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Phencyclidine in Combination with *d*-Amphetamine: Differential Effects on Acquisition and Performance of Response Chains in Monkeys[1]

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THOMPSON, D. M. AND J. M. MOERSCHBAECHER. *Phencyclidine in combination with d-amphetamine: Differential effects on acquisition and performance of response chains in monkeys.* PHARMACOL BIOCHEM BEHAV 20(4) 619–627, 1984.—In one component of a multiple schedule, patas monkeys acquired a different four-response chain each session by responding sequentially on three keys in the presence of four geometric forms (learning). In the other component, the four-response chain was the same each session (performance). The response chain in each component was maintained by food presentation under a fixed-ratio schedule. Errors produced a brief timeout but did not reset the chain. When phencyclidine was administered alone, overall response rate decreased and percent errors increased in both components with increasing doses. *d*-Amphetamine alone generally decreased rate and increased errors in learning, but increased rate and had no effect on accuracy in performance. When phencyclidine was administered in combination with *d*-amphetamine, the phencyclidine dose-effect curves tended to shift to the left as the dose of *d*-amphetamine was increased. The extent to which the curves shifted, however, depended on both the schedule component and the behavioral measure. For example, with accuracy, the shift was more evident in learning than in performance. Combinations of phencyclidine with a high dose of *d*-amphetamine generally produced supra-additive effects; i.e., the effects on rate and accuracy were greater than expected from simple addition of the effects of each drug given alone.

Repeated acquisition Response chains Multiple schedule Drug interaction Phencyclidine *d*-Amphetamine Key press Monkeys

IN view of epidemiological reports that phencyclidine is frequently taken in combination with amphetamine [19, 29, 30], it is surprising that there has been relatively little laboratory research on the behavioral effects of such combinations. Most of this research has been concerned with drug-induced "stereotypy" in rats. For example, Balster and Chait [3] reported that phencyclidine, at a dose having no effect when given alone, increased *d*-amphetamine-induced stereotypy, as measured by a rating scale. It has also been reported that phencyclidine-induced stereotypy can be increased by a dose of *d*-amphetamine that was ineffective when given alone [24]. In a more recent study, however, phencyclidine in combination with *d*-amphetamine did not result in greater stereotypy than phencyclidine alone, though phencyclidine did "potentiate" the effects of *d*-amphetamine on locomotor activity [9]. It was suggested that this apparent discrepancy may be related to the different rating scales used.

In regard to operant behavior, Poling *et al.* [26] have investigated the effects of phencyclidine and *d*-amphetamine, alone and in combination, on responding under FR 30 and DRL 15-sec schedules of food presentation in rats. When given alone, the two drugs produced similar effects, namely, with increasing doses, response rate under the FR schedule decreased, whereas response rate under the DRL schedule increased. When phencyclidine and *d*-amphetamine were given in combination, the effects on rate under each schedule tended to be less than an arithmetic summation of the effects of the drugs given alone. In other words, certain dose combinations of phencyclidine and *d*-amphetamine produced infra-additive effects, although in most cases the departures from additivity were small.

The purpose of the present research was to investigate the effects of phencyclidine in combination with *d*-amphetamine on complex operant behavior in primates. More specifically, this drug combination was examined in patas monkeys under a multiple schedule of repeated acquisition and performance of response chains. In a previous study using this behavioral baseline, phencyclidine was administered in combination

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with pentobarbital [36]. Doses of each drug that had little or no effect when given alone were found to produce marked behavioral disruption when given in combination; there was a decrease in overall response rate and an increase in percent errors in both acquisition and performance. Moreover, combinations of varying doses of phencyclidine with a high dose of pentobarbital generally produced greater rate-decreasing and error-increasing effects than expected from simple addition of the effects of each drug given alone. Whether such supra-additive effects would also be found with *d*-amphetamine-phencyclidine combinations was a question that led to the present experiment.

METHOD

Subjects

Three adult female patas monkeys served. Each subject had a long history of responding under the multiple-schedule baseline used in the present research (more than 1200 sessions), during which time a variety of drugs were tested, including *d*-amphetamine and cocaine [35] as well as combinations of phencyclidine and pentobarbital [36]. The testing of the latter two drugs was completed approximately eight months prior to the start of the present study. The subjects were maintained at about 90% of their free-feeding weights (range 5.9 to 6.8 kg) on a diet consisting of Noyes banana-flavored food pellets, Purina 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-1001) measuring 66 cm by 74.9 cm by 93.9 cm. A removable response panel (BRS/LVE, model TIP-001), measuring 56 cm by 21.5 cm by 45 cm, was attached to the side of each subject's cage during the experimental session. Three response keys (BRS/LVE, press plate model PPC-012) were centered and aligned horizontally on the panel. The keys were spaced 11.5 cm apart, center to center, and 51.5 cm from the cage floor. Each key required a minimum force of 0.29 N for activation. An in-line projector (BRS/LVE, model IC 901-696), mounted behind each key, could project colors and geometric forms onto the key. A yellow pilot lamp (1.2 cm in diameter) was mounted 22.5 cm to the right and 17 cm up from the center of the right-hand key. A press on this lamp (0.34 N minimum force) closed a switch on which it was mounted. A food pellet aperture (5.5 cm in diameter) was located 15.5 cm to the right and 8 cm down from the center of the right-hand key. The response panels were connected to solid-state scheduling and recording equipment located in an adjacent room.

Procedure

Baseline. A multiple schedule with learning and performance components served as the baseline. During the *learning* component, one of four geometric forms (horizontal line, triangle, vertical line, circle) was projected onto a red background on all three response keys. The subject's task was to learn a four-response chain by pressing the correct key in the presence of each form, e.g., horizontal line—Left correct; triangle—Right correct; vertical line—Center correct; circle—Right correct. When the chain was completed, the keylights turned off and the yellow lamp over the food pellet aperture was illuminated. A press on the yellow lamp then reset the chain. The four-response chain was maintained by food presentation under an FR 5 schedule; i.e., every fifth completion of the chain produced a food pellet (500 mg) when the yellow lamp was pressed. When the subject pressed an incorrect key (e.g., the left or right key when the center key was correct), the error was followed by a 5-sec timeout. During the timeout, the keys were dark and responses were ineffective. An error did not reset the chain; i.e., the stimuli on the keys after the timeout were the same as before the timeout.

To establish a steady state of repeated acquisition, the four-response chain in the learning component was changed from session to session. The chains were carefully selected to be equivalent in several ways and there were restrictions on their ordering across sessions [33]. An example of a typical set of six chains is as follows: Left-Right-Center-Right (LRCR), CLRL, LRLC, RCRL, CLCR, RCLC; the order of the associated forms was always the same: horizontal line, triangle, vertical line, circle (reinforcement).

During the *performance* component of the multiple schedule, the four geometric forms were projected on a green background and the four-response chain remained the same (LCLR) from session to session. In all other aspects (FR 5 schedule of food reinforcement, timeout duration of 5 sec, etc), the performance component was identical to the learning component.

Sessions were conducted daily, Monday through Friday. Each session began in the learning component, which then alternated with the performance component after 10 reinforcements or 15.5 min (±30 sec), whichever occurred first. Each session was terminated after 100 reinforcements or 2 hr, whichever occurred first. 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 [(errors/total responses) × 100] in each component. In addition to these measures based on session totals, within-session changes in responding were monitored by a cumulative recorder. For example, acquisition of the response chain in the learning component was indicated by within-session error reduction, i.e., a decrease in the frequency of errors (per reinforcement) as the session progressed.

Drug testing. Dose-effect data were first obtained for phencyclidine hydrochloride. The drug was dissolved in saline and injected IM *(gluteus m.)* 5 min presession. The doses of phencyclidine were tested in a mixed order and there were generally two determinations for all of the effective doses and for the highest ineffective dose. Next, 0.1 mg/kg of *d*-amphetamine sulfate (dissolved in saline) was administered alone, IM 5 min presession. Varying doses of phencyclidine (in a mixed order) were then administered in combination with the 0.1 mg/kg dose of *d*-amphetamine. Both drugs were injected IM (one on the right side, the other on the left) 5 min presession. Two determinations were generally made for all of the effective dose combinations. The 0.1 mg/kg dose of *d*-amphetamine was then administered alone again. Next, using the same testing procedure, a higher dose of *d*-amphetamine, either 0.3 mg/kg (Monkeys EV and B) or 0.17 mg/kg (Monkey EL), was administered alone and in combination with varying doses of phencyclidine; prior research [35] had indicated that Monkey EL was more sensitive than the other two subjects to the effects of

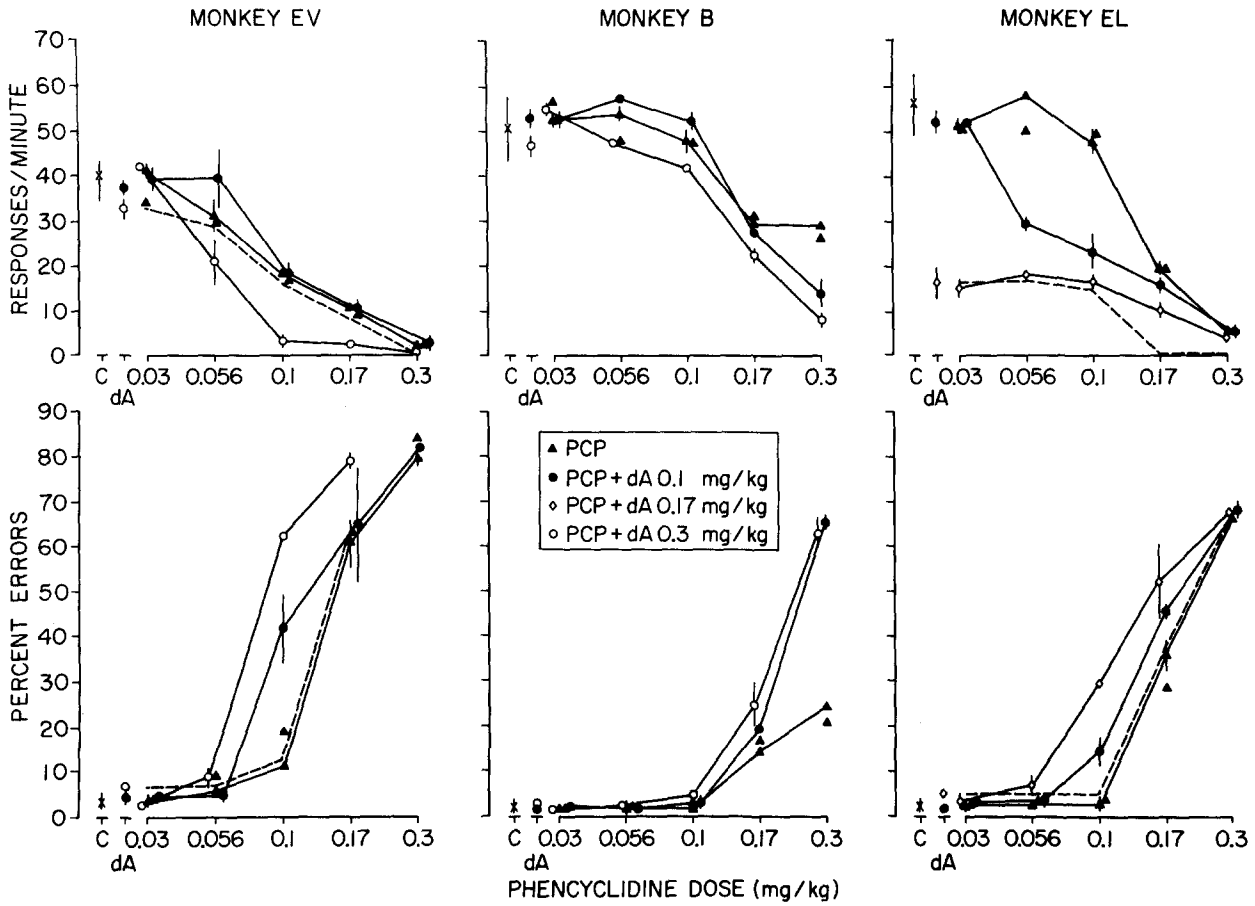

FIG. 1. Effects of phencyclidine (PCP) and *d*-amphetamine (dA), alone and in combination, on the overall response rate and percent errors in the *learning* component of the multiple schedule for each subject. The points with vertical lines at C indicate the mean and range for 25 control (saline) sessions. The points with vertical lines at dA indicate the mean and range for two determinations at each dose of *d*-amphetamine alone, with the symbols the same as those for phencyclidine + *d*-amphetamine; the points without vertical lines at dA (percent errors) indicate that the range is encompassed by the point. Note that 0.3 mg/kg of *d*-amphetamine was tested in Monkeys EV and B, whereas the 0.17 mg/kg dose was tested in Monkey EL. The points with vertical lines in the dose-effect curves indicate the mean and range for two determinations; the points without vertical lines indicate either a single determination or, occasionally, an instance in which the range is encompassed by the point. Points for percent errors have been omitted in cases where the overall response rate was virtually zero. The unconnected triangles show a redetermination of the dose-effect data for phencyclidine alone after phencyclidine was tested in combination with *d*-amphetamine. The dashed lines show the predicted outcome of combining phencyclidine with *d*-amphetamine if the effects of phencyclidine alone (connected triangles) and the effects of *d*-amphetamine alone (0.3 or 0.17 mg/kg) were additive.

d-amphetamine alone. In Monkeys EV and B, 0.56 mg/kg of *d*-amphetamine was then administered alone (IM 5 min presession). This was done to determine whether the effects obtained with phencyclidine in combination with 0.3 mg/kg of *d*-amphetamine were similar to the effects of a higher dose of *d*-amphetamine alone. Finally, the dose-effect data for phencyclidine alone were redetermined in all three subjects.

Throughout testing, drug sessions were generally conducted on Tuesdays and Fridays, with control sessions (saline, IM 5 min presession) occurring on Thursdays, and baseline sessions (no injections) on Mondays and Wednesdays. The volume of each injection was 0.05 ml/kg body weight. All doses are expressed in terms of the salt of each drug.

RESULTS

Figure 1 shows the effects of phencyclidine and *d*-amphetamine, alone and in combination, on the overall response rate and percent errors in the *learning* component of the multiple schedule for each subject. When phencyclidine was administered alone, the response rate decreased and the percent errors increased with increasing doses. Administration of 0.1 mg/kg of *d*-amphetamine alone had no effect on either overall rate or overall accuracy in the learning component. When this dose of *d*-amphetamine was administered in combination with phencyclidine, however, the dose-effect curves for percent errors tended to shift to the left relative to those for phencyclidine alone. The greater error-increasing effect of this combination was most apparent at intermediate doses of phencyclidine (e.g., 0.1 mg/kg) in Monkeys EV and EL and at the highest dose of phencyclidine in Monkey B. In contrast, a similar shift in the dose-effect curves for response rate was evident in only one subject (Monkey EL), although there was another instance (at

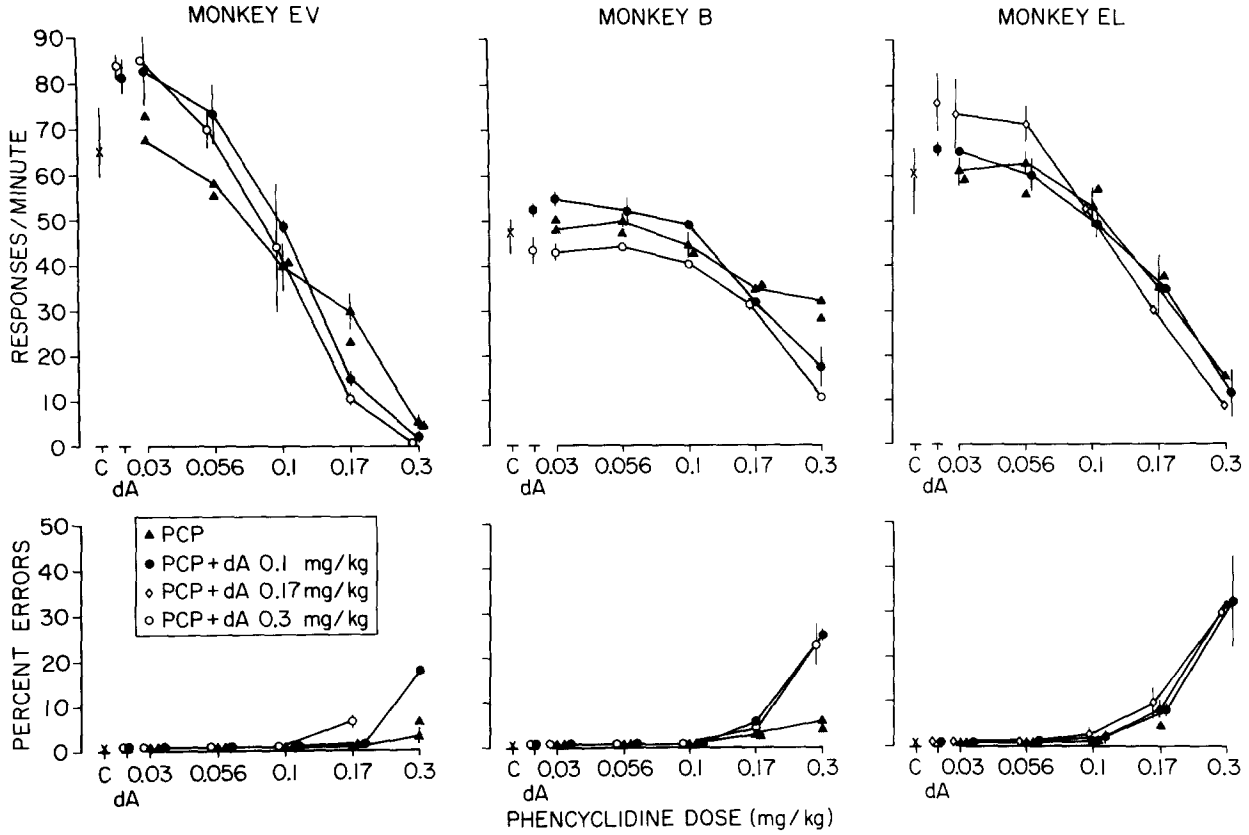

FIG. 2. Effects of phencyclidine (PCP) and *d*-amphetamine (dA), alone and in combination, on the overall response rate and percent errors in the *performance* component of the multiple schedule for each subject. Abbreviated key: C=control; dA=*d*-amphetamine alone; unconnected triangles=redetermination for phencyclidine alone. For other details, see legend for Fig. 1.

0.3 mg/kg of phencyclidine in Monkey B) where the *d*-amphetamine (0.1 mg/kg)-phencyclidine combination consistently produced greater rate-decreasing effects than those produced by phencyclidine alone. When the higher doses of *d*-amphetamine (0.3 mg/kg in Monkeys EV and B and 0.17 mg/kg in Monkey EL) were administered alone, the response rate decreased and the percent errors increased in Monkeys EV and EL but were unaffected in Monkey B. Note that in Monkey EL the rate-decreasing effect was substantial. The higher doses of *d*-amphetamine in combination with phencyclidine generally shifted the dose-effect curves for percent errors further to the left than did the 0.1 mg/kg dose of *d*-amphetamine, though this difference was relatively small in Monkey B. The corresponding dose-effect curves for response rate were also shifted to the left relative to those for phencyclidine alone in all three subjects. A striking example of differential effects on rate and accuracy can be seen in the data of Monkey EL, where 0.1 mg/kg of phencyclidine in combination with 0.17 mg/kg of *d*-amphetamine produced essentially the same rate-decreasing effect as this dose of *d*-amphetamine alone, whereas the error-increasing effect was much greater with the drug combination. In general, the effects of phencyclidine alone were replicated after the *d*-amphetamine-phencyclidine combinations were tested (see the unconnected triangles).

The dashed lines in Fig. 1 show the predicted outcome of combining phencyclidine with *d*-amphetamine if the effects of phencyclidine alone (connected triangles) and the effects of *d*-amphetamine alone (0.3 or 0.17 mg/kg) were additive. (Dashed lines are not shown for Monkey B since 0.3 mg/kg of *d*-amphetamine alone had no effect; the predicted outcome here is simply the dose-effect curve for phencyclidine alone.) When administered alone, each drug was considered to have an effect on response rate or percent errors to the extent that the data points fell outside of the control range [36]. Accordingly, the rate-decreasing effect of phencyclidine alone was calculated by subtracting the overall response rate at a given dose of phencyclidine from the minimum control rate, yielding a difference score. If the response rate at a given dose of phencyclidine fell within the control range, the dose was considered to have no effect, and the difference score was assigned a value of 0. The same type of calculation was made for *d*-amphetamine alone, and the sum of the two difference scores defined the additive effect on response rate [36]. The additive effect on percent errors was determined in the same way, except that the error-increasing effect of each drug alone was calculated by subtracting the maximum control value for percent errors from the percent errors at a given dose. As can be seen, when phencyclidine and *d*-amphetamine (0.3 or 0.17 mg/kg) were administered in combination, the effects on rate and accuracy were generally greater than expected from simple addition of the effects of each drug given alone; i.e., most of these *d*-amphetamine-phencyclidine combinations produced supra-additive effects. A notable exception occurred at the higher doses of phencyclidine in Monkey EL, where the rate-decreasing effect of the combination was less than additive.

Figure 2 shows the effects of phencyclidine and

d-amphetamine, alone and in combination, on the overall response rate and percent errors in the *performance* component of the multiple schedule for each subject. A comparison of Fig. 2 with Fig. 1 indicates that the performance component tended to be less sensitive than the learning component to the error-increasing effects of the drugs. For example, when *d*-amphetamine was administered alone, none of the doses had any effect on percent errors in the performance component, whereas the higher doses (0.3 or 0.17 mg/kg) produced small but reliable error-increasing effects in the learning component in Monkeys EV and EL. When phencyclidine was administered alone in Monkey EV, a higher dose was required to produce a reliable increase in percent errors in the performance component (0.3 mg/kg) than in the learning component (0.1 mg/kg). The greater sensitivity of the learning component to error-increasing effects was also evident when the two drugs were administered in combination. For example, in Monkey EL, the phencyclidine dose-effect curves for percent errors in the learning component shifted to the left as the dose of *d*-amphetamine was increased, whereas the corresponding curve in the performance component was essentially unchanged. In Monkey EV, although increasing the dose of *d*-amphetamine tended to produce a shift to the left in the phencyclidine dose-effect curve for percent errors in the performance component, this occurred at higher doses of phencyclidine and the effects were smaller in comparison to the learning component.

In regard to the effects on response rate in the performance component (Fig. 2), phencyclidine alone produced dose-related decreases in rate that were similar to the effects obtained in the learning component (Fig. 1). *d*-Amphetamine alone, however, increased response rate in the performance component but not in the learning component. Such rate-increasing effects were seen in all three subjects, although the effective doses of *d*-amphetamine varied and the magnitude of the increase was relatively small in Monkey B. The differential effects on response rate in learning and performance are most evident in the data of Monkey EL, where 0.17 mg/kg of *d*-amphetamine alone produced a clear rate-increasing effect in the performance component but decreased rate substantially in the learning component. In the performance component, the lower doses of phencyclidine in combination with *d*-amphetamine generally produced rate-increasing effects that were comparable to those produced by *d*-amphetamine alone. As the dose of phencyclidine in the combinations increased, the response rate in the performance component decreased. Note that the higher doses of phencyclidine in combination with *d*-amphetamine produced greater rate-decreasing effects than those produced by phencyclidine alone. As was the case in the learning component, the effects of phencyclidine alone in the performance component were generally replicated after the *d*-amphetamine-phencyclidine combinations were tested.

In regard to the question of additivity of drug effects in the performance component, the error-increasing effects obtained with the drug combinations could be considered supra-additive in two of the subjects (Monkeys EV and B) since *d*-amphetamine alone had no effect on percent errors (Fig. 2). (As in Fig. 1, dashed lines indicating the predicted outcome if the effects were additive are not shown here because the predicted outcome is simply the dose-effect curve for phencyclidine alone.) Since *d*-amphetamine alone and phencyclidine alone produced different types of effects on response rate in the performance component (increase and decrease, respectively), it would be inappropriate to ask whether their combined effects on performance rate were additive [10].

Figure 3 shows the pattern of responding during a representative control session (one that approximated the mean for both overall response rate and overall accuracy in each schedule component) and during several drug sessions for Monkey EV. In the control record (top), errors decreased in frequency in the learning component as the session progressed, i.e., acquisition occurred. After the first 6 min of this session, there were long runs of correct responses that were separated by brief pauses in both components and virtually no errors were made. The rate of responding during these runs was generally higher in the performance component than in the learning component. When 0.3 mg/kg of *d*-amphetamine was administered alone, responding was disrupted in the learning component but not in the performance component. In the learning component, there was a clear decrease in the rate of correct responding and a small increase in the frequency of errors, though acquisition was still evident. In contrast, in the performance component, the overall rate of correct responding was increased (due to the elimination of pausing) but the frequency of errors remained at zero. When 0.1 mg/kg of phencyclidine was administered alone, responding was disrupted in both components. In the learning component, there was a large error-increasing effect, a long pause, and no sign of acquisition until the third cycle of the multiple schedule. In the performance component, there was a clear rate-decreasing effect, which diminished as the session progressed, though accuracy remained unaffected (no errors). When 0.3 mg/kg of *d*-amphetamine was administered in combination with 0.1 mg/kg of phencyclidine, the rate-decreasing effect in the learning component was much greater than that produced by this dose of phencyclidine alone, and there was no sign of acquisition during the session. In the performance component, however, there was relatively little disruption in the rate of responding, except during the first cycle of the multiple schedule.

A comparison of Fig. 3 (bottom) with Fig. 4 (top) shows that the effects obtained with phencyclidine in combination with 0.3 mg/kg of *d*-amphetamine were similar to the effects of a higher dose of *d*-amphetamine alone (0.56 mg/kg). In both cases, there was marked disruption of responding in the learning component but not in the performance component of the multiple schedule. Such differential effects are in contrast to those obtained with a higher dose of phencyclidine alone (Fig. 4, bottom), where 0.17 mg/kg disrupted responding in both components. There was, however, less disruption in the performance component (smaller rate-decreasing effect and no error-increasing effect). In general, the within-session effects of *d*-amphetamine and phencyclidine, alone and in combination, in Monkey EV (Figs. 3 and 4) were replicated in Monkey B, although the particular doses and the magnitude of the effects varied.

Figure 5 shows some within-session effects of *d*-amphetamine and phencyclidine, alone and in combination, in Monkey EL. The administration of 0.17 mg/kg of *d*-amphetamine alone, which was a high dose for this subject, produced the same type of differential effects on learning and performance as those obtained with high doses of *d*-amphetamine in the other two subjects (e.g., Fig. 4, top). The duration of these effects, however, was relatively short in Monkey EL; note that acquisition occurred during the third cycle of the multiple schedule following a period in which errors were emitted at a higher frequency than control

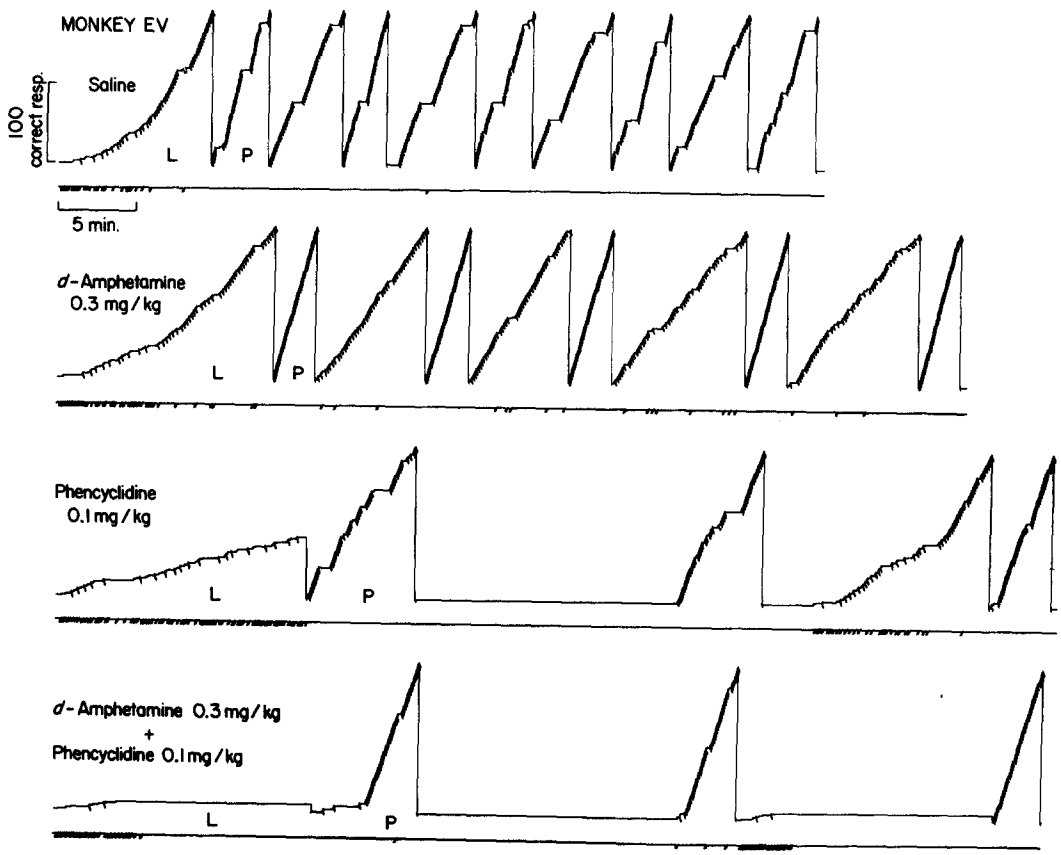

FIG. 3. Cumulative records for Monkey EV showing the pattern of responding under a multiple schedule with learning (L) and performance (P) components during a representative control session (saline) and during sessions preceded by injections of *d*-amphetamine (0.3 mg/kg) and phencyclidine (0.1 mg/kg), alone and in combination. The upper two records are complete sessions (100 reinforcements each). In each of the lower two records, only the first three cycles of the multiple schedule are shown. The response pen stepped upward with each correct response and was deflected downward each time the four-response chain was completed. Errors are indicated by the event pen (below each record), which was held down during each timeout. A change in components of the multiple schedule reset the stepping pen.

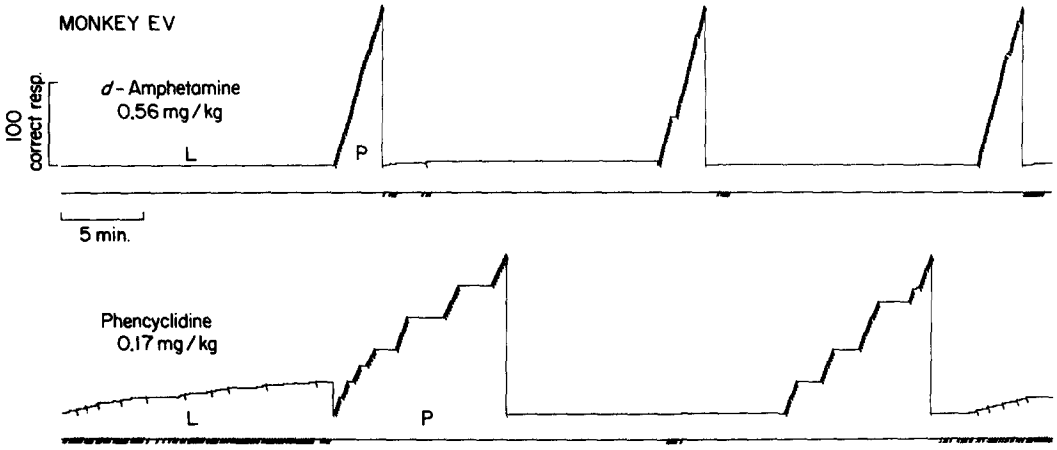

FIG. 4. Cumulative records for Monkey EV showing the within-session effects of high doses of *d*-amphetamine and phencyclidine when administered alone. The first hour of each session is shown. The recording details are the same as in Fig. 3.

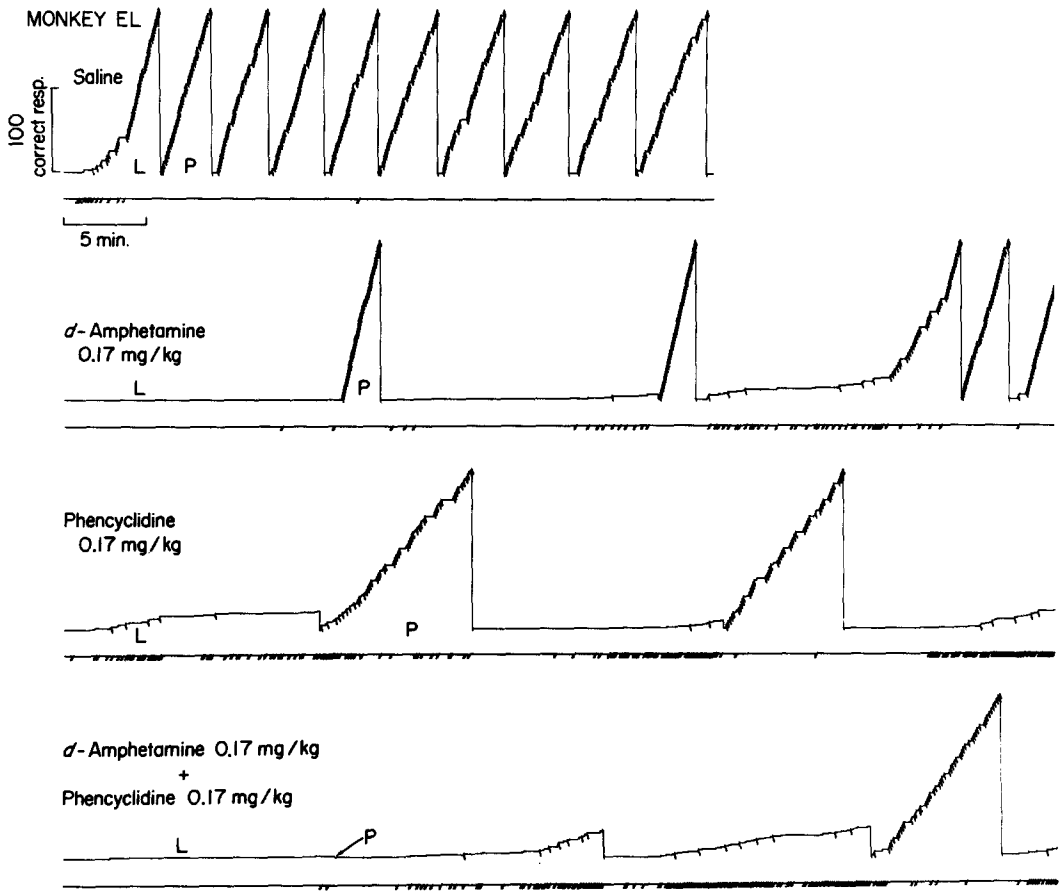

FIG. 5. Cumulative records for Monkey EL showing the pattern of responding under a multiple schedule with learning (L) and performance (P) components during a representative control session (saline) and during sessions preceded by injections of *d*-amphetamine (0.17 mg/kg) and phencyclidine (0.17 mg/kg), alone and in combination. The first hour of each session is shown, except for the saline session, which terminated after 100 reinforcements. The recording details are the same as in Fig. 3.

(e.g., see saline session, top). In contrast to the differential effects obtained with *d*-amphetamine, 0.17 mg/kg of phencyclidine alone produced rate-decreasing and error-increasing effects in both components of the multiple schedule, though there was less disruption in the performance component. Except for the initial increase in errors in the performance component, these effects are similar to those obtained with this dose of phencyclidine in Monkey EV (Fig. 4, bottom). There was even greater disruption of responding in both components when 0.17 mg/kg of phencyclidine was administered in combination with 0.17 mg/kg of *d*-amphetamine. The substantial rate-decreasing and error-increasing effects in the first performance component are noteworthy since this dose of *d*-amphetamine alone increased the rate of correct responding without increasing errors in the performance component. Note also that as the session progressed, the disruptive effects of the drug combination on rate and accuracy began to diminish more quickly in the performance component than in the learning component. In summary, the within-session effects produced by high doses of phencyclidine and *d*-amphetamine in combination in Monkey EL were more similar to the effects of phencyclidine alone than to the effects of *d*-amphetamine alone. This is in contrast to the within-session effects produced by a lower dose of phencyclidine in combination with *d*-amphetamine in Monkey EV (Fig. 3, bottom), which were more similar to the effects of *d*-amphetamine alone (Fig. 4).

DISCUSSION

The rate-decreasing and error-increasing effects obtained in the present study when phencyclidine was administered alone are consistent with previous research showing that phencyclidine produces dose-related disruptive effects on behavior in various discrimination tasks. For example, Brown and Bass [5] found that phencyclidine disrupted the performance of rhesus monkeys in an oddity-discrimination task; it decreased the rate of correct responding in a dose-dependent manner and, at higher doses, increased errors. In baboons trained to respond in a standard psychophysical procedure to determine auditory and visual thresholds, high doses of phencyclidine completely disrupted performance [20]. More recently, McMillan [21] reported that phencyclidine disrupted the performance of pigeons in a delayed matching-to-sample task; matching accuracy was decreased at doses that decreased response rate. Phencyclidine has also been reported to disrupt the acquisition [31] and performance [32] of a brightness discrimination in rats. Finally, in research more closely related to the present study, it was found that phencyclidine disrupted the behavior of patas monkeys under a multiple schedule of repeated acquisition and performance of either conditional discriminations [23] or

four-response sequences [22,36]. As in the present study, with increasing doses of phencyclidine the overall response rate in each schedule component decreased, the percent errors in each component increased, and there was less within-session error reduction (acquisition) in the learning component. The performance component tended to be less sensitive than the learning component to the drug effects.

When *d*-amphetamine was administered alone, the higher doses decreased the overall response rate and increased percent errors in the learning component in two of three subjects. However, in the performance component, *d*-amphetamine generally increased the overall response rate but had no effect on percent errors. Such differential effects of *d*-amphetamine on learning and performance have previously been found in repeated-acquisition studies with patas monkeys [22, 23, 35], although a rate-increasing effect in the performance component is not a consistent finding. The error-increasing effect of *d*-amphetamine in the learning component complements the results obtained with other discrimination techniques, such as matching to sample [7, 12, 27], fixed consecutive number [16,18] and related procedures [1, 4, 15, 17, 25, 34]. With these techniques, it has been shown that performance accuracy generally decreases with increasing doses of *d*-amphetamine in rhesus monkeys, squirrel monkeys, pigeons, and rats. That *d*-amphetamine did not increase performance errors in the present study may be related to the possibility that the doses tested were simply not high enough. This is unlikely, however, because in a previous study with the same subjects and behavioral baseline, *d*-amphetamine generally failed to increase errors in the performance component even at doses that produced substantial rate-decreasing effects in that component [35].

An alternative explanation is that the behavior in the performance component was under relatively strong stimulus control, as indicated by near-zero baseline error levels, and accuracy was therefore unaffected by *d*-amphetamine. It has been shown in a variety of situations that behavior under strong stimulus control is more resistant to disruption by drugs than behavior under weak stimulus control [17,34]. While this explanation may also apply to other cases in which *d*-amphetamine produced little or no effect on performance accuracy in discrimination tasks (e.g., [11, 14, 21]), it would seem less applicable to the results obtained when phencyclidine was administered alone. For example, in the present study, although the performance component tended to be less sensitive than the learning component to the disruptive effects of phencyclidine, the higher doses did increase performance errors (Figs. 2 and 5).

In general, when phencyclidine was administered in combination with *d*-amphetamine, the phencyclidine dose-effect curves tended to shift to the left as the dose of *d*-amphetamine was increased (Figs. 1 and 2). The extent to which the curves shifted, however, depended on both the schedule component (learning vs. performance) and the behavioral measure (rate vs. accuracy). With the accuracy measure, the shift to the left was more evident in the learning component than in the performance component. With the rate measure, the shift to the left was not usually seen in the performance component at the lower doses of phencyclidine. In fact, in the performance component, the lower doses of phencyclidine in combination with *d*-amphetamine generally produced rate-increasing effects that were comparable to those produced by *d*-amphetamine alone, whereas the higher doses of phencyclidine in combination with *d*-amphetamine produced rate-decreasing effects that were greater than those produced by phencyclidine alone. The shift to the left in the dose-effect curves can not be attributed to the development of "supersensitivity" to phencyclidine (i.e., an increased sensitivity due to repeated drug administration) since the effects of phencyclidine alone were replicated after the *d*-amphetamine-phencyclidine combinations were tested. Probably the most reasonable interpretation of the shift in the phencyclidine dose-effect curves is that *d*-amphetamine "potentiated" the effects of phencyclidine (cf., [13]). This interpretation is supported by the finding that combinations of phencyclidine with a high dose of *d*-amphetamine (0.17 or 0.3 mg/kg) generally produced greater rate-decreasing and error-increasing effects than expected from simple addition of the effects of each drug given alone.

The present finding that *d*-amphetamine-phencyclidine combinations generally produced supra-additive effects in monkeys responding in a repeated-acquisition task is not in agreement with the results reported by Poling *et al.* [26]. In that study, certain dose combinations of phencyclidine and *d*-amphetamine produced infra-additive effects in rats responding under FR and DRL schedules of food presentation. The discrepancy between the results of the two studies may be related to several methodological differences. Apart from the obvious difference in the species used and in the complexity of the baselines, the two studies also differed in the procedures used for drug testing. Unlike the present study, Poling *et al.* did not redetermine the dose-effect curves for phencyclidine alone after the drug combinations were tested. It is therefore possible that the apparent infra-additive effects of the drug combinations reflect nothing more than the development of tolerance due to repeated drug administration. As Poling *et al.* ([26] p. 360) pointed out, "this possibility emphasizes the difficulties inherent in conducting and interpreting studies designed to evaluate drug combinations."

As in the present study of *d*-amphetamine-phencyclidine combinations, a previous experiment using the same subjects and behavioral baseline showed that pentobarbital-phencyclidine combinations generally produced rate-decreasing and error-increasing effects that were supra-additive [36]. The results of the two studies differed, however, in some other respects. The pentobarbital-phencyclidine combinations produced only rate-decreasing effects in the performance component of the multiple schedule, whereas the *d*-amphetamine-phencyclidine combinations produced both rate-increasing and rate-decreasing effects in that component. This difference in the effects of the two drug combinations is probably related to the different effects obtained when pentobarbital and *d*-amphetamine were administered alone, namely, response rate in the performance component was decreased by pentobarbital, but increased by *d*-amphetamine. That phencyclidine was similar to pentobarbital but differed from *d*-amphetamine in this regard could not have been predicted on the basis of results obtained with less complex schedule-controlled behavior. For example, Wenger [37] reported that phencyclidine and *d*-amphetamine produced similar effects, which differed from those of pentobarbital, in pigeons responding on a single key under a multiple FR FI schedule of food presentation. Although results such as these have led to the widely held view that phencyclidine has amphetamine-like effects on schedule-controlled performance in rats, pigeons and monkeys (e.g., [2, 6, 8, 26, 28, 37]), the present research (e.g., Fig. 4) indicates that this generalization may not apply to more complex operant behavior.

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