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EFFECTS OF COCAINE AND d-AMPHETAMINE ON THE REPEATED ACQUISITION AND PERFORMANCE OF CONDITIONAL DISCRIMINATIONS[1]

JOSEPH M. MOERSCHBAECHER, JOHN J. BOREN, JOHN SCHROT, AND JOSE CARLOS SIMOES FONTES

THE AMERICAN UNIVERSITY, WASHINGTON, D.C.

The acute and chronic effects of cocaine and *d*-amphetamine on food-reinforced behavior were investigated in pigeons responding on a two-component multiple schedule. In one component, the behavioral task consisted of the same chain of conditional discriminations each session (performance). In the other component, the chain of conditional discriminations was changed from session to session (learning). In comparison to control sessions, both acute cocaine and *d*-amphetamine increased errors in each component of the multiple schedule. Responding in the learning component, however, was generally disrupted at lower doses than those that affected responding in the performance component. At high doses, both drugs produced pauses in responding in each component in three of the four subjects. Pausing engendered by *d*-amphetamine was approximately twice as long as that under cocaine. Upon chronic administration, both the pausing and error-increasing effects of each drug diminished. Drug-induced changes in timeout responding, however, did not decrease during chronic administration. Redeterminations of the *d*-amphetamine dose-effect curves following chronic cocaine administration suggested the existence of cross-tolerance between cocaine and *d*-amphetamine. Both the acute and chronic data are consistent with the view that conditions of stimulus control may modulate the behavioral effects of drugs.

Key words: repeated acquisition, stimulus control, *d*-amphetamine, cocaine, key peck, pigeons

A conditional discrimination is one in which the reinforcement of a response in the presence of one stimulus depends on, or is conditional upon, other stimuli (*cf.* Catania, 1968). Moerschbaecher, Boren, and Schrot (1978) described a procedure that used a repeated acquisition technique (*cf.* Boren, 1963) to study the acquisition of conditional discriminations. In this procedure, pigeons acquired a two-member chain of conditional discriminations involving two response keys and eight combinations of two colors and four forms. For example, in the first member of the chain the stimulus, triangle-red, might require a left-key response and the stimulus, cross-red, a right-key response, whereas in the second member, the same forms projected on a green background required the opposite response, *i.e.*, triangle-green, right, and cross-green, left. Each session the form associated with each color, which set the occasion for a left-key response, was changed. The behavioral result was a steady state of repeated acquisitions of a complex discrimination in which errors decreased within each session. A further finding was that the repeated acquisition of conditional discriminations was affected by behavioral variables similar to those shown to affect the repeated acquisition of serial-response sequences (*cf.* Boren, 1969; Boren and Devine, 1968).

Thompson (1973) used a repeated acquisition technique to investigate the effects of drugs on the acquisition of response sequences. In this procedure, pigeons responded on three keys, each illuminated at the same time by one of four colors. During each session, the subject's task was to acquire a different four-response sequence (*e.g.*, left-right-center-right) by pecking the correct key in the presence of

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each color. Increasing doses of phenobarbital, chlordiazepoxide, and *d*-amphetamine increased errors above baseline levels and decreased the rate at which sequences were acquired. For comparison, Thompson (1975) also tested the effects of drugs using a performance baseline in which the sequence was the same each session. Under successive experimental conditions, the repeated acquisition baseline was generally found to be more sensitive to the drug effects than was the performance baseline. When drugs were administered chronically on these same baselines, behavioral tolerance to the error-increasing effects developed more slowly under the acquisition baseline than under the performance baseline, and in some instances tolerance developed only in the performance condition (Thompson, 1974, 1977).

The purpose of the present study was to investigate the acute and chronic effects of *d*-amphetamine and cocaine on the acquisition and performance of conditional discriminations. A multiple schedule of acquisition and performance baselines was used to determine whether the differential sensitivity of the two baselines reported by Thompson across successive experimental conditions could be obtained within a multiple schedule.

METHOD

Subjects

Four drug-naive Silver King pigeons were maintained at approximately 80% of their free-feeding body weights throughout the experiment. Water and grit were always available in the home cages. All subjects had experimental histories involving the repeated acquisition of conditional discriminations.

Apparatus

The experimental space was a ventilated plywood chamber measuring 43 cm by 61 cm by 42 cm. The response panel contained five response keys (LVE model 121-16), four of which were spaced to form a rectangle 10.5 by 15 cm edge to edge. The remaining key was located in the center of the rectangle. Each key required a minimum force of 0.18 N for activation. Only the center and lower two keys were used. An in-line stimulus projector (Grason Stadler Model 15b), mounted behind each key, projected colors, geometric forms, or combinations of both on the key. A relay behind the response panel clicked with each response. A 6-cm by 6-cm feeder aperture was located in the middle of the response panel 6 cm above the floor; the feeder was illuminated with white light during the reinforcement cycle. Masking noise was present in the experimental room at all times. Programming and data-collection instruments were located in an adjacent room.

Baseline Procedure

A chain of conditional discriminations constituted the task in each component of a multiple schedule. In one component (performance), the conditional discriminations were the same each session. In the other component (learning), the conditional discriminations changed each session. In each component, the subject was required to respond to different combinations of colors and forms, responding on the left key in the presence of two different discriminative stimuli (first and second links of a chained schedule) and on the right key in the presence of six different discriminative stimuli.

Performance component. Geometric forms (a cross, horizontal bar, vertical bar, and three horizontal dots), superimposed on a red or yellow background, served as stimuli and were projected on the center key. A peck on the center key illuminated the lower left and right keys white (R1 in Figure 1). These keys went dark after a response on either one. Responses on a dark key had no consequences. At the beginning of the chain, the center key was red, with any one of four forms superimposed. When a vertical bar appeared on the red background, a left-key response was correct (R3 on Trial 2 in Figure 1). This response changed the background color on the center key from red to yellow. When a horizontal bar appeared on the yellow background, a left-key response was correct and produced 3 sec access to mixed grain (R3 on Trial 5). Following reinforcement, the background color changed back to red (*i.e.*, the chain reset). When either a cross, three dots, or a horizontal bar was superimposed on the red background, a right-key response was correct (*e.g.*, R2 on Trial 1). Similarly, when a cross, three dots, or a vertical bar was superimposed on the yellow background, a right-key response was also correct (*e.g.*, R2 on Trials 3 and 4). Following a correct response

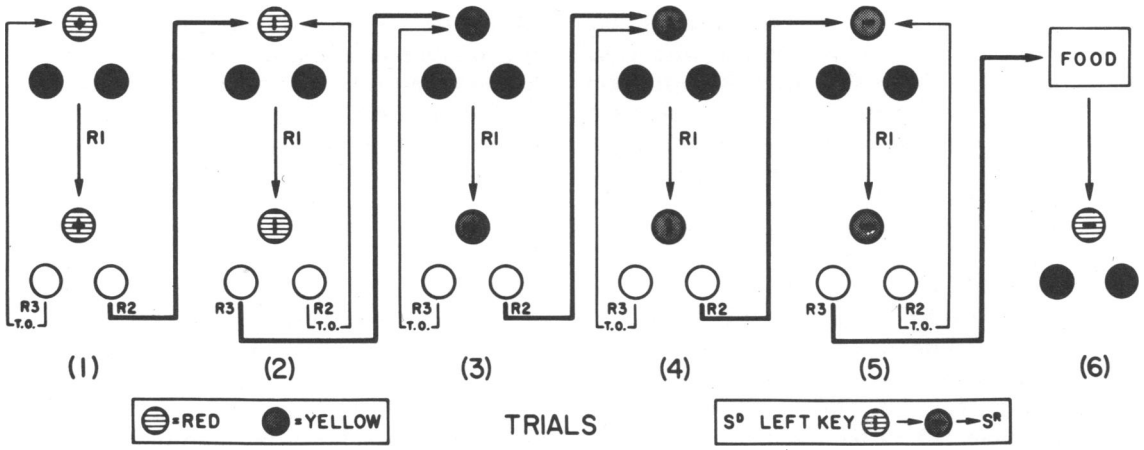

Fig. 1. An example of the conditional discrimination procedure showing five possible trials progressing from left to right. See text for full description of the procedure.

on either the right or left key, the occurrence of each of the four forms was equiprobable (*i.e.*, the probability of a different form coming up was p = 0.75). Only correct left-key responses advanced the chain (*i.e.*, changed the background color or produced food). The requirements for reinforcement were, therefore, two correct left-key responses and a variable number of correct right-key responses. In other words, since the number and sequence of the different forms could vary from chain to chain, the schedule was a variable-ratio chain with a minimum of two (left-key) correct responses. The discriminative stimuli for left- and right-key responses remained the same from session to session.

As shown in Figure 1, incorrect responses made on either the left (*e.g.*, R3 Trial 1) or right (*e.g.*, R2 Trial 2) key resulted in a 10-sec timeout, during which the chamber was dark and responses had no consequences. Following a timeout, the same stimulus was repeated.

Acquisition component. The basic behavioral procedure was identical to that in the performance component. Geometric forms (square, circle, triangle, and an "X"), superimposed on a blue or green background, served as stimuli and were projected on the center key. As in the performance component, a peck on the center key illuminated the lower left and right keys white, while responses on a dark key had no consequences. At the beginning of the chain, the center key was blue and one of four forms superimposed. When, for example, a triangle appeared on the blue background, a left-key response was correct. This response changed the background color on the center key from blue to green. When a circle appeared on the green background, a left-key response was again correct and was reinforced with grain. All other stimulus combinations (*e.g.*, square-blue, triangle-green, *etc.*) were discriminative stimuli for a right-key response. As in the performance component, the occurrence of each of the four forms was equiprobable following a correct left- or right-key response. The consequences for an error were also identical to those in performance. Unlike the performance component, however, the two discriminative stimuli for a left-key response changed each session. For example, during one session, the left-key discriminative stimuli were triangle-blue and circle-green, as described above. In the subsequent session, the discriminative stimuli for a left-key response were square-blue and "X"-green. The geometric forms were programmed as left-key stimuli in the first and second positions in the chain in the following sequence: triangle-circle, square-"X", circle-triangle, "X"-square, triangle-circle, *etc.*

In summary, during each session, the subject acquired a different chain of conditional discriminations in one component (learning) of a multiple schedule while in the other component (performance) the chain of conditional discriminations remained the same from session to session. The components alternated after 10 reinforcements or 15 min, whichever occurred first, with a 10-sec blackout separating the two components. Each session terminated after 60 reinforcements. Sessions were con-

ducted daily with few exceptions and began in either the learning or performance component on alternating days. In each component of the multiple schedule, per cent errors (errors/correct plus errors) and running time (total session time minus time spent in timeout) were used as dependent variables. Responses during the timeout were also recorded.

Drug Procedures

Drug testing began when behavior on the multiple schedule was stable, *i.e.,* when no systematic changes occurred from session to session in either the percentage errors or in running time (45 to 60 sessions). The drugs tested were amphetamine sulfate and cocaine hydrochloride, dissolved in a saline solution, which also served as the vehicle control. Injections were given intramuscularly (pectoral muscles) 5 min before the start of the session. The volume of each injection was 0.1 ml/100 g body weight. Initially, dose-effect curves for each drug were determined. Doses (expressed in terms of the salts) were given in a mixed order, with acute administrations separated by five days, during which time there were baseline sessions and saline control sessions. After the dose-effect curves were determined, chronic drug administration began. Generally, the smallest dose that reliably increased errors was chosen for chronic administration. If no reliable error-increasing effect was observed, the same criterion was applied to running time. If the behavioral effects of a given dose disappeared (*i.e.,* tolerance developed), the dose was increased and the chronic administration was continued. The number of sessions at each dose for each subject is indicated in Figures 4 and 6. Following the first chronic administration, the dose-effect curve for the second drug was redetermined. Finally, chronic administration of the second drug was instituted under the same criterion as before.

For P115 and P116, the order of acute and chronic drug administration was: acute cocaine, acute *d*-amphetamine, acute cocaine, chronic cocaine, acute *d*-amphetamine, chronic *d*-amphetamine. For P117 and P118, the order was: acute *d*-amphetamine, acute cocaine, acute *d*-amphetamine, chronic *d*-amphetamine, acute cocaine, chronic cocaine. The data for each subject were analyzed by comparing a given drug session with the control range of variability for that subject (*i.e.,* eight saline sessions for the acute determinations and the 10 baseline and saline sessions preceding each chronic administration). A drug was considered to have an effect when the dose data fell outside this control range.

RESULTS

Acute Effects

Cocaine and *d*-amphetamine dose-effect curves are shown in Figure 2. Dose-effect curves for each subject are shown in the order in which they were determined. Data for running time and per cent errors are shown respectively in the upper and lower portions of each panel. The median and range for eight saline (S) sessions are shown at the left. Typically, in these control sessions, running time and errors were higher in the learning component than in the performance component.

The effects of cocaine on responding were comparable in three of the four subjects tested (P115, P116, and P117). For P115 and P116, lower doses (0.56 to 1.8 mg/kg) generally had no effect on errors or running time in either the performance (circles) or learning (triangles) components, though behavior in the learning component for P117 was disrupted at this dose range. At higher doses (3.2 to 4.2 mg/kg), cocaine typically increased errors and running time in both components of the multiple schedule. The highest dose of cocaine tested in each subject produced long pauses in responding. Following these pauses, errors in the learning component were within the baseline range, as were errors in performance, with the exception of P117. In these same three subjects, behavior in the learning component was more sensitive to the drug effects than in the performance component. That is, responding in the learning component was disrupted at doses lower than those required to affect performance. For example, as is shown for P116 in the lower-left panel of Figure 2, 4.2 mg/kg of cocaine increased errors in learning but not in the performance component. Similar differential effects between components of the multiple schedule were obtained in Subjects P115 (3.2 mg/kg) and P117 (1.8 mg/kg).

As can be seen in the lower-right panel of Figure 2, the effects of cocaine on Subject P118 differed from those of the other subjects, particularly in regard to running time. The pausing produced by cocaine observed in the other

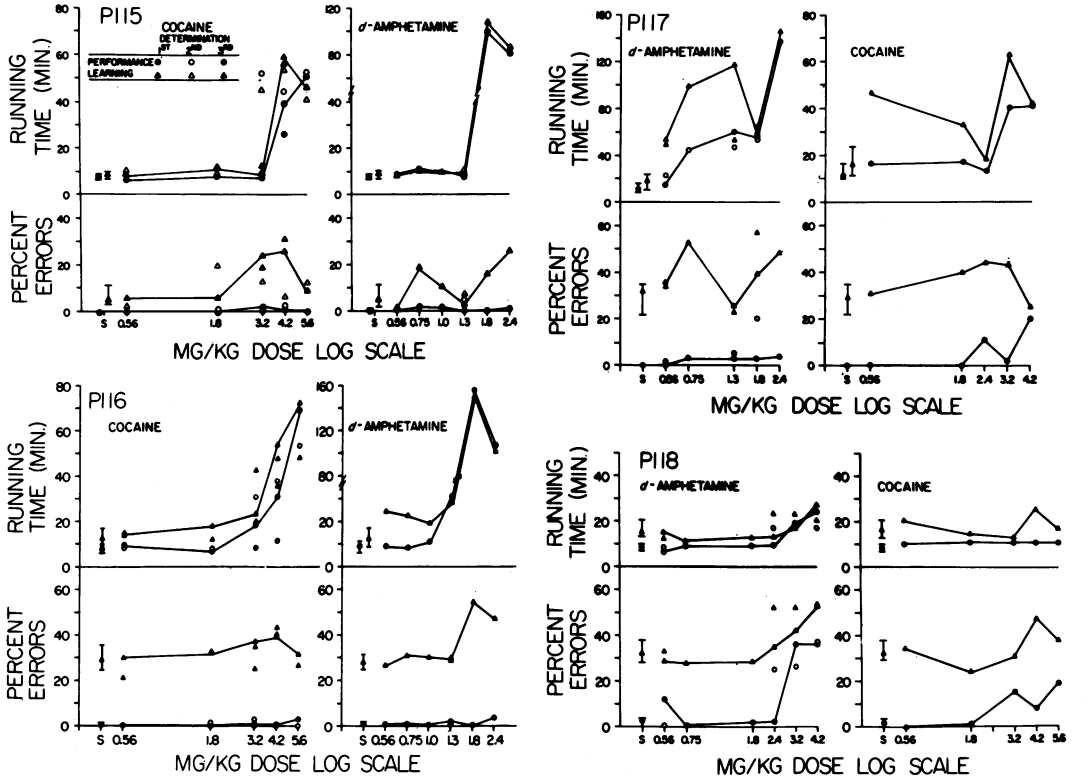

Fig. 2. Dose-effect curves for cocaine and *d*-amphetamine. The control range and median for eight saline sessions (S) are shown in the brackets. The per cent errors per session indicates the accuracy in each component. Running time indicates total time in each component minus the time spent in timeout. In all cases the points connected are those of the first determination.

subjects occurred infrequently in this subject. Running time increased only slightly at a single dose (4.2 mg/kg). Errors in learning increased only at the 4.2 mg/kg dose, while errors in performance increased at doses of 3.2, 4.2, and 5.6 mg/kg. These effects may have been related to the fact that within-session acquisition during control sessions was relatively poor in this subject.

As illustrated in Figure 2, the effects of *d*-amphetamine on errors were similar to those of cocaine. *d*-Amphetamine, however, produced substantially larger increases in running time than those obtained with cocaine (note the different ordinate scales). For P115, P116, and P117, errors in both components were generally within the control range at low to moderate doses (0.56 to 1.3 mg/kg), though errors in learning did increase in two subjects (P115 and P117) at the 0.75 mg/kg dose. These same doses increased running time, primarily in the learning component, in P116 and P117. There were little or no effects on running time for P115. At higher doses (1.8 to 2.4 mg/kg) of *d*-amphetamine, both errors and running time were increased in each component. As was found with cocaine, responding in the learning component tended to be more sensitive to *d*-amphetamine than in performance. For example, as shown for P116 in the lower-left panel of Figure 2, one dose (1.8 mg/kg) increased errors and others (0.56, 0.75, and 1 mg/kg) increased running time in the learning component without affecting behavior in performance. Similar effects on both errors (*e.g.*, P115, 1.8 mg/kg) and running time (*e.g.*, P117, 0.56 mg/kg) were found in the other subjects.

For Subject P118, the effects of *d*-amphetamine were similar to those obtained with cocaine. Doses ranging from 0.56 to 1.8 mg/kg typically had no effect. Though the first determination at 0.56 mg/kg increased errors in the performance component, this data point represents the first time that this subject received a drug, and the effect did not replicate on the second determination. At higher doses,

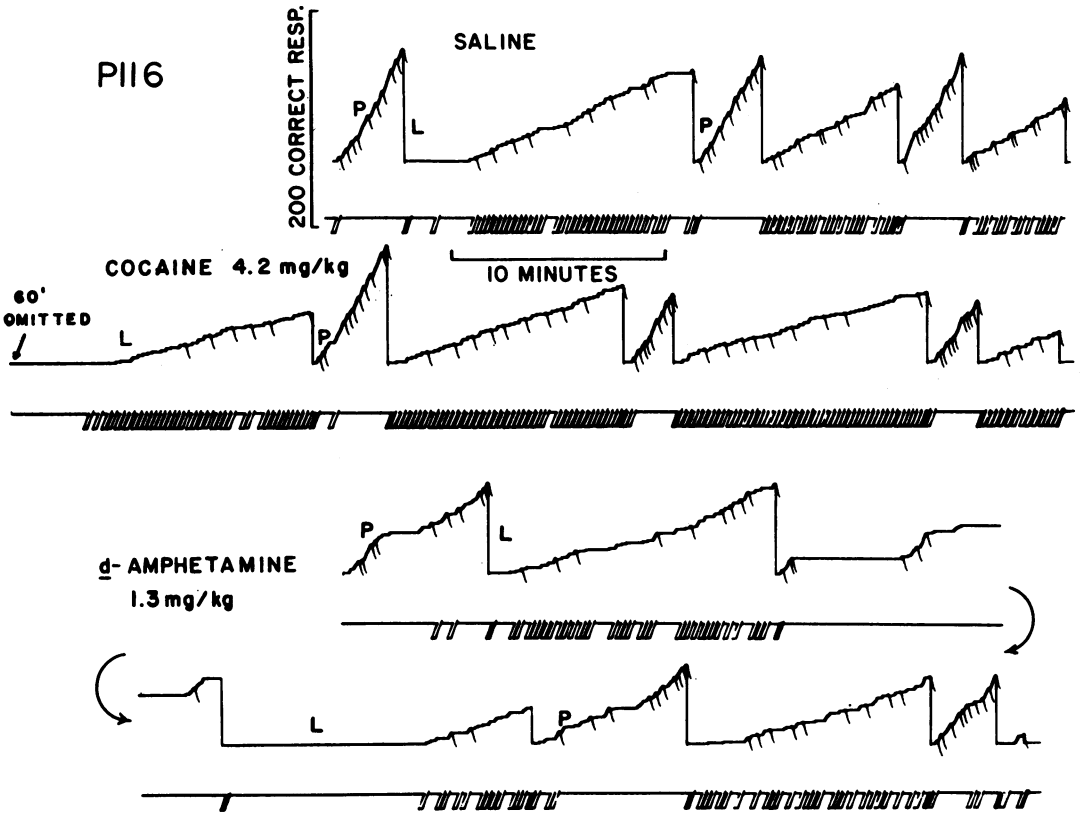

Fig. 3. Cumulative records for P116 for both acute cocaine and *d*-amphetamine drug sessions. A representative saline record is shown at the top of the figure. Performance (P) and learning (L) components alternated during each session following 10 reinforcements or 15 min, whichever occurred first. Solid deflections of the event pen and the reset of the stepping pen indicate the delay that separated a component change. Correct responses stepped the pen upward and reinforcement is indicated by a brief deflection of the same pen. Errors are shown as displacements of the event pen at the bottom of the record.

both errors and running time generally increased in both components.

An example of the effects of cocaine and *d*-amphetamine on within-session acquisition for one subject, P116, can be seen in the cumulative records shown in Figure 3. In these records, solid deflections of the event pen and the reset of the stepping pen indicate the delay that separated a component change. Correct responses stepped the pen upward and reinforcement is indicated by the brief deflection of the same pen. Errors are shown as displacements of the event pen at the bottom of the record. As can be seen in the top cumulative record (saline), under control conditions few errors were made in the performance (P) components and errors tended to decrease across successive learning (L) components, *i.e.*, the highest frequency of errors occurred in the first learning component and the fewest in the last component. In comparison, under cocaine (4.2 mg/kg) errors in learning increased and tended to occur at a constant rate across the session. Errors in the performance component, however, were still infrequent. This selective effect on within-session acquisition is typical of that found in all subjects, with the exception of P118. As can be seen in the cumulative record for *d*-amphetamine (1.3 mg/kg), shown at the bottom of Figure 3, the increases in running time observed with this drug were primarily due to periodic pausing that occurred throughout the session, rather than the prolonged pausing at the start of the session that was found to occur with cocaine. Additionally, even though total errors were not increased at this dose (*cf.* Figure 2), it is apparent from the cumulative record that, in comparison to saline, *d*-amphetamine decreased the rate of within-session acquisition.

In summary, acute administrations of cocaine and *d*-amphetamine were typically found to increase errors and running time in each component of the multiple schedule. *d*-Amphetamine produced greater increases in running time than did cocaine. In three of four subjects, drug effects were more marked in the learning component, *i.e.*, responding in the learning component was disrupted at doses lower than those required to affect performance.

Chronic Effects

Session-by-session effects of cocaine administered chronically are shown for each subject in Figure 4. Running time in both learning (open circles) and performance (closed circles) components are shown in the upper half of each panel. Per cent errors in each component are shown in the lower half. Baseline sessions preceding and following the chronic administration are also shown.

The initial doses in the chronic cocaine series increased errors and running time in the learning component in all subjects. Running time in the performance component also increased in three of the four subjects (P115, P116, and P117), but errors increased in only one subject (P117). The effects of cocaine tended to decrease with chronic administration. When errors and running time returned to within the baseline range in three of four subjects (P115, P116, P118), the dose was increased and the chronic administration continued. The effects of this higher dose also decreased with chronic administration. For example, as is illustrated for P116 in the upper-right panel of Figure 4, cocaine (4.2 mg/kg) initially increased running time in both components. Errors, however, were increased only in the learning component. With repeated administrations (Sessions 1 to 21) these effects decreased until both errors and running time were within the baseline range (*i.e.*, behavioral tolerance developed). In Session 22, the dose was increased to 5.6 mg/kg. Running time, in both components, initially increased and then decreased to near the control range (Sessions 22 to 36). Errors generally remained within the control range. Terminating the chronic regimen had no effect on behavior (postchronic baseline Sessions 1 to 8).

Although the behavioral effects of cocaine decreased in all subjects with repeated administrations, perturbations did occur during the chronic series. Errors in the learning component increased during cocaine Sessions 24, 27, and 31 for P116, and similar reversals for errors and running time may be seen for P115

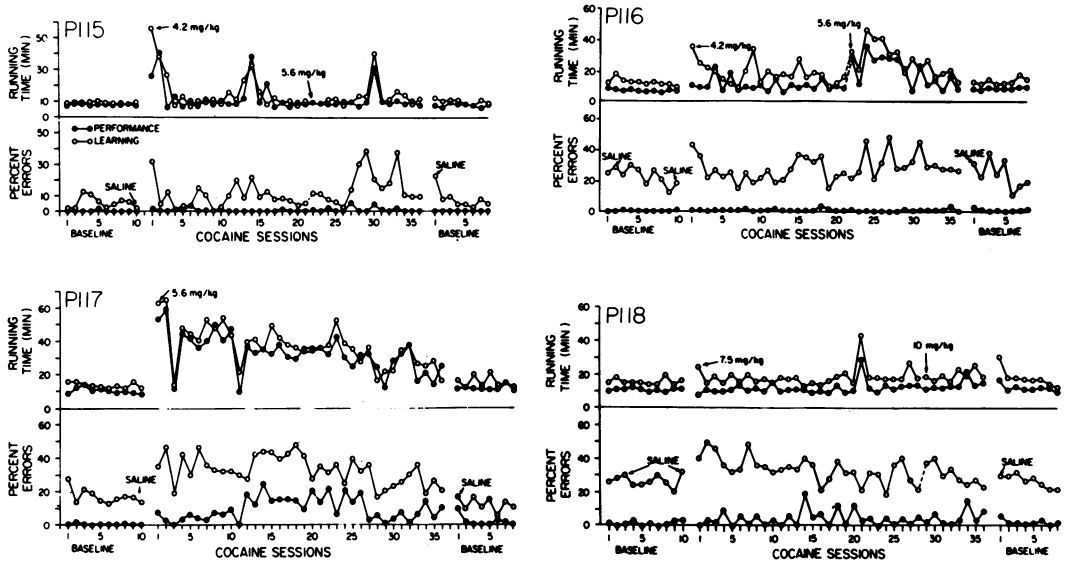

Fig. 4. The effects of chronic cocaine administration on errors and running time in both the performance and learning components of the multiple schedule. The data are shown for each subject for each session of the chronic administration. Control sessions immediately preceding and following chronic administration indicate the baseline range of variability.

(*e.g.*, Sessions 14, 30, and 33). In the case of P118 (lower-right panel of Figure 4), errors in the performance component alternately increased and decreased across sessions. This patterning depended on whether learning or performance was the first component of the session. For those sessions where performance was the first component, performance errors were high, with the majority occurring during this first component. For those sessions where learning was the first component, errors in the performance component were much lower.

Further evidence for the development of behavioral tolerance to cocaine can be seen in the cumulative records of P116, shown in Figure 5. The record for the saline session immediately preceding chronic administration is at the top. Note that during cocaine Session 1 (middle records), each learning component terminated on the basis of time (rather than reinforcements) because of both increased pausing and errors. Pausing and errors were equally distributed across the session in each learning component and the usual within-session error reduction did not occur. Errors did not, however, increase in the performance components. The cumulative record for cocaine Session 21 is shown at the bottom of Figure 5. Note that in comparison to Session 1, both pausing and errors have declined substantially. Acquisition, in terms of decreased errors across successive learning components, is also apparent in this record. In short, the record for Session 21 is very similar to the saline control record.

Session-by-session effects of *d*-amphetamine, administered chronically, are shown in Figure 6. *d*-Amphetamine initially increased both errors and running time in the learning component in all subjects. Running time and errors were also increased in the performance component, with the exception of P116. With chronic administration, these effects generally decreased. In two subjects (P117 and P118), running time in both components and errors in the learning component did not return to the baseline range. Errors in the performance

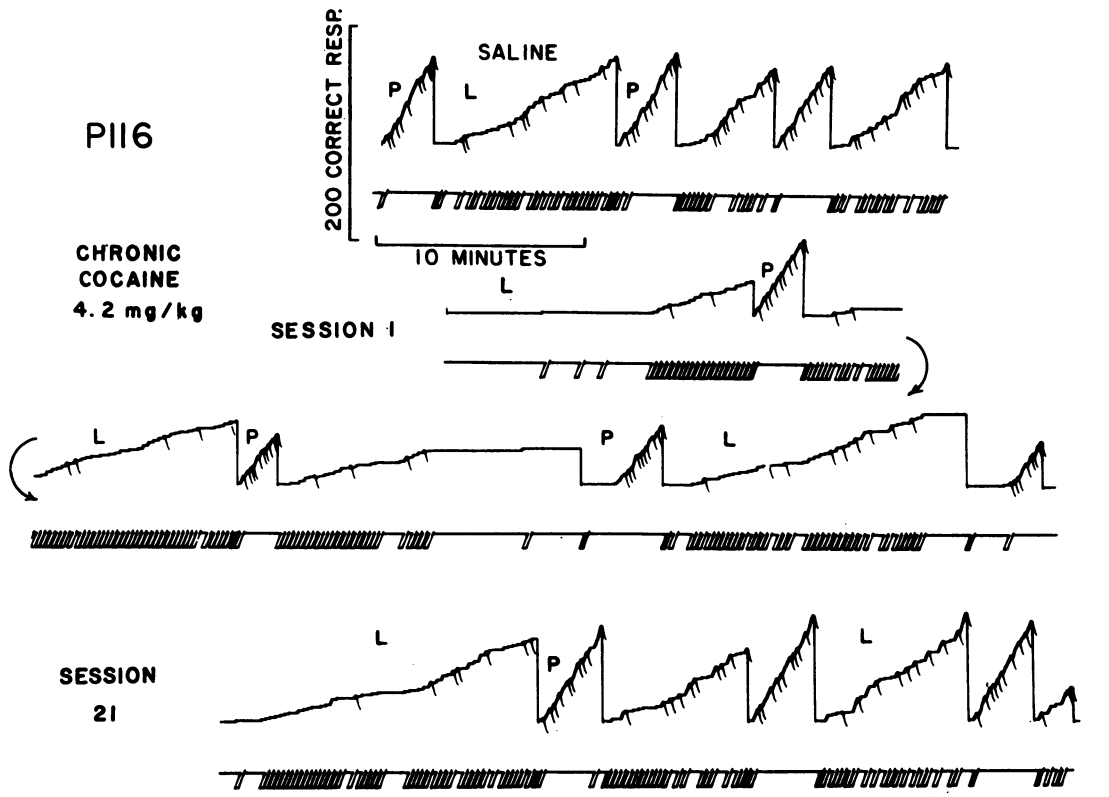

Fig. 5. Cumulative records for selected chronic cocaine sessions (*i.e.*, Sessions 1 and 21) for P116. The record for the saline session immediately preceding the start of the chronic administration is shown at the top of the figure. (See legend of Figure 3 for recording details.)

component, however, did. When errors and running time in both components returned to within the baseline range for P115 and P116, the dose of *d*-amphetamine was increased and the chronic administration continued. In every instance, the effects of the higher dose on errors and running time also decreased with chronic administration. For example, as is illustrated for P116 in the upper-right panel of Figure 6, *d*-amphetamine (2.4 mg/kg) initially increased running time in both components. Errors, however, were increased only in the learning component. With repeated administrations, errors in learning rapidly returned to the control range, while tolerance developed more slowly to the drug's effect on running time (*d*-amphetamine Sessions 1 to 12). In Session 13, the dose of *d*-amphetamine was increased to 3.2 mg/kg. In subsequent sessions (14 to 30), running time in each component and errors in the learning component increased and then decreased. When chronic *d*-amphetamine administration was stopped, errors in the learning component increased during the first postchronic baseline session. With this exception, no other behavioral effects related to drug termination were observed. Development of tolerance to *d*-amphetamine was more systematic than was found with cocaine, although occasional perturbations may be seen in Figure 6 (*e.g.*, P115, Sessions 11 and 21; P116, Session 27).

Tolerance also developed to *d*-amphetamine's effects on the within-session pattern of responding. Figure 7 shows cumulative records from Subject P116. The saline session immediately preceding chronic administration is at the top. During Session 1 of chronic administration (middle records), *d*-amphetamine (2.4 mg/kg) initially decreased response rate in both components of the multiple schedule. In the learning component, errors were increased and the normal within-session error reduction was virtually eliminated. *d*-Amphetamine had similar initial effects on the within-session distribution of errors in the learning component in the other subjects. *d*-Amphetamine had no effect on errors in performance. The cumulative record for the last session of chronic administration of 2.4 mg/kg (Session 12) is shown at the bottom of Figure 7. Note that both the rate-decreasing and error-increasing effects of *d*-amphetamine have disappeared.

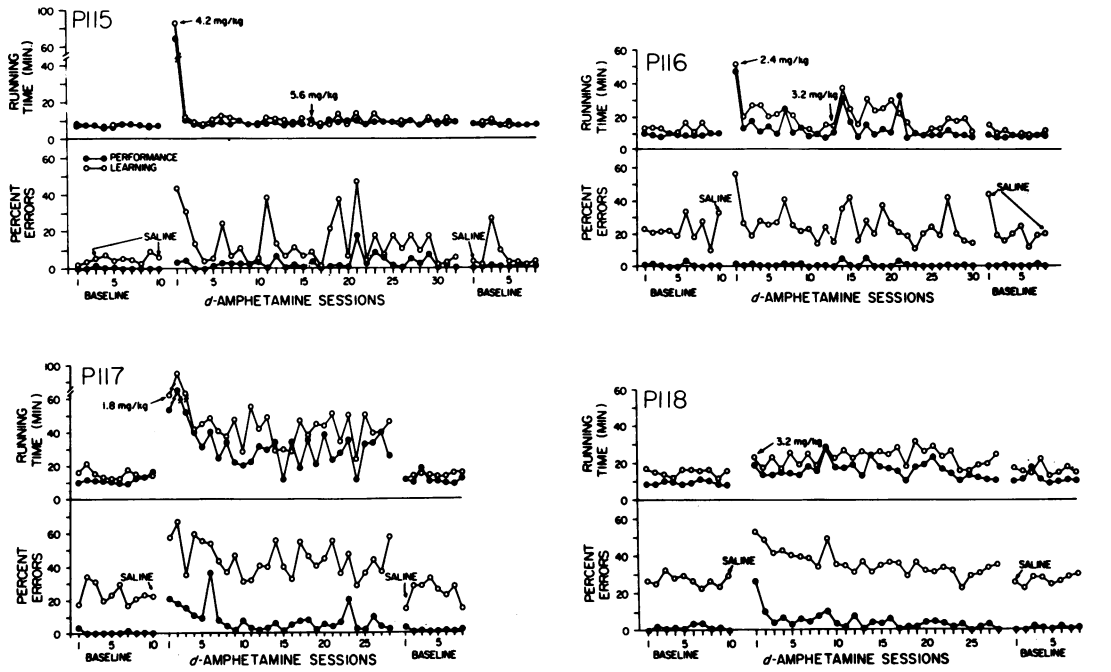

Fig. 6. The effects of chronic *d*-amphetamine administration on errors and running time in both the performance and learning components of the multiple schedule. The data are shown for each subject for each session of the chronic administration. Control sessions immediately preceding and following chronic administration indicate the baseline range of variability.

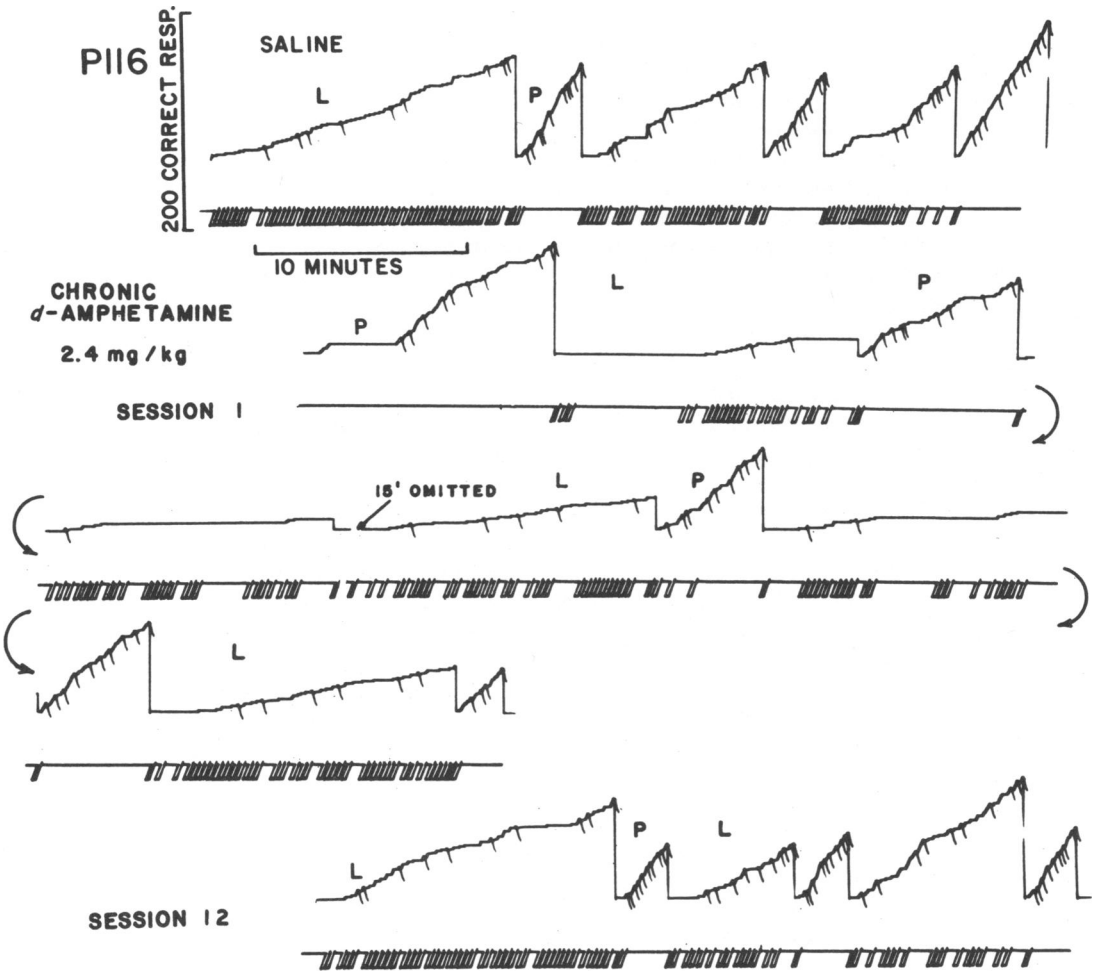

Fig. 7. Cumulative records for selected chronic *d*-amphetamine sessions (*i.e.*, Sessions 1 and 12) for P116. The record for the saline session immediately preceding the start of the chronic administration is shown at the top of the figure. (See legend of Figure 3 for recording details.)

In summary, the effects of cocaine and *d*-amphetamine on errors and running time decreased with chronic administration. Two types of drug-behavior interactions were observed during the chronic regimens. First, in those instances where the drug increased errors in both components of the multiple schedule (cocaine, P117 and P118; *d*-amphetamine, P115, P117, and P118), behavioral tolerance developed first to the drug's disruptive effects in the performance component. In some of these instances, tolerance subsequently developed to the error-increasing effects in the learning component (cocaine, P118; *d*-amphetamine, P115). In other cases, errors in the learning component decreased with chronic administration but did not return to the predrug control range (cocaine P117; *d*-amphetamine, P117 and P118). Second, there were instances of a selective error-increasing effect in the learning component (cocaine, P115 and P116; *d*-amphetamine P116). In each case, tolerance developed to the disruptive effects of the drug. For both drugs, there were generally no selective effects on running time between components of the multiple schedule, though greater initial drug effects tended to occur in the learning component. With repeated administrations, the initial effects produced by a drug decreased, and in most cases behavioral tolerance developed.

Timeout responses. Three of the four subjects (P115, P116, P117) rarely responded during the timeout periods, and this rate was not

changed by the drugs. Subject P118, however, responded at higher levels (median = 20 responses, range 8 to 48) during baseline sessions, and both *d*-amphetamine and cocaine decreased timeout responding to near zero in this subject. The decrease in timeout responding persisted throughout the chronic administrations of both drugs.

Postchronic acute redeterminations. Following the chronic administration of the first drug, the dose-effect curve for the second drug was redetermined in each subject before chronic administration of the second drug. This was done to evaluate any cross-tolerance that may have developed. For Subjects P115 and P116, the dose-effect curves for *d*-amphetamine were redetermined following chronic cocaine administration. These redeterminations are shown in Figure 8. The highest dose of *d*-amphetamine given before chronic cocaine was redetermined first. Note that after chronic cocaine, the *d*-amphetamine dose-effect curves for both subjects shifted to the right. That is, the potency of *d*-amphetamine (on a mg/kg basis) decreased after chronic cocaine administration, indicating the development of cross-tolerance between the two drugs. Following chronic *d*-amphetamine administration, the dose-effect curve for cocaine was again determined for Subjects P117 and P118 (not shown). Of the doses tested, only the highest dose (5.6 mg/kg) in the prechronic cocaine dose-effect curve was redetermined. This dose had a smaller effect on performance errors in both subjects. Errors in learning and effects on running time were either unchanged or greater. Since only a single point in the prechronic dose-effect curve was redetermined, it is difficult to substantiate the existence of cross-tolerance for these two subjects.

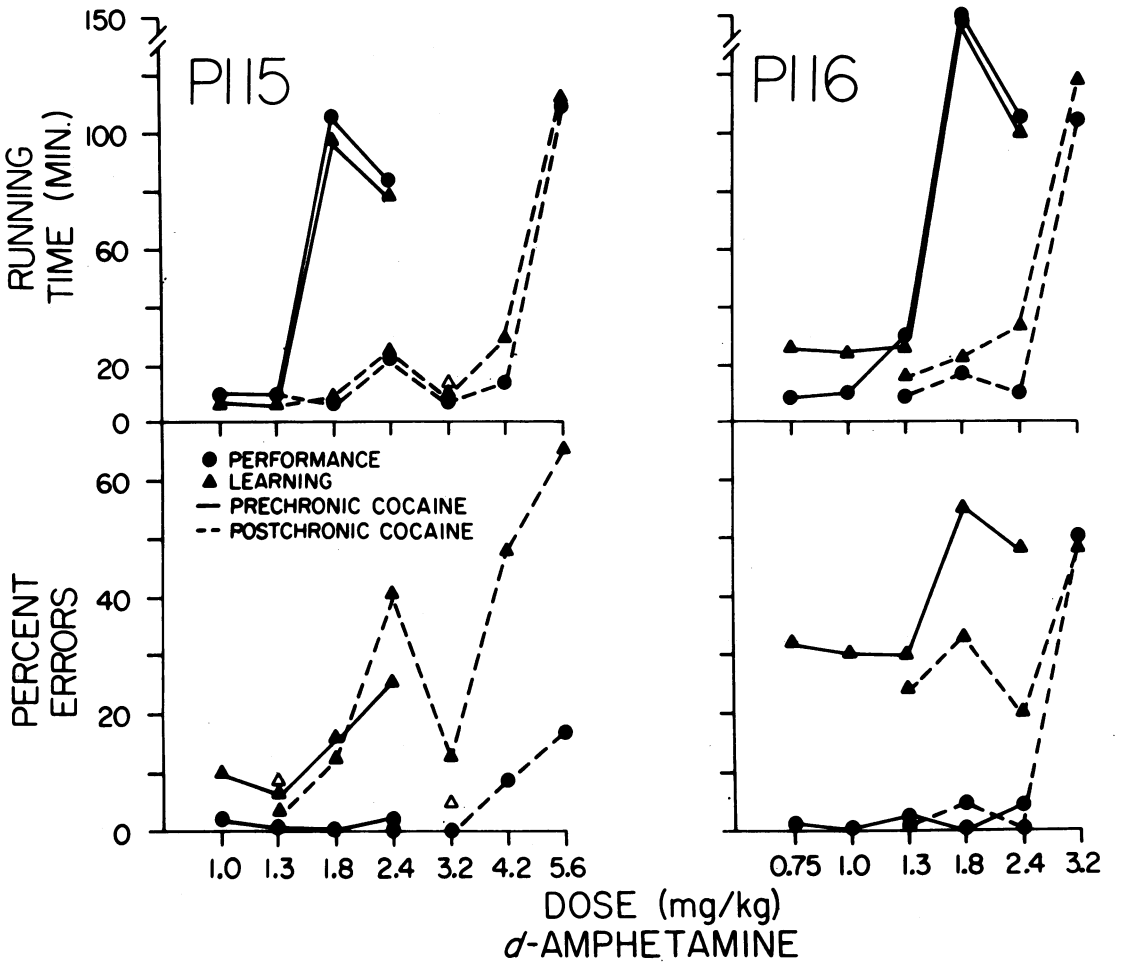

Fig. 8. The effects of *d*-amphetamine on errors and running time following chronic administration of cocaine.

DISCUSSION

A generally accepted definition of stimulus control is differential responding in the presence of different stimuli. This differential control of responding may be reflected in variations in either the rate, patterning, or accuracy of responses. In the present experiment, stimulus control was reflected in the differences in baseline error levels between the learning and performance components. Laties (1975) proposed that variations in stimulus control may function to modulate drug action, so that behavior under strong control by external stimuli is less affected by drugs than behavior under weak control by external stimuli. In support of this interpretation, a reduction in the magnitude of a drug effect has been demonstrated in a variety of behavioral procedures when behavior is under strong external stimulus control (*e.g.*, Laties, 1972; Laties and Weiss, 1966; Thompson and Corr, 1974). For example, Laties and Weiss (1966) found that the distribution of responses in a fixed-interval (FI) schedule of reinforcement is less affected by amphetamine and scopolamine when stimuli signalling different parts of the interval (*i.e.*, added clock) are present than when they are not. Results contrary to Laties' (1975) conclusion also have been reported (*e.g.*, Leander and McMillan, 1974; Thomas, 1966).

In the present study, the performance component of the multiple schedule, where the chain of conditional discriminations was the same each session, represented an instance of strong external stimulus control (*i.e.*, error levels were low). By comparison, stimulus control in the learning component, where the chain of conditional discriminations changed from session to session, was weak (*i.e.*, error levels were high). Consistent with Laties' conclusion, behavior in the performance component was less affected by the drugs than was the behavior in the learning component. That is, administration of drugs generally disrupted responding in the learning component at lower doses than those required to affect performance. The data also suggest that the degree of stimulus control may have modified the chronic effects of cocaine and *d*-amphetamine. Whenever errors initially were increased in both components, behavioral tolerance developed first in the performance component. This differential sensitivity between components during chronic administration is also consistent with Laties' interpretation. In the case of chronic administration, the error-increasing effects of the drug should diminish (*i.e.*, tolerance develop) first in the condition where external stimulus control is stronger, (*i.e.*, performance).

Using the repeated acquisition and performance of response sequences as baselines, Thompson (1973, 1974, 1977) obtained results similar to those of the present study. In these experiments, *d*-amphetamine and cocaine were tested under a repeated acquisition condition and under a separate performance condition. On both an acute and chronic basis, the drug effects were attenuated on the performance baseline in comparison to the acquisition baseline. These results also show that the degree of stimulus control can function as a determinant of a drug's effect. Thus, the present study confirms and extends Thompson's findings to a multiple-schedule situation and to a conditional discrimination procedure.

In a discussion of the circumstances under which behavioral tolerance might develop, Schuster, Dockens, and Woods (1966) pointed out the critical importance of reinforcement frequency as a determining variable. They hypothesized that:

> Behavioral tolerance will develop in those aspects of the organism's behavioral repertoire where the action of the drug is such that it disrupts the organism's behavior in meeting the environmental requirement for reinforcements. Conversely, where the actions of the drug enhance or do not affect the organism's behavior in meeting reinforcement requirements we do not expect the development of behavioral tolerance. (p. 181)

This hypothesis has since been confirmed in several behavioral procedures (see review by Corfield-Summer and Stolerman, 1978), as well as in the present study. Both cocaine and *d*-amphetamine reduced the frequency of reinforcement by increasing both errors and running time, and the effects of both drugs on each of these variables generally decreased with chronic administration. In the instance where the drug also affected timeout responding (which had no effect on reinforcement frequency), tolerance did not develop. The present results also suggest that an extension of

the same hypothesis may account for cross tolerance between drugs when the action of each drug reduces the frequency of reinforcement.

Components of a multiple schedule that differ in reinforcement frequency have been shown to be differentially sensitive to a variety of nonpharmacological variables (*cf.*, Nevin, 1974, Experiments I and II). For example, Blackman (1968, Experiment II) showed that when response rates are equated, suppression to a stimulus correlated with shock is greatest in the component with the lowest frequency of reinforcement. With some exceptions (*e.g.*, MacPhail and Gollub, 1975), in most studies using multiple schedules, differences in either the rate of responding or conditions of stimulus control are confounded with differences in the frequency of reinforcement (see review by Thompson, 1978). Since frequency of reinforcement appears to be a determinant of a drug's chronic effects on behavior (Schuster *et al.*, 1966), it may also influence a drug's acute effects or determine differential drug effects within a multiple schedule. In the present study, the baseline rate of reinforcement in the components of the multiple schedule may have influenced the nature of the drug effects. During baseline sessions, the frequency of reinforcement was lower in the learning component than in performance. In a multiple schedule where the units of behavior are similar in each component, the component where frequency of reinforcement is lower may be more sensitive to a drug's effect (*i.e.*, the learning component in the present study). Similarly, for chronic administration, where the initial effects of the drug are such that reinforcement frequency is decreased in both components, tolerance should develop first in that component where the absolute change in reinforcement frequency is the greatest. Such was the case for all subjects. For example, in Subject P118 (Figure 6) *d*-amphetamine initially decreased reinforcement frequency more in the performance component than in the learning component (decrease of 2.3 reinforcers per minute in performance *versus* 0.67 reinforcers per minute in learning). In the present study, however, it is difficult to evaluate the degree to which differences in reinforcement frequency may have contributed to the observed drug effects. Any such interaction would be indirect, since the conditions of stimulus control in part determined the frequency of reinforcement; *i.e.*, errors produced timeout which decreases the frequency of reinforcement per unit time. Nevertheless, the role of reinforcement frequency in the modulation of drug effects on behavior seems to warrant further study.

REFERENCES

Blackman, D. Response rate, reinforcement frequency, and conditioned suppression. *Journal of the Experimental Analysis of Behavior,* 1968, **11,** 503-516.

Boren, J. J. Repeated acquisition of new behavioral chains. *American Psychologist,* 1963, **17,** 421.

Boren, J. J. Some variables affecting the superstitious chaining of responses. *Journal of the Experimental Analysis of Behavior,* 1969, **12,** 959-969.

Boren, J. J. and Devine, D. D. The repeated acquisition of behavioral chains. *Journal of the Experimental Analysis of Behavior,* 1968, **11,** 651-660.

Catania, A. C. Glossary. In A. C. Catania (Ed), *Contemporary research in operant behavior.* Glenview, Illinois: Scott, Foresman, 1968. Pp. 327-349.

Corfield-Summer, P. K. and Stolerman, I. P. Behavioral tolerance. In D. Blackman and D. Sanger (Eds), *Contemporary research in behavioral pharmacology.* New York: Plenum, 1978. Pp. 391-448.

Laties, V. G. The modification of drug effects on behavior by external discriminative stimuli. *Journal of Pharmacology and Experimental Therapeutics,* 1972, **183,** 1-13.

Laties, V. G. The role of discriminative stimuli in modulating drug action. *Federation Proceedings,* 1975, **34,** 1880-1888.

Laties, V. G. and Weiss, B. Influence of drugs on behavior controlled by internal and external stimuli. *Journal of Pharmacology and Experimental Therapeutics,* 1966, **152,** 388-396.

Leander, J. D. and McMillan, D. E. Rate dependent effects of drugs. I. Comparisons of *d*-amphetamine, pentobarbital, and chlorpromazine on multiple and mixed schedules. *Journal of Pharmacology and Experimental Therapeutics,* 1974, **188,** 726-739.

MacPhail, R. C. and Gollub, L. R. Separating the effects of response rate and reinforcement frequency in the rate-dependent effects of amphetamine and scopolamine on the schedule-controlled performance of rats and pigeons. *Journal of Pharmacology and Experimental Therapeutics,* 1975, **194,** 332-342.

Moerschbaecher, J. M., Boren, J. J., and Schrot, J. Repeated acquisition of conditional discriminations. *Journal of the Experimental Analysis of Behavior,* 1978, **29,** 225-232.

Nevin, J. A. Response strength in multiple schedules. *Journal of the Experimental Analysis of Behavior,* 1974, **21,** 389-408.

Schuster, C. R., Dockens, W. S., and Woods, J. H. Behavioral variables affecting the development of amphetamine tolerance. *Psychopharmacologia,* 1966, **9,** 170-182.

Thomas, J. R. Differential effects of two phenothiazines on chain and tandem performance. *Journal of*

Pharmacology and Experimental Therapeutics, 1966, **152,** 354-361.

Thompson, D. M. Repeated acquisition as a behavioral baseline for studying drug effects. *Journal of Pharmacology and Experimental Therapeutics,* 1973, **184,** 506-514.

Thompson, D. M. Repeated acquisition of behavioral chains under chronic drug conditions. *Journal of Pharmacology and Experimental Therapeutics,* 1974, **188,** 700-713.

Thompson, D. M. Repeated acquisition of response sequences: stimulus control and drugs. *Journal of the Experimental Analysis of Behavior,* 1975, **23,** 429-436.

Thompson, D. M. Development of tolerance to the disruptive effects of cocaine on repeated acquisition and performance of response sequences. *Journal of Pharmacology and Experimental Therapeutics,* 1977, **203,** 294-302.

Thompson, D. M. Stimulus control and drug effects. In D. Blackman and D. Sanger (Eds), *Contemporary research in behavioral pharmacology.* New York: Plenum, 1978. Pp. 159-207.

Thompson, D. M. and Corr, P. B. Behavioral parameters of drug action: signalled and response-independent reinforcement. *Journal of the Experimental Analysis of Behavior,* 1974, **21,** 151-158.

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