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Stimulus Control and the Effects of *d*-Amphetamine in the Rat

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Abstract. External discriminative stimuli can modify the behavioral effects of *d*-amphetamine. Previous work with the pigeon has demonstrated that some aspects of performance on the fixed consecutive number schedule are changed less if a discriminative stimulus indicates when reinforcement is available. This effect has now been replicated with the rat using both simple and multiple schedules. Moderate doses of *d*-amphetamine (0.56–1.0 mg/kg) usually produced large decreases in reinforced runs when no external cue indicated the possibility of reinforcement. Adding discriminative stimuli when the number requirement was met decreased the drug effect. As was true in the pigeon, response rate measures did not differ between the two stimulus control conditions. Thus, external stimulus control diminishes the drug effect in both species, despite the fact that key pecking was studied in the pigeon and lever pressing in the rat. Evidence was also seen of a possible increase in discriminative stimulus control by *d*-amphetamine.

Key words: *d*-Amphetamine – Stimulus control – Fixed consecutive number – Schedule of reinforcement – Chained and tandem schedules – Prepared response principle

Operant behavior under strong control of external discriminative stimuli remains unaffected by amphetamine doses that produce marked changes in behavior not so controlled (Laties 1975; Thompson 1978 for reviews). Some of the strongest evidence for this proposition comes from Laties (1972): Pigeons were tested after being trained on the fixed consecutive number schedule of reinforcement, on which a specified minimum number of consecutive responses had to be made on one key before a single response on a second key would be reinforced. Little drug effect was seen on ability to satisfy the minimum response requirement if the experimenter presented a discriminative stimulus after the required number had been completed. If, on the other hand, no stimulus signalled the completion of the response requirement, much greater changes were seen after doses of *d*-amphetamine.

The present study extends this work to the rat, yielding data relevant to whether the interaction with level of stimulus control that occurs in the pigeon is also present in the rat. Specifically, two experiments were conducted: In the first, two levels of stimulus control were studied independently and successively; in the second, they were studied as parts of a multiple schedule.

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Materials and Methods

In experiment 1, four adult Long-Evans rats were maintained at 350 g, which was about 80% of their free feeding weights as determined at the start of the experiment. In experiment 2, five Long-Evans rats were maintained at 300 g for the duration of the study. Water was always available in the individual home cages. Purina laboratory chow was used for maintenance feedings.

Apparatus. A Lehigh Valley Electronics rat chamber with two Gerbrands levers mounted on the front wall, a white jewel light above each, was used for these experiments. A 76 dB white noise was always present. Sweetened condensed milk diluted with two parts water was used as the reinforcer. The milk (0.1 ml) was presented for 3 s. Approximately 0.26 N was required to move the right lever and record a response, whereas 0.18 N was required for the left lever.

Experiment 1: Simple Schedules. The rats were first trained to press the right lever, with every response being reinforced. The left lever was then activated and at least one response on it was required before a response on the right (reinforcement) lever would produce milk delivery. The number of responses required upon the left lever was increased rapidly until it reached the final criterion of eight consecutive responses. A press on the right lever after one to seven responses on the left lever had no programmed consequence aside from resetting the requirement. This fixed consecutive number schedule will be abbreviated FCN. It is equivalent to a tandem schedule (Ferster and Skinner 1957) with the components being the consecutive number requirement on one lever followed by a fixed ratio 1 on the other lever. Each session was composed of 101 runs (i.e., switches to the reinforcement lever following a run of one or more responses on the left lever). The first run of each session was discarded. A month of training, plus ten sessions during which no systematic trends in performance were seen on any of the measures, preceded drug experiments. After drug data had been collected with this schedule, the procedure was modified.

In order to investigate the effect of stimuli presented when the response requirement was met, the eighth consecutive response on the left lever was followed by illumination of both lever lights and an 80 dB Sonalert tone (SC 628) with a frequency of 2.9 kHz. The animal was then required to respond once on the right lever. Emission of fewer than eight responses on the left lever followed by a response on the right lever reset the requirement. Since the light-tone complex served as a discriminative stimulus (SD), the schedule will be

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abbreviated FCN-SD: It is equivalent to a chained schedule. Twenty-five sessions on the new schedule were run and, during the last ten of these sessions, no further changes were apparent in the performance of the rats. Drug dose-effect curves were then redetermined.

The rats were given *d*-amphetamine sulfate or saline IP 10 min before a session, usually on Tuesdays or Fridays. Noninjection control sessions occurred on the remaining weekdays, but data collected on Monday and on any Wednesday after a drug dose were discarded. Drug concentrations were varied to allow for constant injection volume of less than 1 ml/kg. Doses are in terms of the salt. At least two determinations were made for all doses except for a single determination for 3.0 mg/kg under the FCN-SD condition. Four or five saline control sessions were obtained for each rat under each condition. These did not differ from noninjection controls; therefore, all control data have been pooled. A total of 24 control sessions have been used to generate confidence intervals for the FCN schedule and ten for the FCN-SD schedule.

Experiment 2: Multiple Schedule. Rats were first trained on the FCN-SD schedule and, after reaching 90% reinforcement level, were put on the multiple schedule. Each session started with the FCN-SD component, which remained in effect for 11 runs, the first of which was discarded. The FCN component was then present for ten runs and the two alternated until a total of 100 runs (50 per component) had been completed. During the FCN component, the house light was on at all times. During the FCN-SD component, the house light remained off (except during the reinforcement presentation) and the left lever light was illuminated; completion of the minimum response requirement turned out the left lever light and turned on both the right lever light and the Sonalert tone. The right lever press then turned off these stimuli, which collectively served as a compound discriminative stimulus, and delivered the reinforcer. Premature switching to the right lever had no programmed consequences other than resetting the response requirement on the left lever.

Drug data, collected as described in experiment 1, are presented for four rats that showed clear evidence of differential performance under the control conditions. Between ten and 15 control sessions, including four or five saline, were gathered for each rat. Drug data were not collected on a fifth rat, which did not come under appropriate control of the multiple schedule as rapidly as the others.

The following measures were analyzed: the rate of responding during a whole session on the left lever, excluding the time occupied by food presentation and by the first run of each session (overall rate); the rate between the first response on the left lever and the response on the reinforcement lever that ended the run (running rate); the percentage of runs long enough to set up milk delivery for a subsequent response on the reinforcement lever (reinforced runs), which also indicates the probability that the rat will meet at least the minimum requirement before switching. Finally, the conditional probability measure answers the question: Given a particular run length, how likely is it that the subject will switch to the reinforcement lever? This last measure uses, as a denominator for each run length, the number of times that run length has been reached (cf. Mechner 1958). For example, a switch after a run of five responses does not yield any information on the probability of the subject switching after longer runs, but performance on that run has given data on the probability of switching after run lengths of one, two, three, four, and five responses. Data are not used from a session after the denominator has been diminished to fewer than 20 runs.

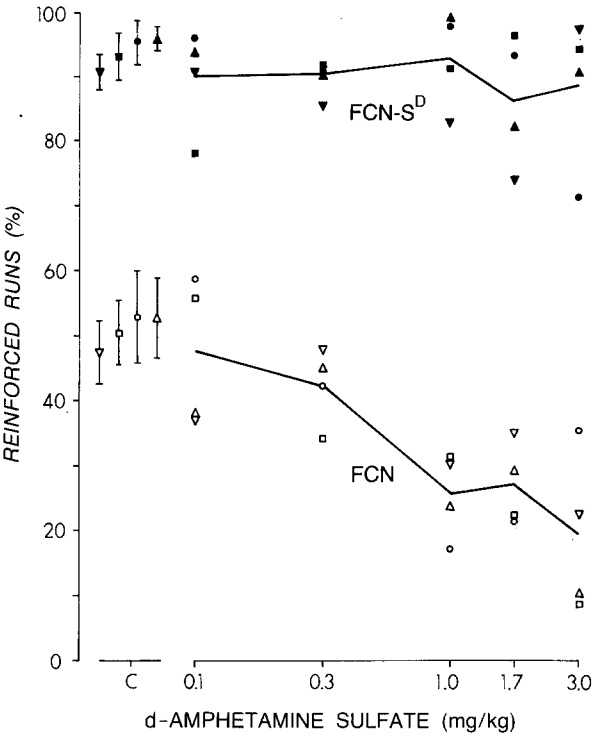

Fig. 1. Effects of *d*-amphetamine sulfate on the percentage of runs on the fixed consecutive number (FCN) schedule that were long enough to be reinforced (experiment 1). The two versions of the FCN schedule were studied separately (experiment 1). Mean values are connected by the solid lines. The vertical lines above C give the 95% confidence intervals for each rat. In each case, these are based upon either 24 sessions (for FCN) or ten sessions (FCN-SD). Each rat is represented by a unique symbol (filled for FCN-SD, open for FCN) that represents the mean value for sessions at that dose level; inverted triangles (rat 1), squares (rat 2), circles (rat 3), and triangles (rat 4)

Results

Experiment 1: Reinforced Runs. The most straightforward measure of stimulus control is the percentage of runs that meet the minimum response requirement for reinforcement. Under control conditions on the FCN, about 50% of all runs were eight or more responses long and were reinforced (Fig. 1). When an exteroceptive discriminative stimulus signalled when a right key press would be reinforced (FCN-SD), over 90% of the run lengths were equal to or longer than eight responses.

Doses of *d*-amphetamine sulfate (0.1 – 3.0 mg/kg) did not produce consistent diminution of percent of runs reinforced on FCN-SD. However, in the absence of the discriminative stimulus, a consistent reduction in reinforced runs was observed at doses of 1.0 mg/kg and above. With only rare exceptions (e.g., rat 3, represented by the circles in Fig. 1, at 3.0 mg/kg), the effects on the individual animals are adequately represented by the group means.

Experiment 1: Conditional Probability. This effect is shown in more detail in Fig. 2, which presents conditional probability data for a typical animal (rat 2) under both stimulus con-

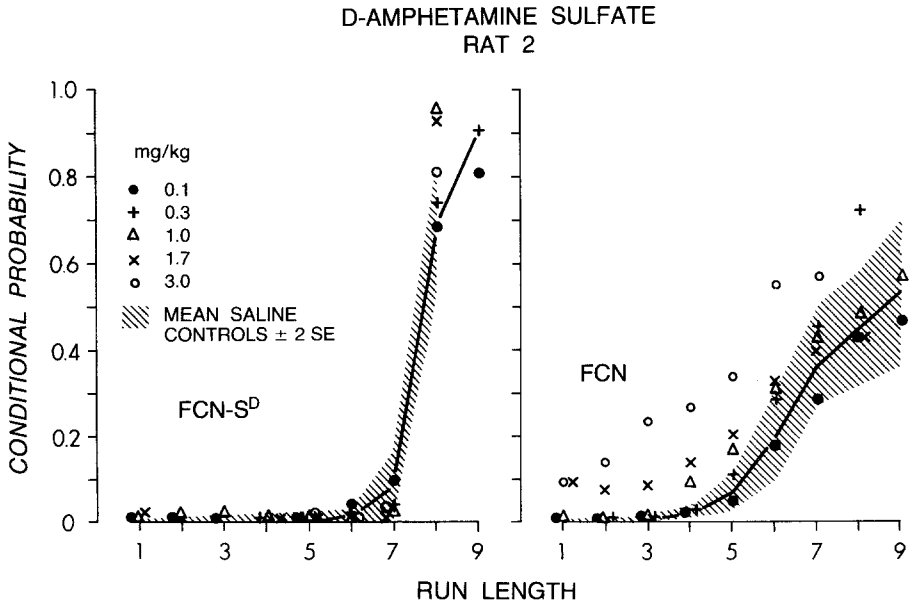

Fig. 2
Conditional probability data for a single rat in experiment 1. The Y-axis gives the probability that the rat will stop after the number of consecutive responses given on the X-axis and press the right (reinforcement) lever

ditions at all drug doses. Whereas Fig. 1 describes the likelihood of satisfying the minimum response requirement, Fig. 2, shows the likelihood of a switch to the reinforcement lever after each response in the sequence; i.e., given n responses in a row on the left lever, the probability that the rat would then switch. For this rat (identified in Fig. 1 by squares), drug doses of 1.7 mg/kg and above usually increased the probability of switches earlier in the sequence in the absence of a discriminative stimulus (right panel, FCN, Fig. 2). A dose of 1.0 mg/kg increased switching after four and five successive responses. However, no increases in probability of early switching were observed when the external stimulus was present (left panel, FCN-SD).

We noticed that *d*-amphetamine increased the likelihood of a response by rat 2 immediately after the appearance of the discriminative stimulus. The probability of such responses was examined for the other animals as well. For all rats, the doses of 1.0 and 1.7 mg/kg always increased the probability of a switch after the eighth response to a level greater than 2 SE above the saline control value. The 3.0 mg/kg dose increased this probability greatly in two of the four rats. Thus, increases occurred in 10 of 12 available cases. Doses below 1 mg/kg were never effective. A possible control for nonspecific changes by the drug is afforded by examining switching behavior after the eighth response on the FCN schedule. The same three high doses with the four rats showed that such immediate switches occurred on only four of nine possible occasions. (In three other cases, the denominator of the conditional probability fraction was reduced to fewer than 20 runs, which made reliability of the figure suspect).

Experiment 1: Response Rate. Response rates for the control conditions did not differ, as was also true with the pigeon (Laties 1972). The overall response rates for the pooled control conditions were 0.78/s (SE 0.044) for FCN and 0.74/s (SE 0.087) for FCN-SD. Similarly, the running rates did not differ (FCN 1.69/s, SE 0.292, FCN-SD 1.87/s, SE 0.341). The absence of rate differences for the two schedules makes interpretation of any drug effects less ambiguous, since rate dependency explanations lose relevance in the absence of initial rate differences.

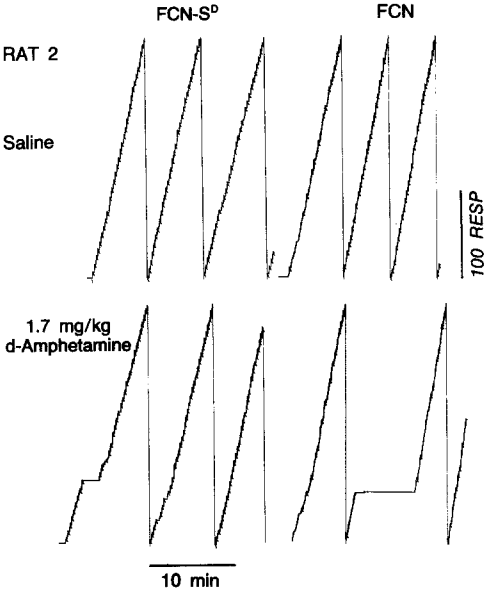

Fig. 3. Cumulative records of performance on FCN and FCN-SD schedules of reinforcement (experiment 1). Time flows from left to right. Each left-lever response moves the pen upward until it resets at the limit of its travel. Diagonal strokes of the pen indicate reinforcer deliveries caused by right-lever responses following runs of eight or more left-lever responses

d-Amphetamine produced only decreases in mean response rate and this was true for both types of stimulus control. For instance, at 1.7 mg/kg, a dose that produced large differential effects on other performance measures, the FCN mean overall response rate was 0.47/s (SE 0.085) and FCN-SD rate was 0.52/s (SE 0.184): Running rate was affected less, with comparable rates being 1.64/s (SE 0.434) and 1.50/s (SE 0.273), respectively. Again, these findings resemble those for the pigeon (Laties 1972). The absence of striking changes in response rate or pattern, aside from occasional drug-induced pauses, is illustrated by the cumulative records in Fig. 3.

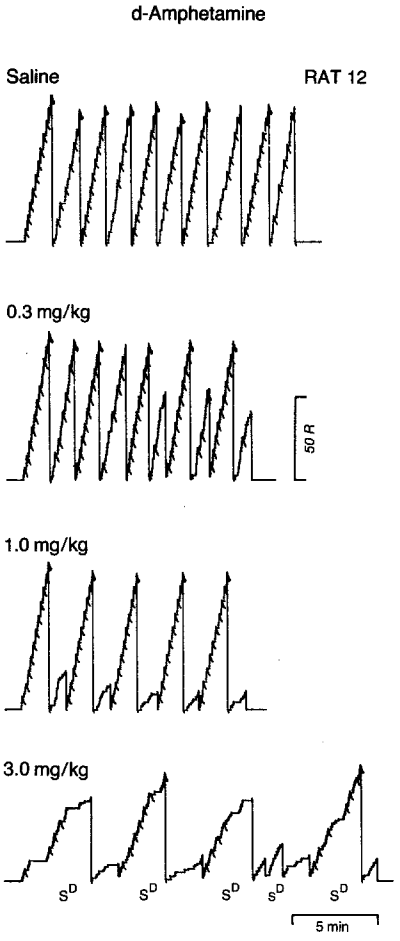

Fig. 4. Cumulative records of performance on the multiple FCN-FCN-SD schedule of reinforcement (experiment 2). Responses on the left lever moved the pen upward. Reinforcements are indicated by diagonal lines. The pen reset to the baseline with completion of the tenth run in each component of the schedule

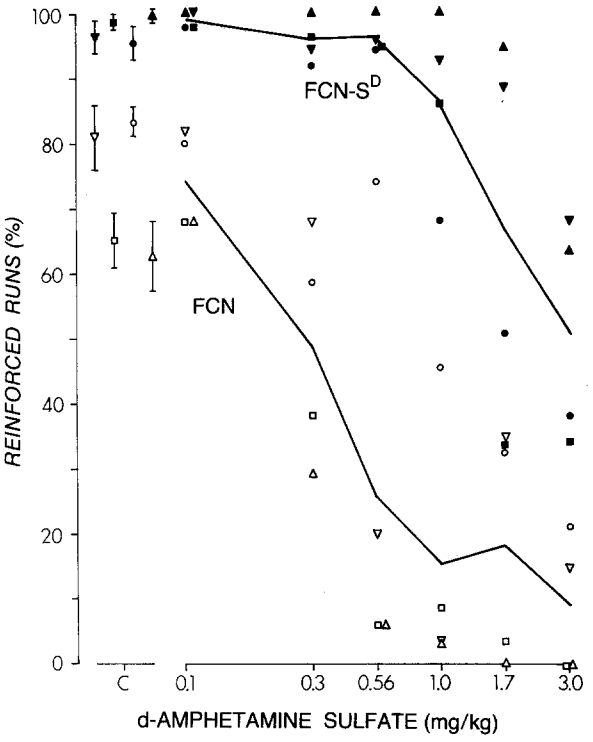

Fig. 5. Effects of *d*-amphetamine sulfate on the percentage of runs that were long enough to be reinforced (experiment 2). The two versions of the FCN schedule were embedded within a multiple schedule. The vertical lines above *C* give the 95% control confidence intervals, based upon data from 10–15 sessions, for each rat. Mean values are connected by the solid lines. Each rat is represented by a unique symbol (filled for FCN-SD and open for FCN); circles (rat 10), squares (rat 11), triangles (rat 12), and inverted triangles (rat 14)

Experiment 2. The pattern of responding on the multiple schedule is displayed for one rat in Fig. 4. These patterns were similar after saline and 0.3 mg/kg. Rates were relatively unaffected at 0.3 mg/kg, although a marked reduction occurred in the number of runs that met the minimum criterion for reinforcement. At 1.0 mg/kg, performance on FCN-SD was unaffected, whereas performance without the added stimulus was profoundly impaired. At 3.0 mg/kg, disruption was apparent in both components. Similar effects were seen in the other animals, whose data are discussed below.

Experiment 2. Reinforced Runs. The control levels for reinforced runs under FCN-SD were over 95% (Fig. 5). These are comparable to those attained in experiment 1. However, FCN levels averaged about 20 percentage points higher when embedded in the multiple schedule.

Clear differential effects of *d*-amphetamine appeared in rats 11 and 12 at 0.3 mg/kg and in rats 11, 12, and 14 at 0.56 and 1.0 mg/kg (Fig. 5). At 1.7 mg/kg, only rats 12 and 14 continued at the 90% level in the FCN-SD condition, while dropping to 0 and 35%, respectively, when the discriminative stimulus was not present. Rat 10, indicated by the circles in the figure, showed graded changes under both conditions at doses larger than 0.56 mg/kg. However, even with this rat, the percent change produced by the drug was consistently greater in the FCN condition at all dose levels. Taken as a whole, these data confirm the results seen in experiment 1,

Experiment 2: Conditional Probability. The probability of early switching to the reinforcement lever increased with drug treatment in a generally dose-related fashion under both conditions (Fig. 6). However, the number of doses after which this effect occurred and the magnitude of the effect were both greater under the FCN condition. Note that, where very large increases in conditional probabilities occurred at short run lengths, very few points are plotted subsequently because the run length denominator had been exhausted (e.g., rat 11, FCN-SD; rat 12, FCN).

The probability that the rat would switch immediately upon presentation of the discriminative stimulus increased on 20 of 24 occasions after *d*-amphetamine (Fig. 6, left panel). Inspection of the right panels shows that similar increases occurred on only five occasions after the eighth run with the FCN schedule, with no information available due to exhaustion of the conditional probability fraction denominator on 12 occasions.

Experiment 2: Response rate. The addition of a discriminative stimulus did not affect control response rates: The FCN and FCN-SD overall response rates were 0.85/s (SE 0.076) and 0.83/s (SE 0.083), respectively. The running rates were 1.89/s (SE 0.283) and 2.01/s (SE 0.314), respectively.

The *d*-amphetamine decreased both overall and running rates. The largest separation between the schedules in per-

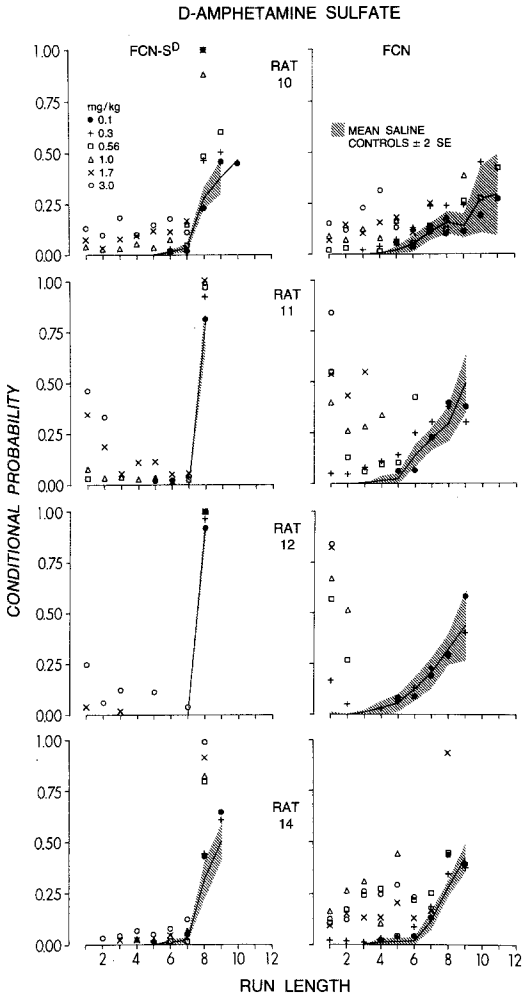

Fig. 6. Conditional probabilities for the four rats of experiment 2. The Y-axis gives the probability that the rat will stop after a run of the length given on the X-axis and switch to the reinforcement lever. Probabilities lower than 0.01 have not been plotted and neither have points based upon fewer than 20 runs

centage of reinforced runs occurred at 1.0 mg/kg. At that dose, the overall response rates had decreased to 0.51/s (SE 0.113) for FCN and 0.70/s (SE 0.059) for FCN-SD. Comparable figures for the running rates were, for FCN, 0.97/s (SE 0.124) and for FCN-SD, 1.28/s (SE 0.229).

Discussion

This study was undertaken partially because of the suggestion that the interaction between degree of stimulus control and the effect of amphetamine may be limited to the key-pecking response studied by Laties (1972). As Scheuer and Moore (1974, p 430) put it:

... the response selected for study may be a highly critical variable when discussing drug effects on behavior maintained by internal vs. external cues... key-pecking in pigeons is a highly prepared response in appetitive situations. It would follow that this type of behavior would be more difficult to disrupt than more arbitrary (unprepared) behaviors such as leverpressing. In the area of behavioral pharmacology, limitations on the type of generalizations that can be made are perhaps of more concern than in other lines of behavioral research. We should, therefore, be more critical of the type of response selected for study. It is quite feasible that external-stimulus control may be disrupted by amphetamines to the extent that the behavior is one which is not an evolutionarily prepared one for the organism:

Our data show no more disruption of an externally cued discrimination using rat lever pressing than we previously reported for similar behavior using pigeon key-pecking. The results demonstrate that the rat does show a diminished sensitivity to drug disruption of the discrimination under strong exteroceptive control. This conclusion is important because Scheuer and Moore (1974) has been cited as evidence of a 'prepared response' principle in behavioral pharmacology. For example, Frontali et al. (1976, p 20) assert that the difference between the outcomes of the Scheuer and Moore (1974) and Laties (1972) studies

...'seems to confirm that pecking outputs of amphetamine-treated pigeons are modulated to obey positive reinforcement requirements more efficiently than manipulatory responses of treated rats...'

And Peters et al. (1978, p. 305), after reviewing these studies, conclude that:

'It seems that stimulus factors may influence potential behavioral changes elicited by drug treatments; however, experiential and species factors may determine the nature of the stimulus and drug interaction.'

These conclusions are too strong. Neither Scheuer and Moore (1974) nor the present authors have designed a study sophisticated enough to assess the role of response preparedness in determining *d*-amphetamine's effects in this situation. Such work, which would explore systematically various combinations of response and reinforcer, has yet to be done. However, it is clear that although response form probably influences the actions of amphetamine, as do many other experiential, physiological, and biochemical variable, form does not appear to vitiate the importance of strength of stimulus control. Indeed, the latter may well overwhelm many other variables in determining the extent to which the amphetamines, as well as other drugs, influence learned behavior.

Scheuer and Moore (1974) may have failed to find the differential effect because they confined their investigation to a single 1 mg/kg dose which may have been an insensitive point on the dose-response curve. For instance, if we had used only 0.3 mg/kg on the rats shown in Fig. 1, we would also have reported no difference. In any case, this study was not an attempt to replicate that one; it was rather an attempt to see whether it was possible to find the difference as a function of stimulus control level.

One other line of evidence makes us believe that the difference between rat lever pressing and pigeon key-pecking is relatively unimportant in determining interactions between drugs and stimulus control. Scopolamine has been studied by Wagman and Maxey (1969) in rats and by Laties (1972) in pigeons on the FCN and FCN-SD schedules. Despite differences in species and response form, both studies reported similar effects. On the FCN schedule scopolamine increased the number of runs too short for reinforcement, whereas the same doses did not affect performance on FCN-SD in that way.

Rats showed a greater percentage of reinforced runs on the FCN schedule when it was embedded within the multiple schedule (experiment 2) than when it occurred in isolation (experiment 1). This could represent either an interactive enhancement effect by the FCN-SD component or differences in training history. The greater changes induced by the higher

doses of *d*-amphetamine in the multiple schedule (compare Figs. 1 and 5) could also reflect the influence of such factors. On the other hand, the greater effect could reflect interference with the control exerted by the stimuli that indicated the two components of the multiple schedule.

The apparent increase in switch probability after eight responses at high doses of *d*-amphetamine on the FCN-SD condition may reflect an enhancement of the conditioned reinforcing properties of the stimulus associated with the switch. However, while such enhancement has been shown for pipradrol (Hill 1970; Robbins 1975, 1978), it has not been seen with *d*-amphetamine (Robbins 1978). Alternatively, the present effect may be evidence for an enhancement of discriminative stimulus control, a phenomenon that has been reported before (e.g., Blough 1957). Teasing apart the relative importance of such factors is a task for further research.

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