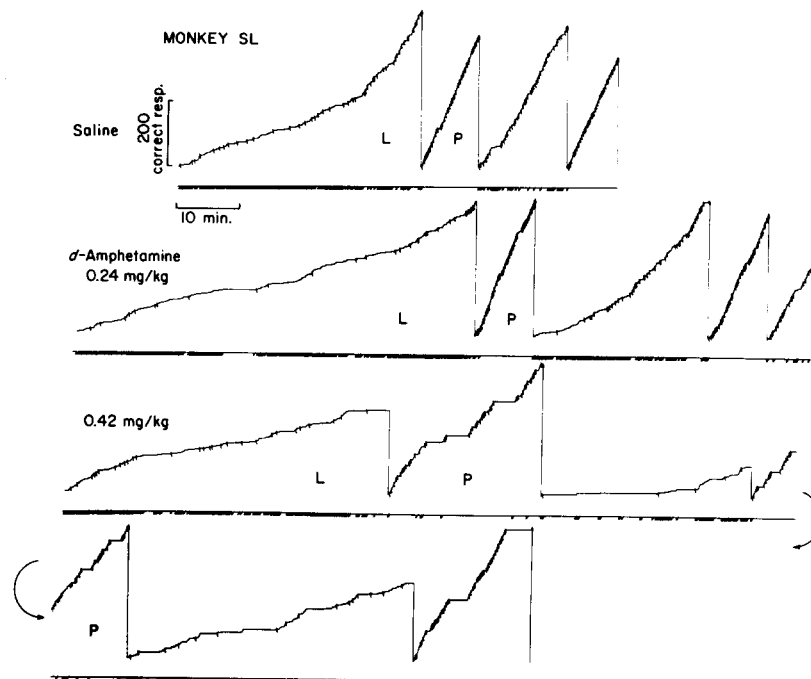


FIG. 6. Effects of two doses of *d*-amphetamine on the within-session responding of monkey SL under the multiple schedule with learning (L) and performance (P) components. The recording details are the same as in Fig. 2.

doses of phencyclidine, which produced long periods of pausing at the start of the session (Fig. 2) and pentobarbital, which produced very little pausing (Fig. 4), this higher dose of *d*-amphetamine produced sporadic periods of pausing throughout the session in both components of the multiple schedule.

Each of the three drugs produced a dose-related increase in percent errors. It is possible, however, that each drug produced this effect on accuracy in a different manner. For example, errors may be increased because a drug reduces the subject's ability to discriminate between the various stimuli. Alternatively, a drug may increase errors by altering the probability that the subject will respond on a particular lever. One way to distinguish among various drug effects on accuracy is through the use of a signal detection analysis. Such an analysis of responding in the acquisition component for each subject, under each drug, is shown in Fig. 7. The data for responding in the performance component are not shown because the control error levels were virtually zero and the drug effects were relatively small. According to a signal detection analysis of these data, movement along the negative diagonal indicates changes in discriminability. For example, a point in the upper left corner would indicate maximal discriminability, while a point on the positive diagonal would indicate that the stimuli were indiscriminable. Movement away from the negative diagonal represents changes in response bias (i.e., lever preference). For example, a point to the upper right would indicate an extreme left-lever preference, while a point to the lower left would indicate an extreme right-lever preference.

Generally, as is shown in Fig. 7, the drug data exhibit considerable variability both in relation to response bias and discriminability. For monkey SL, each drug altered both bias and discriminability; these changes, however, were not dose

related. In addition, replications of the same dose often produced discrepant effects (e.g., monkey SL, phencyclidine 0.24 mg/kg). The data for monkey T show similar effects on both discriminability and bias, though the relatively high degree of accuracy under saline conditions may limit the usefulness of this analysis for this particular subject. In summary, it appears that none of the drugs tested increased errors by selectively affecting either discriminability or bias.

DISCUSSION

In monkeys responding under fixed-ratio schedules of food presentation, phencyclidine, pentobarbital and *d*-amphetamine each produces a dose-dependent decrease in the overall rate of responding in comparison to saline or vehicle controls [4, 6, 12, 14, 16, 21]. The present data are in agreement with these findings. In previous studies of the effects of *d*-amphetamine on the repeated acquisition and performance of discriminations in monkeys, overall response rate has been found to increase at certain doses [19,23]. At no dose, however, did *d*-amphetamine increase response rate in the present study. One fundamental difference which may account for these seemingly discrepant findings is the manner in which food presentation was scheduled. In both of the previous studies, completions of a four-response sequence or chain were reinforced under a fixed-ratio schedule. Responding was therefore maintained under what might be considered a second-order schedule. At certain doses both *d*-amphetamine and pentobarbital have been reported to increase overall response rates in monkeys responding under second-order schedules of food presentation in which the first-order schedule is a fixed ratio [14,15]. That the present study did not employ a second-order schedule may therefore be one reason why no increases in response rate were obtained.

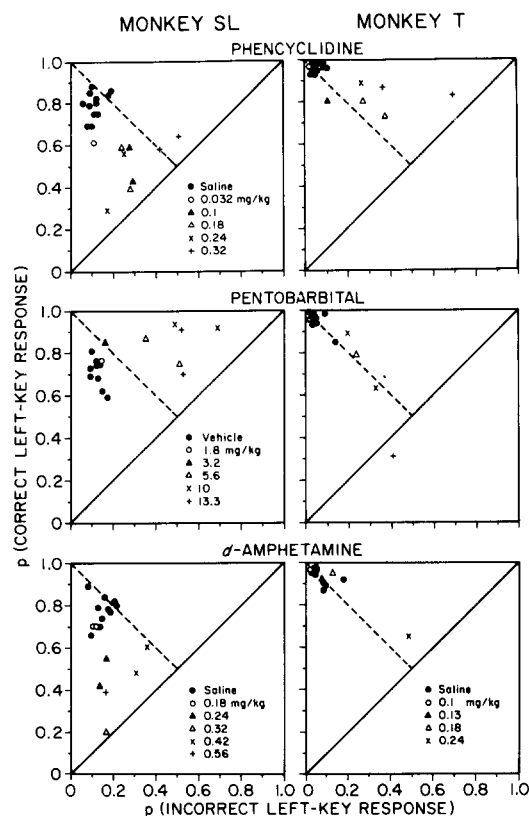


FIG. 7. A signal detection analysis of responding in the learning component for each monkey at selected doses of each drug. Note that the *d*-amphetamine doses are represented by different symbols for each monkey. For phencyclidine and pentobarbital, the symbols represent the same dose for each monkey. See text for details of the analysis.

Though only decreases in overall rate of responding were obtained in the present study, each drug was found to affect the patterning of responding differently. This was especially apparent at the higher doses. In both subjects, phencyclidine at higher doses produced long periods of pausing at the beginning of the session (e.g., Fig. 2, 0.32 mg/kg). In contrast, *d*-amphetamine at the higher doses produced sporadic periods of pausing throughout the session in both subjects (e.g., Fig. 6, 0.42 mg/kg). At the higher doses, pentobarbital's effects on response patterning differed in the two monkeys. In monkey SL, pentobarbital produced very little pausing. Its effects in this subject can be characterized as a reduction in the local rate of responding which tended to persist throughout the session (Fig. 4, 13.3 mg/kg). In monkey T, however, the decrease in the local rate of responding was

accompanied by pausing. The difference between the effects of *d*-amphetamine and phencyclidine on response patterning has also been found in monkeys responding under a multiple schedule of repeated acquisition and performance of tandem response sequences [19]. The present data replicate and extend these findings to a different type of discrimination maintained under a different schedule of reinforcement. Together these results suggest that the effects of phencyclidine on the patterning of responding differ from those of *d*-amphetamine when the behavior under study is the acquisition and performance of a complex discrimination (cf. [25,26]).

Each of the three drugs tested disrupted accuracy under both the acquisition and performance baselines. These data are consistent with previous reports of their effects on the performance of monkeys on a variety of discrimination tasks. For example, the effects of pentobarbital have been investigated in monkeys responding under a simultaneous matching-to-sample procedure [13]. In that study, pentobarbital produced a decrease in response rate at doses of 1, 10 and 20 mg/kg. Accuracy, however, was impaired only at the 20 mg/kg dose. Similarly, in the present study, accuracy in the performance component was disrupted only at the high dose (13.3 mg/kg). The effects of *d*-amphetamine, pentobarbital and phencyclidine on an oddity discrimination have also been investigated [8]. In that study, monkeys were trained to avoid or escape from electric shock by responding to the smaller stimulus in a series of three stimuli. On each trial, two of the stimuli were always the same size, while the size of the third stimulus varied but was always smaller than the other two. *d*-Amphetamine, pentobarbital and phencyclidine each decreased the rate of correct responding in a dose-dependent manner and at higher doses increased errors.

Each of the three drugs tested also produced selective error-increasing effects between the components of the multiple schedule. Generally, errors increased in the acquisition component at lower doses than those required to disrupt behavior in the performance component. The selective error-increasing effects produced by both phencyclidine and *d*-amphetamine are similar to those previously obtained with these drugs in monkeys responding under multiple schedules of repeated acquisition and performance of either behavioral chains [23] or tandem response sequences [19]. The data therefore extend the generality of previous reports of selective effects with *d*-amphetamine and phencyclidine on accuracy in monkeys to a third type of discrimination procedure. Additionally, the *d*-amphetamine data replicate and extend to monkeys previous results obtained in pigeons with the repeated acquisition and performance of conditional discriminations as a baseline procedure [18]. Finally, the present data extend the generality of the finding of selective drug effects on accuracy in monkeys to another prototypical drug, namely, pentobarbital.

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