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SOME EFFECTS OF d-AMPHETAMINE AND PENTOBARBITAL ON PERFORMANCE UNDER A LONG FIXED-INTERVAL SCHEDULE[1]

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The effects of *d*-amphetamine and pentobarbital were studied on performance during 3-hr sessions under fixed-interval 60-min schedules of food presentation. Low doses of *d*-amphetamine increased rates of responding and higher doses decreased rates of responding, both during the entire 3-hr session and during each of the individual fixed intervals. Pentobarbital produced little effect on rates of responding averaged over the 3-hr session, but it decreased rates during the first fixed interval and increased them during the second and third fixed intervals. The effects of *d*-amphetamine were shown to be dependent on the control rate of responding, as has been shown with shorter fixed-interval values. Analysis of *d*-amphetamine effects in terms of the point at which the probability of responding is greater than zero was not descriptive of overall fixed-interval performance.

Key words: long fixed intervals, *d*-amphetamine, pentobarbital, rate dependency, key peck, pigeons

Dews (1958) suggested that the interaction between *d*-amphetamine and schedule-controlled responding could be described in terms of the baseline rate of responding. Generally, if the baseline rate of responding was low, *d*-amphetamine increased the rate, but if the baseline rate was high, *d*-amphetamine decreased the rate. Since these observations by Dews, other investigators have confirmed rate-dependent effects for the amphetamines (Clark and Steele, 1966; McMillan, 1968*a*, *b*, 1969; Smith, 1964).

Some investigators have used the inhomogeneous rates of responding generated by fixed-interval (FI) schedules to study the rate-dependent effects of drugs (Dews, 1964; McMillan, 1968*a*, *b*; Smith, 1964). The rate of responding under an FI schedule can be characterized as being low early in the FI, followed by a gradually increasing rate of responding that becomes maximal just before delivery of the reinforcer (Ferster and Skinner, 1957). When the effects of amphetamines on local rates of FI responding are studied, amphetamines tend to increase the low rates of responding at the beginning of the FI while increasing higher rates at the end of the FI much less, or even decreasing them (McMillan, 1968*a*, *b*; Smith, 1964).

Branch and Gollub (1974) suggested that the characterization of the rate-dependent effect of amphetamine within FI schedules is an artifact of averaging. Relying heavily on analyses of FI responding in pigeons, which have shown the performance to consist of periods of near-zero rates of responding of variable duration, followed by an abrupt transition to a higher terminal rate of responding (Schneider, 1969; Shull and Brownstein, 1970), Branch and Gollub proposed that the apparent gradual increase in rate of responding is an artifact of averaging these "two states" of responding across different FIs. Because Branch and Gollub felt that average rates of FI responding did not adequately describe the actual performance, they proposed that "an analysis in terms of probability of response greater than zero in a specific portion of the interval" be used to describe the relationship between performance under control and drug conditions. They argued that their approach led to as effective a predictive value as did rate-dependency, but was more descriptive of the actual interval-by-interval performance.

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In developing their detailed analysis of the effects of *d*-amphetamine on FI performance, Branch and Gollub (1974) employed FI schedules of 40, 100, and 300 sec. These FI durations, although frequently studied are rather short and may thus limit the generality of the descriptive measures suggested by Branch and Gollub. The purposes of the present experiment were: (1) to study the effects of *d*-amphetamine on responding maintained by some comparatively long FIs (60 min); (2) to determine if amphetamine effects on this performance could best be characterized in terms of rate-dependent effects or in terms of probability of responding at a rate greater than zero in a specific part of the interval; (3) to compare the effects of pentobarbital on responding under the long FI with those of *d*-amphetamine; and (4) to use rates of responding in single FIs to study the time course of drug-behavior interactions.

METHOD

Subjects

Three male White Carneaux pigeons, weighing between 500 and 538 g when given free access to food and water, were maintained at 80% of their free-feeding weights throughout the experiment. Water was freely available in both the living cage and the test apparatus. Before this experiment, the pigeons had been trained to respond under a multiple fixed-ratio 30 response, fixed-interval 5-min schedule (*mult* FR 30 FI 5-min) of food presentation and had been used to study the effects of narcotic antagonists on performance under this schedule.

Apparatus

The experimental chamber was a modification of that described by Ferster and Skinner (1957). A translucent plastic response key, 2 cm in diameter, was mounted on a false wall inside each chamber about 19 cm above the chamber floor. The minimum force necessary to operate the key was about 15 g (0.15 N). Closure of the key contacts defined the pecking response. The key could be transilluminated by red lamps. Directly below the response key at a point 4 cm above the floor of the chamber was a rectangular opening through which the pigeon could be given access to grain after a response. The chamber was illuminated by a 25-W bulb and white noise was present in the chamber at all times. Conventional relay programming and recording apparatus were employed.

Procedure

The multiple schedule (see Subjects) was changed to an FI 60-min with a limited hold of 15 min. Under this schedule, the first key-peck response after 60 min in the presence of red keylight resulted in three consecutive 5-sec periods of access to grain. If the pigeon did not respond within 15 min after the FI 60-min had elapsed, all lights in the chamber were turned off for 5 sec, after which a new 60-min FI began without delivery of the reinforcer. Each session terminated after the occurrence of three FIs, a period slightly longer than 3 hr. After 50 sessions of training, drugs were administered.

Drugs

Pentobarbital was used as the sodium salt and *d*-amphetamine as the sulfate. Doses are given in terms of these salts. Injections were given in distilled water at a volume of 1 ml/kg. Distilled water also was given as a control injection. The pigeons were studied five days a week, with injections given on Tuesdays and Fridays; the data from Thursdays served as nondrug control data. All injections were made in the breast muscle and were given immediately before a session began. Dose levels were given in a random order, although the effects of *d*-amphetamine were studied before those of pentobarbital in all birds. Duplicate observations of drug effects were made in each bird at each dose level and five observations were made with distilled water.

Measurement of Drug Effects

Average rates of responding were determined for the entire session by dividing the cumulated number of responses by the accumulated amount of time required for the intervals to terminate. Average rates of responding were determined for each of the three FIs in the session by dividing the number of responses in each FI by 3600 sec. (Note that any time spent in the limited hold did not enter into the calculations of the "hourly" rates.) Finally, each FI was divided into four 15-min segments and rates of responding were calculated for each 15-min period of each FI.

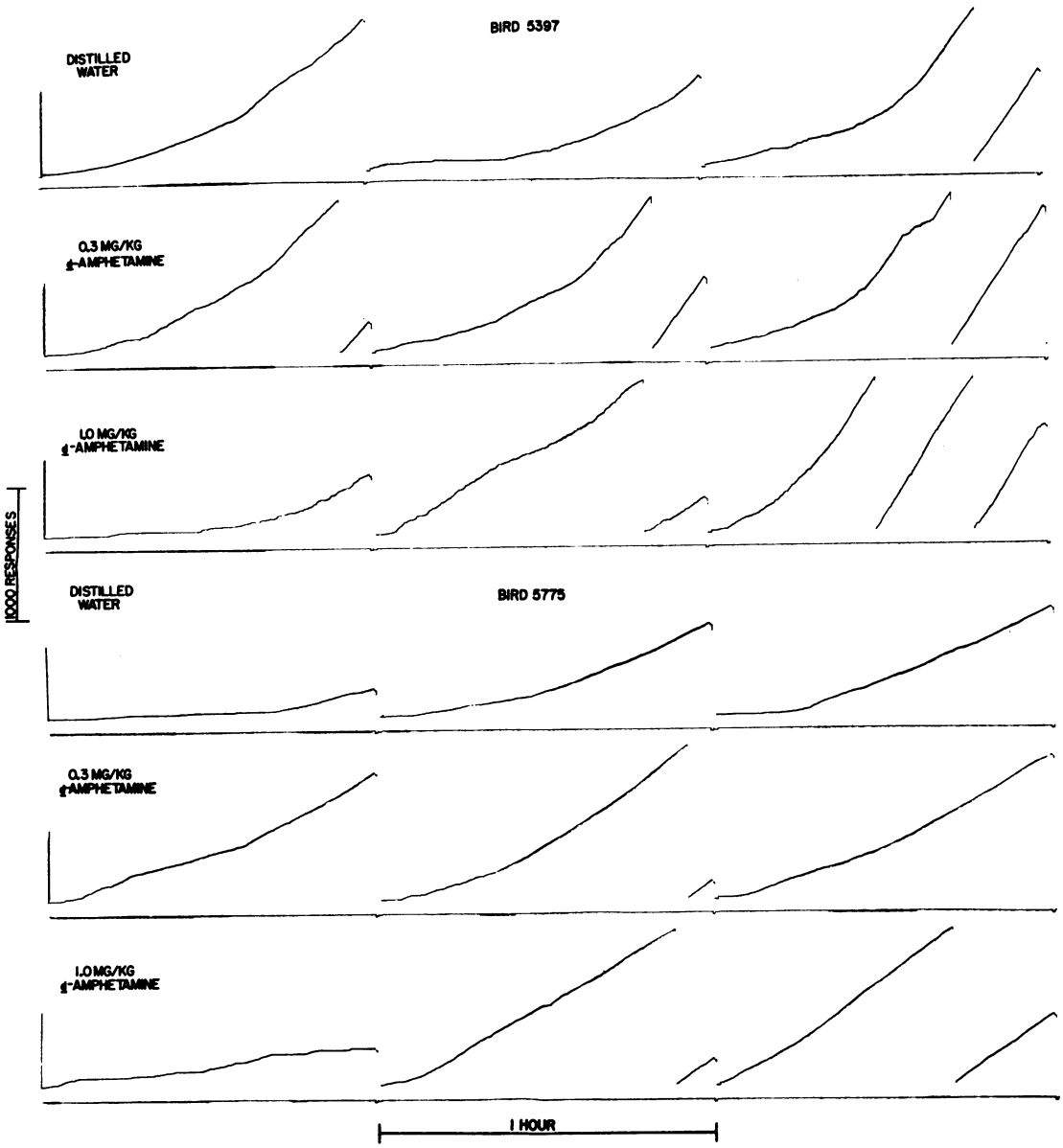

Fig. 1. Cumulative response records of the performance of Birds 5397 and 5775 after distilled water and two doses of *d*-amphetamine. The response pen reset to baseline after 1100 responses or on termination of the FI component (correlated with food delivery in all these records).

The rates of responding were averaged across birds for the Thursday control sessions and ±two standard errors around the mean are shown on the figures. Mean drug effects were considered as real effects if they exceeded this estimate of control variability.

Finally, by measurement of the cumulative response records, the latency to the first response in each FI was calculated in seconds for all injection sessions. Each latency for each bird was plotted for three control injections (distilled water). The latencies for the three birds following each dose of *d*-amphetamine were compared with the range of control latencies.

RESULTS

Figures 1 and 2 show cumulative-response records of the three birds. If the records for

distilled water are examined, it is readily apparent that the pattern of responding was characterized by an initially very low rate of responding, followed by a gradually increasing rate of responding, rather than the two-state pattern of FI responding observed by Branch and Gollub (1974) and by Schneider (1969).

Figure 3 shows the dose-effect curves averaged across the 3-hr session for the three birds. The mean rate of responding was about 0.3 responses per second under control conditions. *d*-Amphetamine, at doses of 0.3 and 1.0 mg/kg, increased the mean rate of responding, while higher doses (3 and 10 mg/kg) decreased the rate. The two lower doses of pentobarbital had no effect on the mean rate for the 3-hr session, while the 17.5 mg/kg produced a small decrease in rate of responding.

Figure 4 divides the session into three individual FI segments and shows the dose-effect curves for *d*-amphetamine during each FI for each bird. During the first hour after injection, rates were highest for all birds after the 0.3

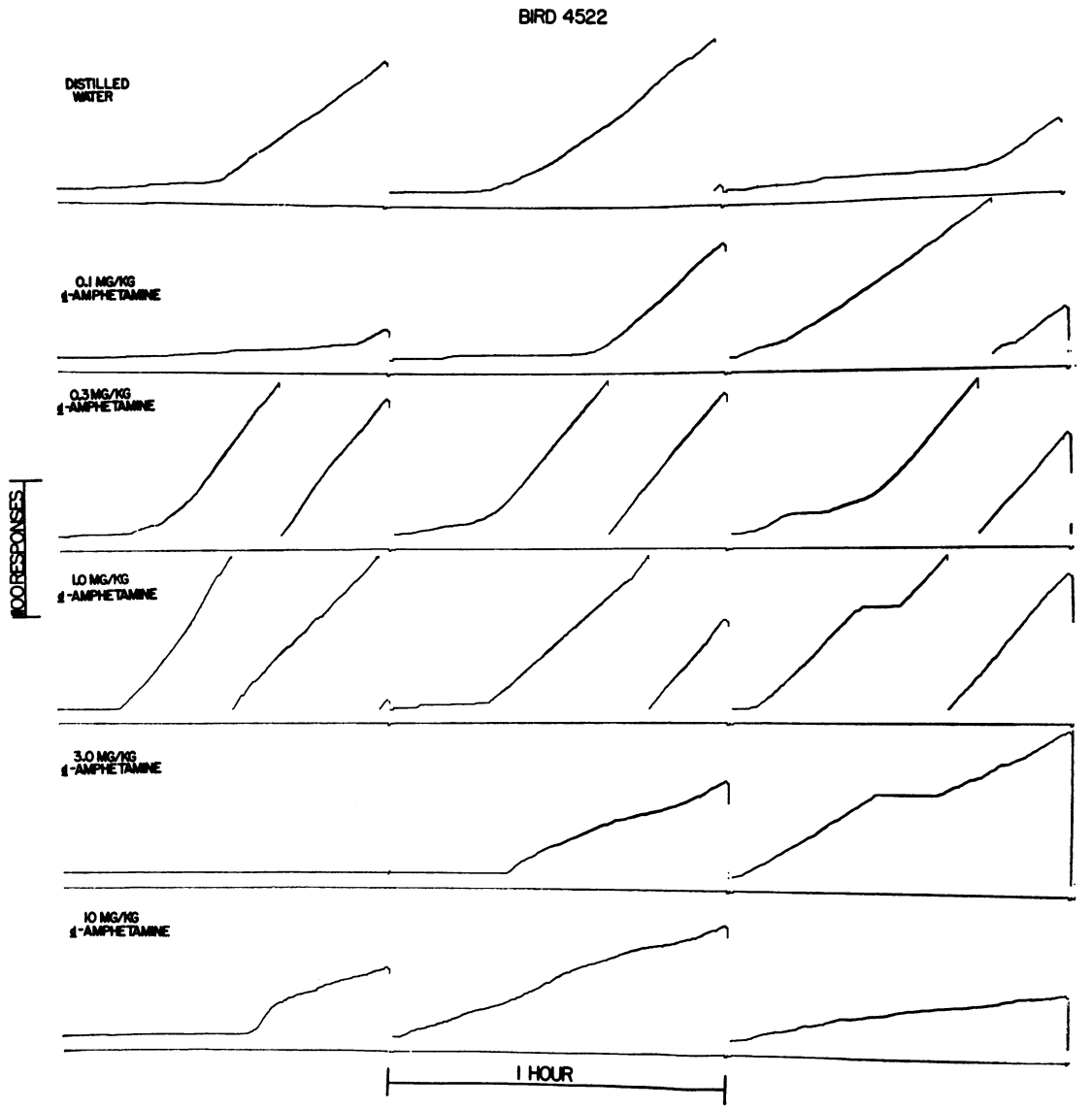

Fig. 2. Cumulative response records of the performance of Bird 4522 after distilled water and *d*-amphetamine. The response pen reset to baseline after 1100 responses or on termination of the FI component. The hash mark on the horizontal line shows termination of an FI without food delivery after a high dose of *d*-amphetamine.

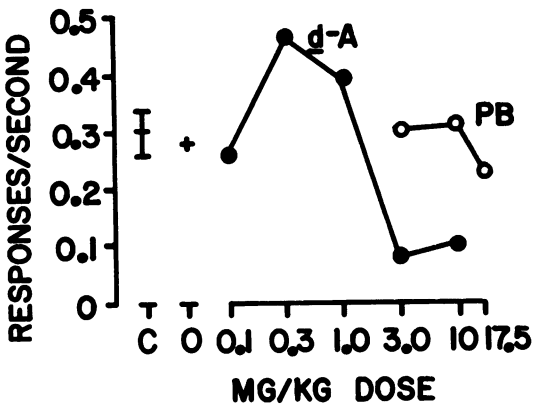

Fig. 3. Effects of *d*-amphetamine and pentobarbital on average rates of responding for the entire session. Ordinate: responses per second averaged over an entire session. Abscissa: mg/kg dose, log scale. The brackets at C show two standard errors above and below the mean of 11 noninjection (Thursday) sessions for all three birds. The points at 0 show the mean of five observations in each bird following injections of distilled water. Each point on the dose-effect curve represents a mean of duplicate observations in each of three pigeons.

mg/kg dose, although rates were markedly increased only for Bird 4522. During the second hour, both 0.3 and 1.0 mg/kg increased the rate, but the peak increase occurred after 0.3 mg/kg for all three birds. The individual dose-effect curves for the second hour reflect most closely what was seen in the 3-hr dose-effect curve. In the third FI, the 0.3 or 1.0 mg/kg dose of *d*-amphetamine increased the rate, with the 1.0 mg/kg dose marking the peak of the dose-effect curve for two of the three birds. Doses of 3 and 10 mg/kg of *d*-amphetamine decreased the rate during all FIs, except for the 10 mg/kg dose in Bird 5775. In general, the dose-effect curves for the individual birds on individual FIs reflected the overall dose-effect curve for the 3-hr session.

These effects seen in the dose-effect curves for *d*-amphetamine in Figure 4 are also readily apparent in the cumulative response records of individual birds in Figures 1 and 2. Notice how the 0.3 mg/kg dose of *d*-amphetamine produces rate increases during the first hour of the session, while during the second and third hours of the session, the rate-increasing effects of the 1 mg/kg dose become more consistent.

Figure 5 shows the time course of the pentobarbital effects. These effects differed during each hour of the session. During the first hour, pentobarbital generally produced a dose-dependent decrease in rates of responding. During the second hour, the 10 mg/kg dose increased the rate for Bird 4522 and rate decreases produced by other doses were less apparent for all birds. During the final hour, no rate decreases were observed with any dose and all doses increased the rate for Bird 5775. Thus, pentobarbital initially decreased the rate of responding, but with the passage of time, the rate decreases began to disappear and some rate increases began to be observed.

A rate-dependency analysis for the effects of selected doses of *d*-amphetamine is shown in Figure 6. In general, low rates of responding were increased and higher rates were increased less or decreased. The 3 mg/kg dose, which decreased only overall rates of responding, occasionally increased the low rates at the beginning of the FI (Bird 4522, hour two, and Bird 5397, hour one), but decreased higher rates later in the interval. By comparing the data in Figure 3 with the data in Figure 6, it is possible to determine how the rate-dependent effects of *d*-amphetamine produced the changes in FI rate seen in Figure 3.

Similar rate-dependency plots are shown for pentobarbital in Figure 7. Although there are clear instances of rate-dependent effects (Bird 4522, second hour; Bird 5397, first hour; Bird 5775, third hour), especially for those doses where increases in FI rates occurred (Figure 3), in many of these long FIs pentobarbital did not produce clear rate-dependent effects.

To study Branch and Gollub's (1974) suggestion that the point at which the probability of responding becomes greater than zero is a good predictor of the amphetamine effect, we measured the cumulative response records to determine the latency in seconds for the first FI response to occur, assuming that the probability of responding becomes greater than zero at the point where the first response occurs. The FI response latencies after *d*-amphetamine are shown in Figure 8. The 0.1 mg/kg dose, which did not increase FI rates during any of the three FIs often decreased the FI response latency, but never increased it. When increases in FI rate occurred (Figure 3) the largest increases in rate during the first 2 hr after drug occurred after the 0.3 mg/kg dose, but this dose sometimes increased the response latency, sometimes decreased it, and sometimes was without effect. In fact, there

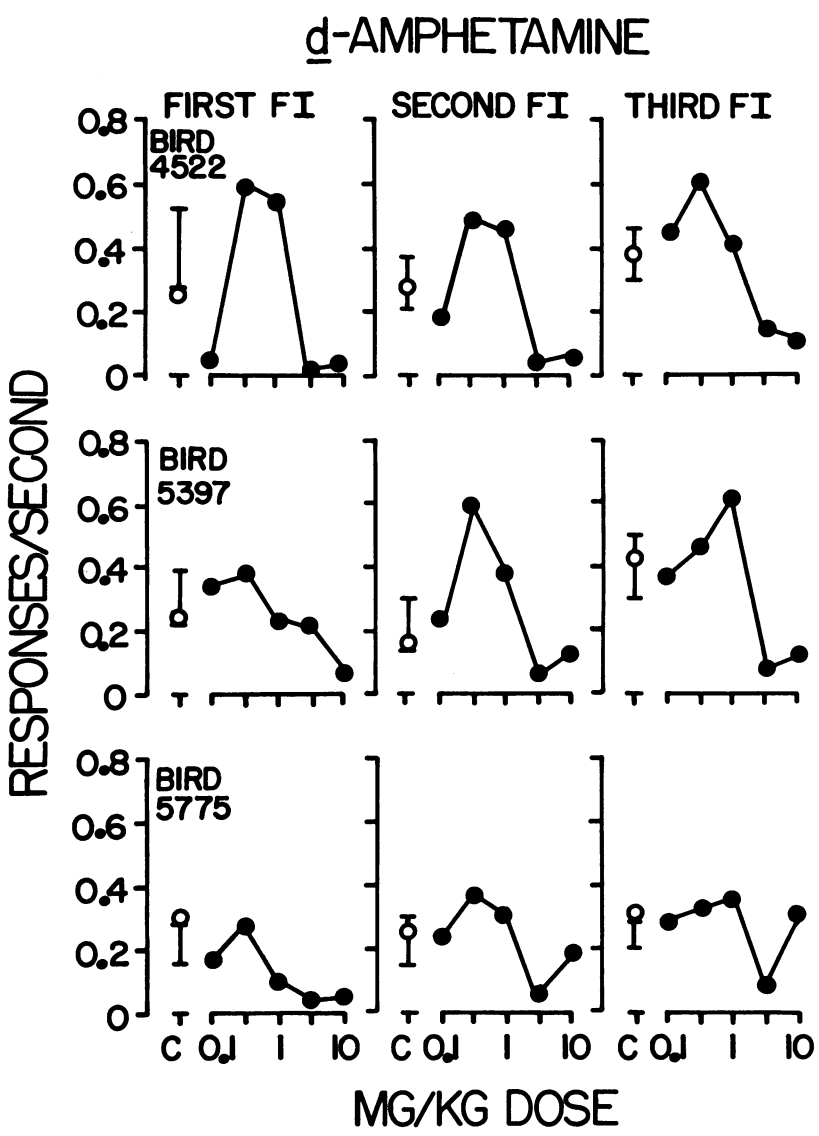

Fig. 4. Effects of *d*-amphetamine on rates of responding for each of the three FIs of a session. Ordinate: responses per second for each bird for each of the FIs. Abscissa: mg/kg dose, log scale. The brackets at C show two standard errors above and below the mean of 11 noninjection sessions (Thursdays) for each of the birds. The open circles at C show the mean of five observations in each bird following injections of distilled water. Each point on the dose-effect curve represents a mean of duplicate observations in each of the three pigeons.

does not seem to be any clear relationship between the dose of *d*-amphetamine and the latency of the first response in each FI, nor does there appear to be a relationship between the latency and the effect of the drug on the rate of responding in the individual FIs.

DISCUSSION

The effects of *d*-amphetamine on responding maintained by these long FI schedules were much like the effects of *d*-amphetamine reported for shorter FI values (Clark and Steele, 1964; Dews, 1958; McMillan, 1968*a*, *b*, 1969; Smith, 1964). The amphetamine dose-response curve for FI 60-min had an inverted U shape, similar to that previously found for FI values from 40 sec to 15 min in the pigeon (Branch and Gollub, 1974; McMillan, 1968*a*, *b*, 1969). Further, the effects of *d*-amphetamine could be described as being rate-dependent, with low rates being increased, and high rates being

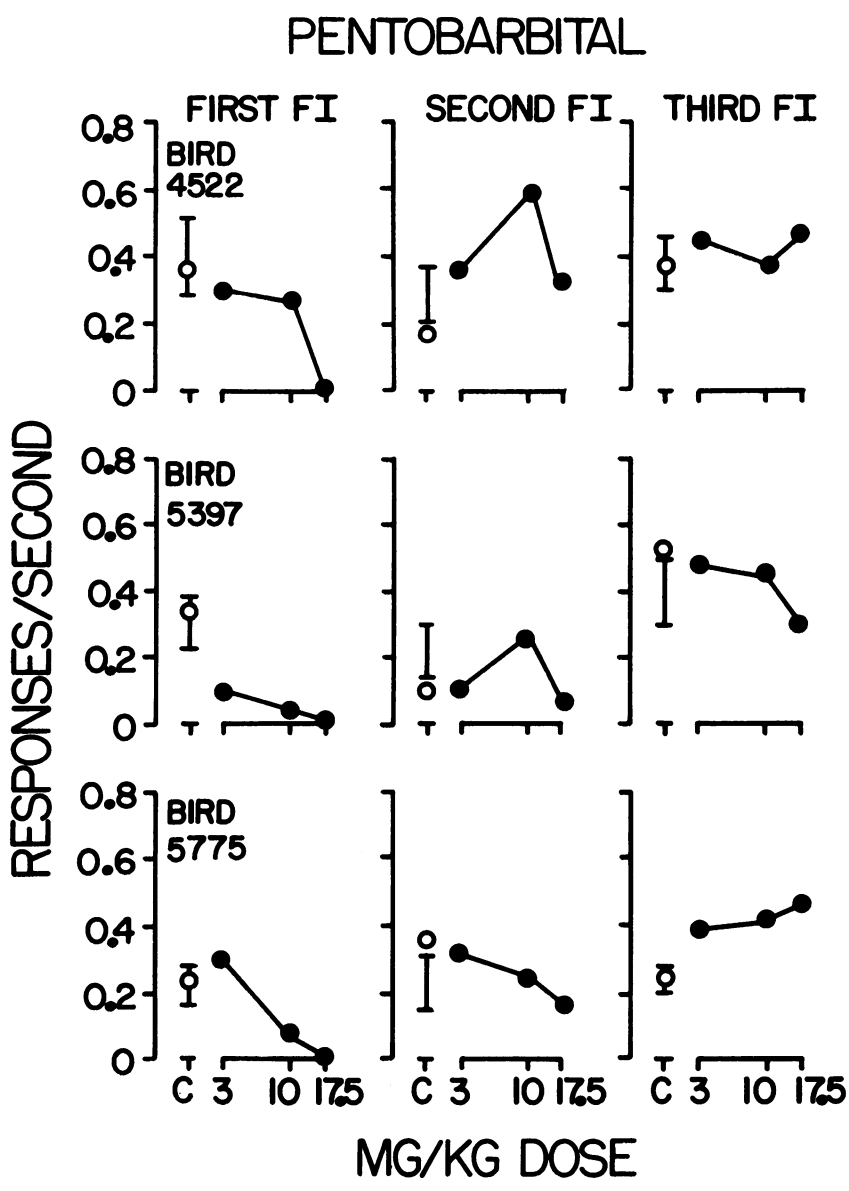

Fig. 5. Effects of pentobarbital on rates of responding for each of the three FIs of a session. Ordinate: responses per second for each of the three FIs of a session for each bird. Abscissa: mg/kg dose, log scale. The brackets at C show two standard errors above and below the control mean of 11 noninjection sessions (Thursdays) for each of the birds. The open circles at C show the mean of five observations in each bird following injections of distilled water. Each point on the dose-effect curve represents a mean of duplicate observations in each of the three pigeons.

increased less or decreased. The rate-dependency data for *d*-amphetamine in Figure 6 are strikingly similar to those plotted previously for shorter FI values (McMillan, 1968*a*, *b*), and the rate-dependent effects of *d*-amphetamine appear to underlie the effects of the drug on rates of responding during individual FIs.

On the other hand, the point at which responding first occurs in the FI did not seem to depend on the dose of *d*-amphetamine, nor did it correlate well with the effects of *d*-amphetamine on the rates of responding during individual FIs. These findings suggest that the predictive value of the Branch and Gollub formulation that amphetamine effects be analyzed in terms of the probability of response

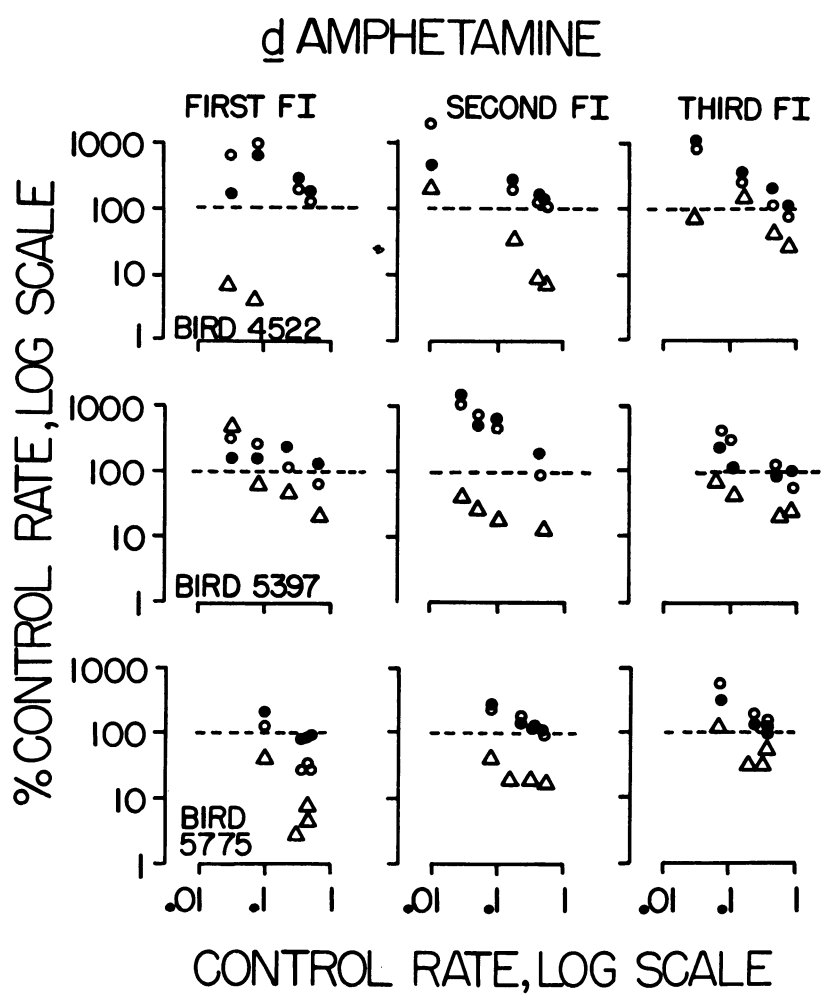

Fig. 6. Rate-dependent effects of three doses of *d*-amphetamine on responding by each of the three birds during 15-min segments of the FI 60-min with each FI in the session shown separately. Abscissa: control rate in responses per second based on the mean of three distilled water injections, log scale. Ordinate: per cent of the control rate, log scale. ● = 0.3 mg/kg; ○ = 1.0 mg/kg; △ = 3.0 mg/kg. Each point is the mean of two determinations in each pigeon.

greater than zero may be useful only at short FI values, or perhaps the Branch and Gollub formulation is useful only if a "two-state" pattern of FI responding occurs. Clearly, our pigeons did not show a two-state pattern of responding; rather, responding was characterized by the gradually increasing rate of responding described by Ferster and Skinner (1957), Keller and Schoenfeld (1950), Skinner (1953), and others.

As suggested by Schneider (1969), the two-state pattern of responding may be a function of extended training, rather than of FI duration, since Cumming and Schoenfeld (1958) showed a two-state pattern of responding with FI durations as long as 30 min. Branch and Gollub (1974) showed that both their formulation and rate-dependency analysis correlate well with the effects of *d*-amphetamine on FI performance when a two-state pattern of responding occurs after more than 90 sessions of training. The present experiment showed the utility of a rate-dependency analysis of amphetamine effects, when control performance is characterized by a gradually increasing rate of responding throughout the FI. However, the correlation between the probability of occurrence of initial responding in the FI and

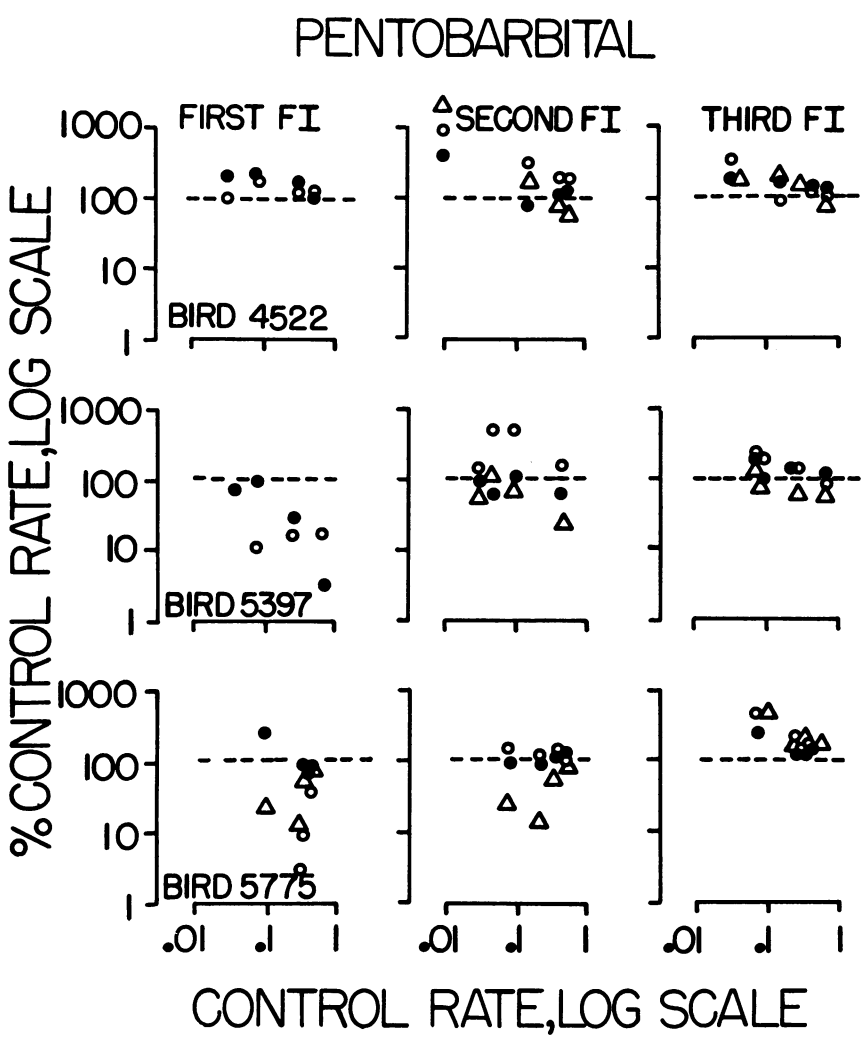

Fig. 7. Rate-dependent effects of pentobarbital on responding by each of the three birds during 15-min segments of the FI 60-min with each FI in the session shown separately. Abscissa: control rate in responses per second based on the mean of three distilled water injections, log scale. Ordinate: per cent of the control rate, log scale. ● = 3 mg/kg; O = 10 mg/kg; △ = 17.5 mg/kg. Each point is the mean of two determinations in each pigeon.

the overall amphetamine effect was low with these long FIs, suggesting that the rate-dependency analysis may have greater generality.

With *d*-amphetamine, the shape of the dose-effect curve did not change much across the three FIs in a session, although the dose-response curve from the second FI was the best predictor of the total FI dose-response curve for the 3-hr session. This clearly was not the case for pentobarbital. During the first hour of the session, the rate-decreasing effects of pentobarbital predominated, while during the second and third hours of the session rates of responding gradually recovered and sometimes were higher than control rates. These hourly effects averaged out to produce a group dose-effect curve, which gave the misleading impression that pentobarbital produced few effects on performance.

Although we obtained some evidence of rate-dependent effects of pentobarbital, pentobarbital did not consistently produce rate-dependent effects on responding maintained by these long FIs. Perhaps the reason for our failure to observe rate-dependent effects of pentobarbital is related to its short duration of action in some animals (Krantz and Carr, 1958). Our rate-dependency analysis was based

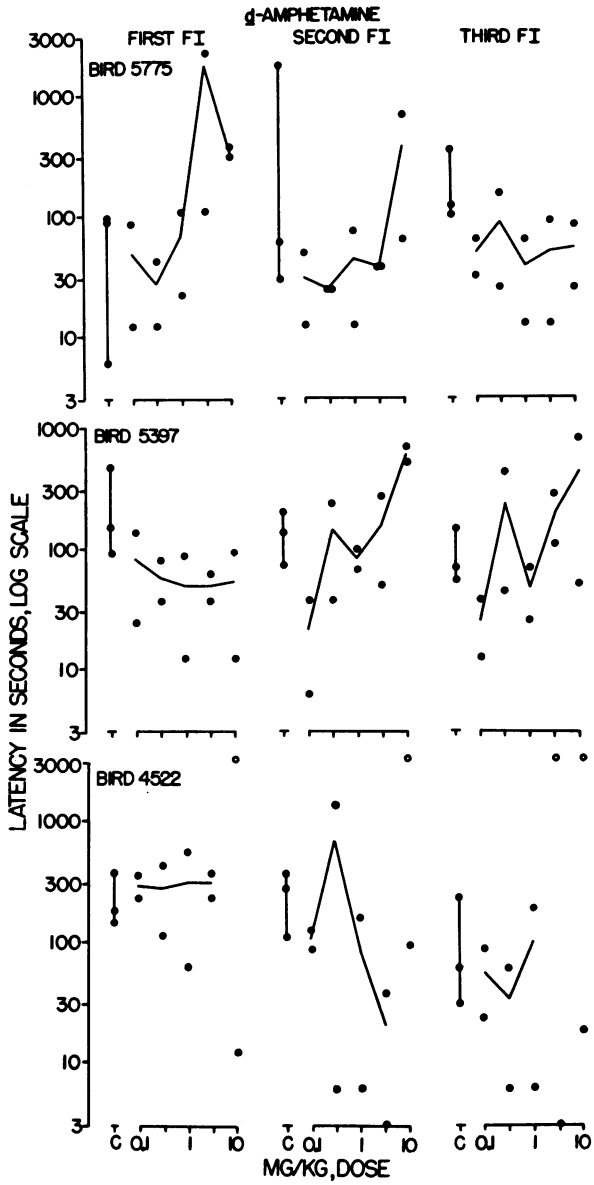

Fig. 8. Latency to the first FI responses as a function of the dose of *d*-amphetamine. Abscissa: mg/kg dose, log scale. Ordinate: seconds to first response in the FI, log scale. Points at C connected by a line show the latencies after saline injections. Filled circles not connected by lines show latencies after *d*-amphetamine. Open circles depict instances when no responding occurred. The lines between the points show the mean latency, which was not determined if no FI responses occurred.

on four 15-min segments of time during hour-long FIs. Thus, if pentobarbital's rate-dependent effects changed or disappeared during an hour-long session, the rate-dependent effects of the drug might be distorted or undetected. Marked rate-dependent effects of pentobarbital for FI responding have been observed for pigeons when rate-dependency was analyzed during 1-min segments of shorter FIs (Leander and McMillan, 1974).

The use of long FIs for the study of drug effects has at least two interesting features. First, the FI 60-min schedule allows convenient measurement of the time-course of a drug effect. Second, the experimenter can study a considerable amount of behavior in 1 hr, with-

out having to average a number of FIs from each animal.

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