

*EFFECTS OF D-AMPHETAMINE IN
A TEMPORAL DISCRIMINATION PROCEDURE:
SELECTIVE CHANGES IN TIMING OR
RATE DEPENDENCY?*

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Two experiments evaluated rate dependency and a neuropharmacological model of timing as explanations of the effects of amphetamine on behavior under discriminative control by time. Four pigeons pecked keys during 60-trial sessions. On each trial, the houselight was lit for a particular duration (5 to 30 s), and then the key was lit for 30 s. In Experiment 1, the key could be lit either green or blue. If the key was lit green and the sample was 30 s, or if the key was lit blue and the sample was 5 s, pecks produced food on a variable-interval 20-s schedule. The rate of key pecking increased as a function of sample duration when the key was green and decreased as a function of sample duration when the key was blue. Acute *d*-amphetamine (0.1 to 3.0 mg/kg) decreased higher rates of key pecking and increased lower rates of key pecking as predicted by rate dependency, but did not shift the timing functions leftward (toward overestimation) as predicted by the neuropharmacological model. These results were replicated in Experiment 2, in which the key was lit only one color during sessions, indicating that the effects were not likely due to disruption of discriminative control by key color. These results are thus consistent with rate dependency but not with the predictions of the neuropharmacological model.

Key words: timing, rate dependency, temporal discrimination, amphetamine, key peck, pigeons

In a neuropharmacological model of time perception, Meck (1996) proposed that dopamine and acetylcholine provide the basis for the operation of major components of scalar expectancy theory (SET; Gibbon, 1977; Gibbon & Church, 1984; Gibbon, Church, & Meck, 1984). Briefly, SET is an information-processing model of timing that posits clock, memory, and decision stages. In the clock stage, pulses from a pacemaker are gated through a switch into an accumulator. The number of pulses in the accumulator represents the amount of time that has passed since the switch closed and timing began. The value from the accumulator can be transferred to reference memory in the memory stage when an important event, such as the delivery of food for a deprived animal, occurs. In the decision stage, the value from the accumulator is compared to the value in ref-

erence memory, and if the ratio of difference between the two is lower than a threshold value, a response occurs.

Meck (1996) suggested that dopamine levels determine the clock process, primarily through influencing pacemaker rate (Hinton & Meck, 1997). The more dopamine present, the faster the clock ticks. An increase in dopamine levels is predicted to produce an immediate leftward shift in the psychophysical timing function (i.e., the animal would overestimate the passage of time and respond prematurely). A decrease in dopamine levels, on the other hand, is predicted to produce an immediate rightward shift in the psychophysical timing function (i.e., the animal would underestimate the passage of time and respond later than usual).

Meck (1996) suggested that levels of acetylcholine determine temporal memory, primarily through influencing the translation constant that modifies the value transferred from the clock stage to the memory stage (Hinton & Meck, 1997). The more acetylcholine present, the shorter the remembered duration of events. An increase in acetylcholine levels is predicted to produce a gradual leftward shift in the psychophysical timing function (i.e., the animal would gradually come to overestimate the passage of time and respond premature-

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ly). A decrease in acetylcholine levels, on the other hand, is predicted to produce a gradual rightward shift in the psychophysical timing function (i.e., the animal would gradually come to underestimate the passage of time and respond later than usual).

The present experiments examined the effects of *d*-amphetamine on the behavior of pigeons in a temporal discrimination procedure. In addition to other neurochemical effects, amphetamine increases dopamine levels by stimulating the release of dopamine from presynaptic terminals and blocking the reuptake of dopamine from the synapse (Seiden, Sabol, & Ricaurte, 1993). Furthermore, although there are some anatomical differences in the avian and mammalian forebrain, the function and organization of the dopamine system is similar in birds (including pigeons) and mammals (including rats; Durstewitz, Kröner, & Güntürkün, 1999; Vischer, Cuénod, & Henke, 1982). Amphetamine has other effects besides increasing dopamine (Seiden *et al.*, 1993), and more specific compounds for altering dopamine levels exist. A substantial amount of the evidence that Meck (1996) offers for the role of dopamine in timing, however, comes from experiments investigating the effects of amphetamine (e.g., Maricq & Church, 1983; Maricq, Roberts, & Church, 1981; Meck, 1983). The current experiments therefore focus on the effects of amphetamine, because this drug has been used to provide support for the neuropharmacological model (Meck, 1996) and because amphetamine has a long history in the investigation of the effects of drugs on timing (e.g., Schuster & Zimmerman, 1961; Sidman, 1955).

In addition to other forms of evidence to support the role of dopamine in timing, Meck (1996) cited experiments showing that amphetamine increases low response rates maintained in the initial portion of fixed-interval (FI) schedules of reinforcement. In an FI schedule, the first response after a fixed time produces access to a reinforcer (Ferster & Skinner, 1957, pp. 133–134). Response rates typically increase across the interval from low or zero rates early in the interval to higher steady rates near the end of the interval. Amphetamine produces robust increases early in the interval in response rates of pigeons (e.g., Katz & Barrett, 1979; McMillan,

1968), rats (e.g., Ksir & Nelson, 1977; McAuley & Leslie, 1986), mice (e.g., Glowa, 1986; McKim, 1980), monkeys (e.g., Goethe & Isaac, 1977; Herling, Downs, & Woods, 1979), and humans (e.g., Stitzer, 1984) maintained by FI schedules.

This increase in responding early in the interval has been interpreted to reflect overestimation of the passage of time (e.g., Killeen, 1991; Maricq *et al.*, 1981; McAuley & Leslie, 1986; Meck, 1996). Within behavioral pharmacology, however, these same types of changes in the temporal patterning of responding within fixed intervals have long been considered an example of rate dependency (e.g., Dews & Wenger, 1977; Kelleher & Morse, 1968; McKearney & Barrett, 1978; see Odum & Schaal, 2000, for discussion). Rate dependency in its most basic form is the empirical generalization that the effects of a drug on behavior depend on the rate of the behavior in the absence of the drug (Dews, 1981). For behavior maintained by FI schedules, drugs from a variety of pharmacological classes increase low rates of behavior early in the interval, but particularly with higher doses, decrease higher rates of behavior later in the interval.

The difficulty in differentiating between a temporal overestimation account and a rate dependency account of the effects of amphetamine on behavior maintained by FI schedules is that the two accounts make the same prediction: Low early rates should increase in both cases. The present experiments attempted to evaluate these two accounts in a novel way by arranging a situation in which they make divergent predictions. Based on a procedure described by Reynolds and Catania (1962), pigeons were presented with a sample duration and then were given the opportunity to peck a response key for 30 s. A range of sample durations was presented across trials. If the key was lit one color, pecks were intermittently reinforced following the shortest sample duration. If the key was lit another color, however, pecks were reinforced only following the longest sample duration.

Figure 1 shows how this procedure differentiates between the predictions of overestimation and rate dependency accounts of the effects of amphetamine on behavior. Under control conditions (top panel), response

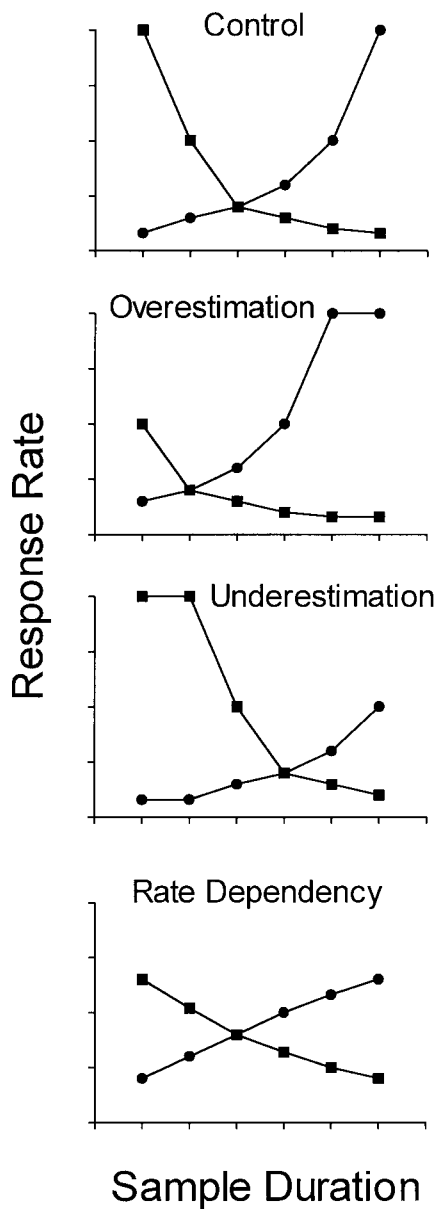


Fig. 1. Explanatory figure with hypothetical data showing response rate as a function of sample duration in the current procedure for control performance and for several possible changes that could be produced by drugs (see text). Circles show data from trials in which responses could be reinforced following the longest sample; squares show data from trials in which responses could be reinforced following the shortest sample.

rates should increase as a function of sample duration in the component in which pecks can produce food following long sample durations, much like during an FI, but should

decrease as a function of sample duration in the component in which pecks can produce food following short sample durations. The corresponding time on the x axis at which the two functions cross is the point of subjective equality (PSE): the sample duration that is perceptually midway between the longest and shortest sample and therefore that at which the response rate is the same in the two components. The rest of the panels show various potential disruptions of timing. If a drug were to produce overestimation of the passage of time (second panel), as amphetamine is suggested to do (Meck, 1996), then the functions would be shifted horizontally, to the left on the x axis, and the PSE would be reduced. Underestimation (third panel) would shift the functions horizontally, to the right on the x axis, and the PSE would be increased. If the effects of a drug were rate dependent (fourth panel), however, the PSE should remain the same, but lower rates should increase and higher rates should decrease.

The present experiments evaluated the role of dopamine in timing as posited by Meck (1996). In Experiment 1, *d*-amphetamine was administered to pigeons responding on the procedure described above. If increases in dopamine increase clock speed, then the timing functions should shift to the left (horizontally). If the effects are largely rate dependent, however, the functions should not shift to the left, but should instead flatten. Experiment 2 evaluated whether the results of Experiment 1 could reflect a disruption in color discrimination rather than changes in timing by arranging the long and short components separately across conditions.

EXPERIMENT 1

METHOD

Subjects

The subjects were 4 adult male White Carneaux pigeons with previous acute exposure to cocaine (Schaal, Miller, & Odum, 1995) and morphine (Odum, Haworth, & Schaal, 1998; Odum & Schaal, 1999) while responding under a multiple fixed-ratio FI schedule or a multiple FI clocked FI schedule of food presentation. The pigeons were maintained at 80% (± 10 g) of their free-feeding weights

through postsession feedings of mixed grain as necessary. Pigeons received no drugs for 40 to 46.5 weeks prior to tests of *d*-amphetamine in the current experiment. When not in experimental sessions, pigeons were individually housed in a temperature-controlled colony under a 12:12 hr light/dark cycle and were allowed free access to water and digestive grit. Sessions were conducted during the light portion of the cycle.

Apparatus

Four custom-made experimental chambers, constructed of wood with aluminum front panels, were used. The internal dimensions were 33 cm across the front panel, 31 cm from the front panel to the back wall, and 37.5 cm from the floor to the ceiling. Three plastic response keys (2.1 cm diameter) on the front panel were mounted 26 cm from the floor. The center key could be lit from behind with green or blue light and required a force of approximately 0.19 N to record a response. The side keys were dark, and pecks to these keys had no programmed consequences. A lamp (28 V, 1.1 W) 7 cm above the center key served as the houselight. A rectangular aperture 16 cm below the center key provided access to a solenoid-operated food hopper filled with mixed grain. White noise and chamber ventilation fans masked extraneous sounds. Contingencies were programmed and data collected by microcomputers located in an adjacent room with Med Associates interfacing and software.

Procedure

Experimental sessions were conducted daily at approximately the same time. Due to the pigeons' previous history, no key pecking or hopper pretraining was necessary. Reinforcement was 3-s access to the food hopper. During hopper presentations, the aperture was lit with white light, and the houselight and keylight were extinguished. Ten minutes after the pigeons were placed in the darkened chamber, the session began with the lighting of the houselight.

The procedure was essentially a multiple-schedule version of the timing procedure of Reynolds and Catania (1962). Two types of trials alternated randomly. Trials began when the houselight was lit for either 5 or 30 s. Then the houselight was turned off and the

center key was lit either blue or green for 30 s. If the houselight duration was 5 s and the key was lit blue, key pecks were reinforced during this period according to a variable-interval (VI) 20-s schedule (composed of 20 intervals generated using the constant-probability method of Catania & Reynolds, 1968, and the BASIC program of Perone; see Lattal, 1991). If the houselight duration was 5 s and the key was lit green, key pecks were not reinforced. If the houselight duration was 30 s, however, pecks when the key was green were reinforced according to the same VI 20-s schedule (i.e., there was only one VI schedule that operated under both circumstances), but pecks when the key was blue were not reinforced. The VI schedule operated only following the 5-s sample duration when the key was blue and following the 30-s sample duration when the key was green. The time during hopper presentations was not included in the 30-s period of access to the lit key. When 30 s elapsed, the center keylight was extinguished and the houselight was lit to begin the next trial (i.e., there was no intertrial interval).

To avoid extinguishing key pecking during the initial exposure to the procedure, during the first session the only durations present were those following which responses could be reinforced (5 s for blue and 30 s for green). Intermediate sample durations (10, 15, 20, and 25 s) were added one at a time in ascending order for blue and descending order for green across the next four sessions. Finally, during the sixth session, the final timing procedure was reached in which each sample duration (5, 10, 15, 20, 25, and 30 s) occurred prior to both key colors. Pecks to the center key after the presentation of the intermediate sample durations did not produce food in either type of trial. Each sample duration was presented 10 times, five times preceding the blue center key and five times preceding the green center key, for a total of 60 trials. The order of trial types was randomly chosen each session. In summary, pecks to the blue key could be reinforced following the shortest houselight presentation (5 s; the short component) and pecks to the green key could be reinforced following the longest houselight presentation (30 s; the long component).

Drug Administration

Pigeons experienced 180 to 198 sessions of the final timing procedure prior to administration of *d*-amphetamine. Drug testing began for individual pigeons when response rates in both components were stable for each sample duration as judged by visual inspection (i.e., showed no increasing or decreasing trends or extreme variability over the final 15 to 20 sessions). A range of doses of *d*-amphetamine (0.1, 0.3, 1.0, and 3.0 mg/kg) and its vehicle (0.9% saline) were administered in a mixed order for each pigeon. *d*-Amphetamine (Sigma) was dissolved in saline and administered in a volume of 1.0 ml/kg of the body weight at 80% of free-feeding weight. Amphetamine and vehicle were administered via intramuscular injections into the breast immediately before the pigeons were placed in the experimental chambers. Tests were separated by at least three consecutive baseline sessions not preceded by injections. The session immediately preceding a *d*-amphetamine or vehicle test session was designated a control session. Dose-effect curves were determined completely before any dose was repeated and four dose-effect curves were completed. Pigeons were weighed prior to and after experimental sessions, and drug tests were not conducted if initial weights were not within 10 g of the appropriate weight for the pigeon. This event rarely occurred.

RESULTS

Figure 2 shows the overall rate of key pecking (i.e., rates averaged across those obtained following all sample durations) as a function of dose of *d*-amphetamine for each pigeon separately for both components. Saline had little systematic effect on the overall rate of key pecking. With increasing doses of amphetamine, rates of key pecking generally increased moderately and then decreased. Rates for P40, however, did not decrease at the largest dose in either component, and rates did not decrease at the largest dose for P10 and P53 in the short component. Across pigeons, mean rates of key pecking were not systematically different between the long component (in which the key was lit green and food was available after the 30-s sample) and the short component (in which the key

was lit blue and food was available after the 5-s sample).

The top row of Figure 3 shows temporal discrimination functions during control sessions for each pigeon. Mean rates of key pecking decreased as a function of sample duration during the short component. During the long component, mean rates of key pecking increased as a function of sample duration. For each pigeon, the two functions crossed between the geometric mean (12.5 s) and the arithmetic mean (17.5 s) of the two extreme sample durations. The lower rows in Figure 3 show the effects of increasing doses of *d*-amphetamine. The smallest dose of amphetamine (0.1 mg/kg; second row) had no large or systematic effects on the rates of key pecking as a function of sample duration. As in control sessions, rates of key pecking increased as a function of sample duration in the long component and decreased as a function of sample duration in the short component. Increasing doses of amphetamine increased lower rates of key pecking and decreased higher rates of key pecking for each pigeon (i.e., the functions relating rate of key pecking to sample duration flattened). The point at which the long and short functions crossed, however, did not change systematically across pigeons. The PSE did not appear to change for P78, shifted to the left for P40, and shifted to the right for P10 and P53.

Figure 4 allows assessment of the rate-dependent effects of amphetamine on key pecking by expressing the data from Figure 3 in another format. Mean rates for each sample duration following *d*-amphetamine administration were divided by control rates for those sample durations for each dose of *d*-amphetamine for each component separately for each pigeon. The resulting number was then multiplied by 100 and plotted on logarithmic axes as a function of the mean control rate during the corresponding sample duration. Rates were largely unaffected by the administration of 0.1 mg/kg *d*-amphetamine (top row). The next highest doses (0.3 and 1.0 mg/kg) elevated low rates somewhat, but usually had little effect on higher rates. At the highest dose (3.0 mg/kg), higher rates were decreased for all birds, with lower rates remaining elevated for 3 of 4 birds. In other words, the effect of *d*-amphetamine on key

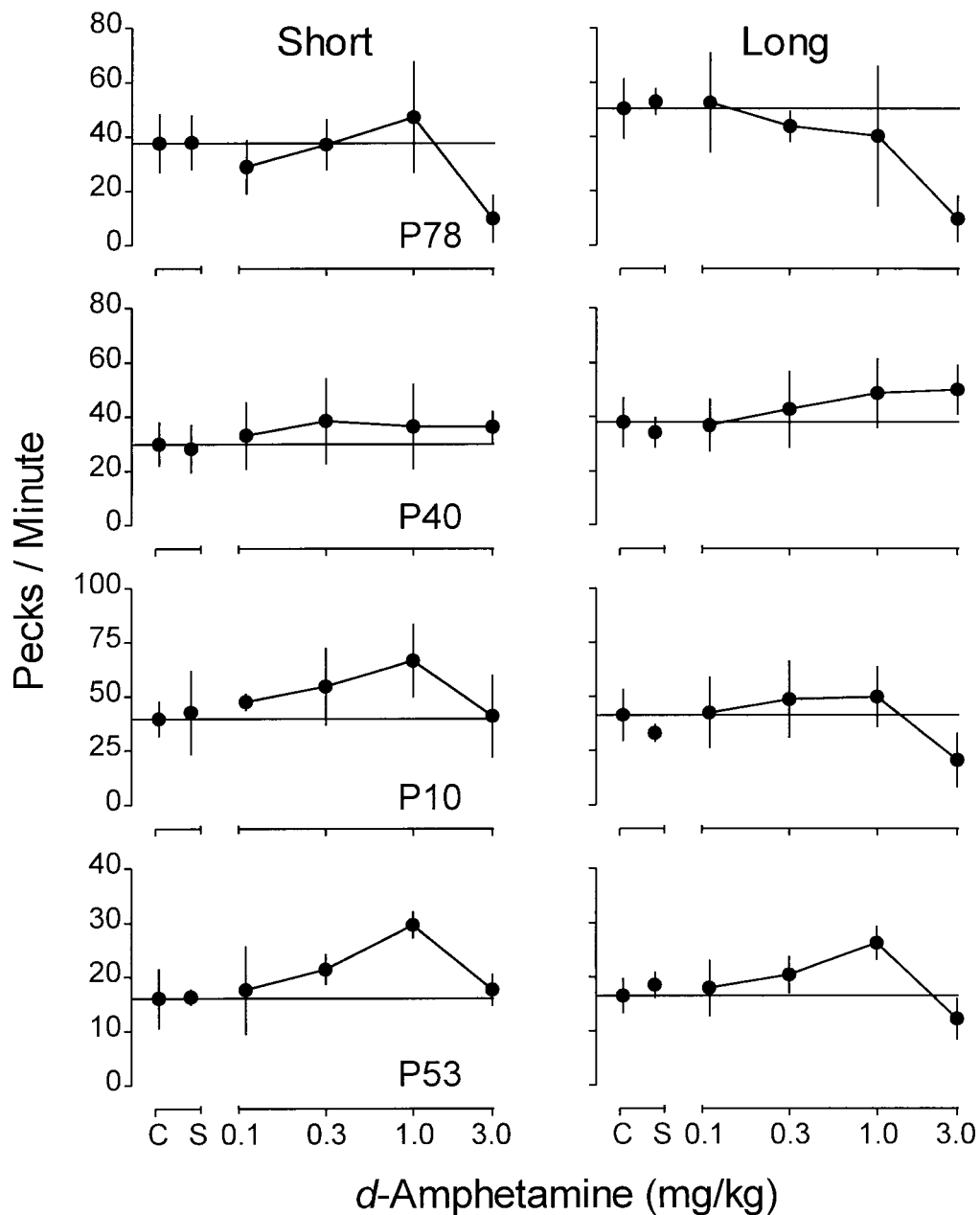


Fig. 2. Effects of injections of *d*-amphetamine on the mean rate of key pecking per session in the short component (left panels) and the long component (right panels) for each pigeon. Unconnected points show means for all control (C) and saline (S) sessions. Lines connect points showing mean rates for four determinations of the effects of each dose. Vertical bars indicate one standard deviation around means. In some cases the variability around a point is encompassed by the point. The horizontal line originating from the y axis shows the control mean for comparison purposes. For clarity, y axes are scaled for individual pigeons.

pecking depended on the usual rate of key pecking. In general, the effects were similar for rates in the long component and rates in the short component. Amphetamine in-

creased the rate of key pecking that usually occurred at a low rate, whereas higher doses of *d*-amphetamine decreased key pecking that usually occurred at a higher rate.

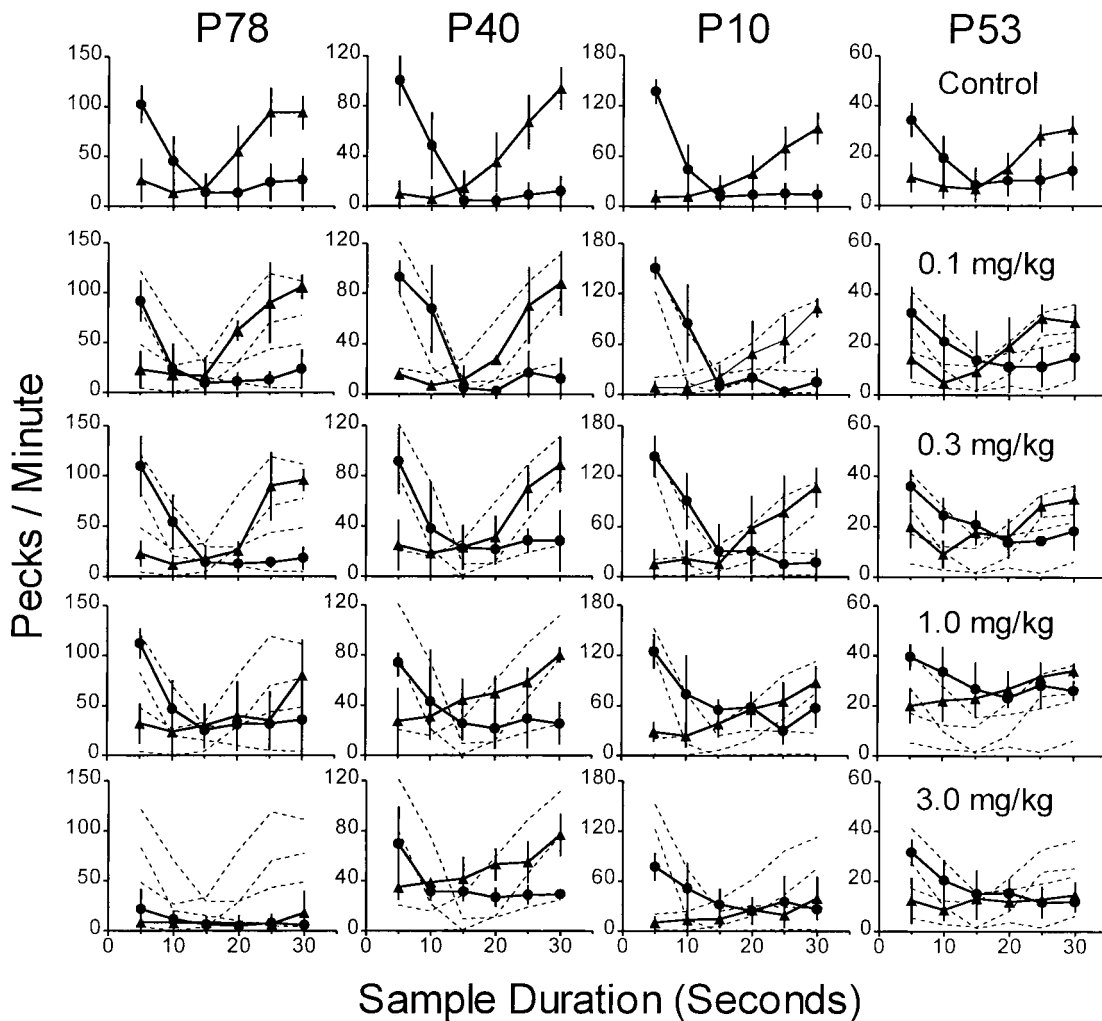


Fig. 3. Mean rates of key pecking as a function of sample duration in the long component (green key; triangles) and short component (blue key; circles) during 16 control sessions (top row) and following administration of four determinations of the effects of increasing doses of amphetamine (descending rows) for each pigeon (columns). Vertical bars indicate one standard deviation around means. For reference, dashed lines indicate one standard deviation above and below means from control sessions preceding injections (control means shown top row). For clarity, y axes are scaled for individual pigeons.

Figure 5 compares mean rates of key pecking per session on S+ trials only (i.e., trials on which food was potentially available; 5 s for the short component and 30 s for the long component) for trials during which food was delivered and for trials during which food was not delivered. There were fewer trials without food per session, and data from these trials were in some cases more variable than data from trials with food. For both the long and short components, during control and saline sessions rates of key pecking were similar for

trials with food and trials without food. Rates during trials without food tended to decrease at lower doses of amphetamine than rates during trials with food. In some instances there was substantial variability across replications, however, and the effect was in some cases small or inconsistent across pigeons or doses.

DISCUSSION

In the absence of *d*-amphetamine, behavior showed evidence of discriminative control by time. The rate of key pecking as a function

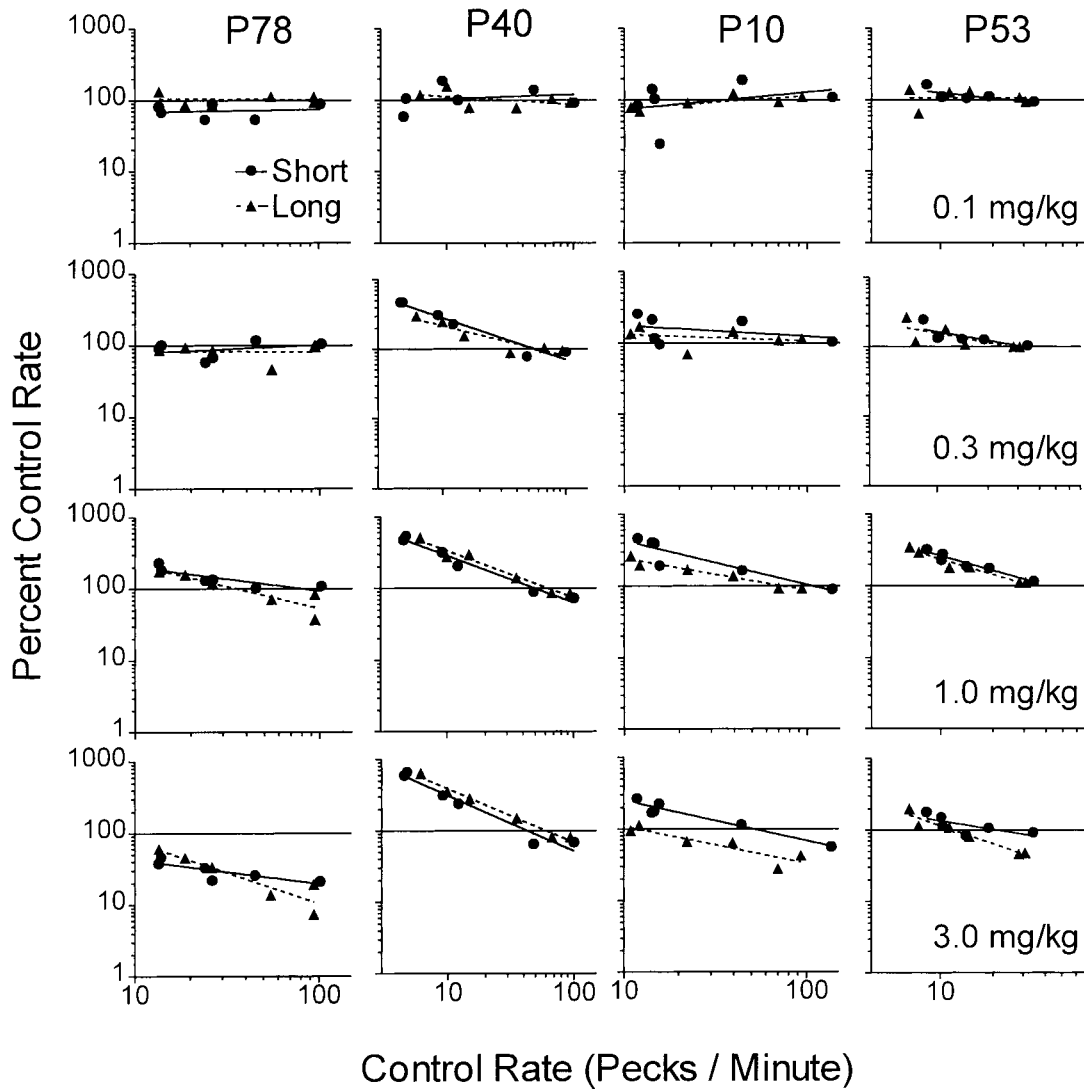


Fig. 4. Response rates during each sample duration following administration of *d*-amphetamine for each of 4 pigeons (columns) at four doses of amphetamine (rows). The *x* axis shows mean control rate during each sample duration, and the *y* axis shows percentage of that control rate during the same sample duration following amphetamine administration. The horizontal line indicates 100% of control rate (i.e., no change relative to control). Points above the line represent rate increases and points below the line represent rate decreases, relative to control rates. Circles depict rates during the short component, and triangles depict rates during the long component. Linear regression lines were fit by the method of least squares. For clarity, *x* axes are scaled for individual pigeons. See text for details of calculations.

of sample duration in control sessions (Figure 3, top row) showed evidence of temporal discrimination: Rates increased as a function of sample duration when food was available following the longest sample, and rates decreased as a function of sample duration when food was available following the shortest sample. These results are similar to those

obtained by Reynolds and Catania (1962) when the key was lit only one color and food was available following either the longest or shortest sample duration across conditions. Furthermore, in the present experiment the functions relating rates of key pecking to sample duration for the long and short components crossed between the geometric and

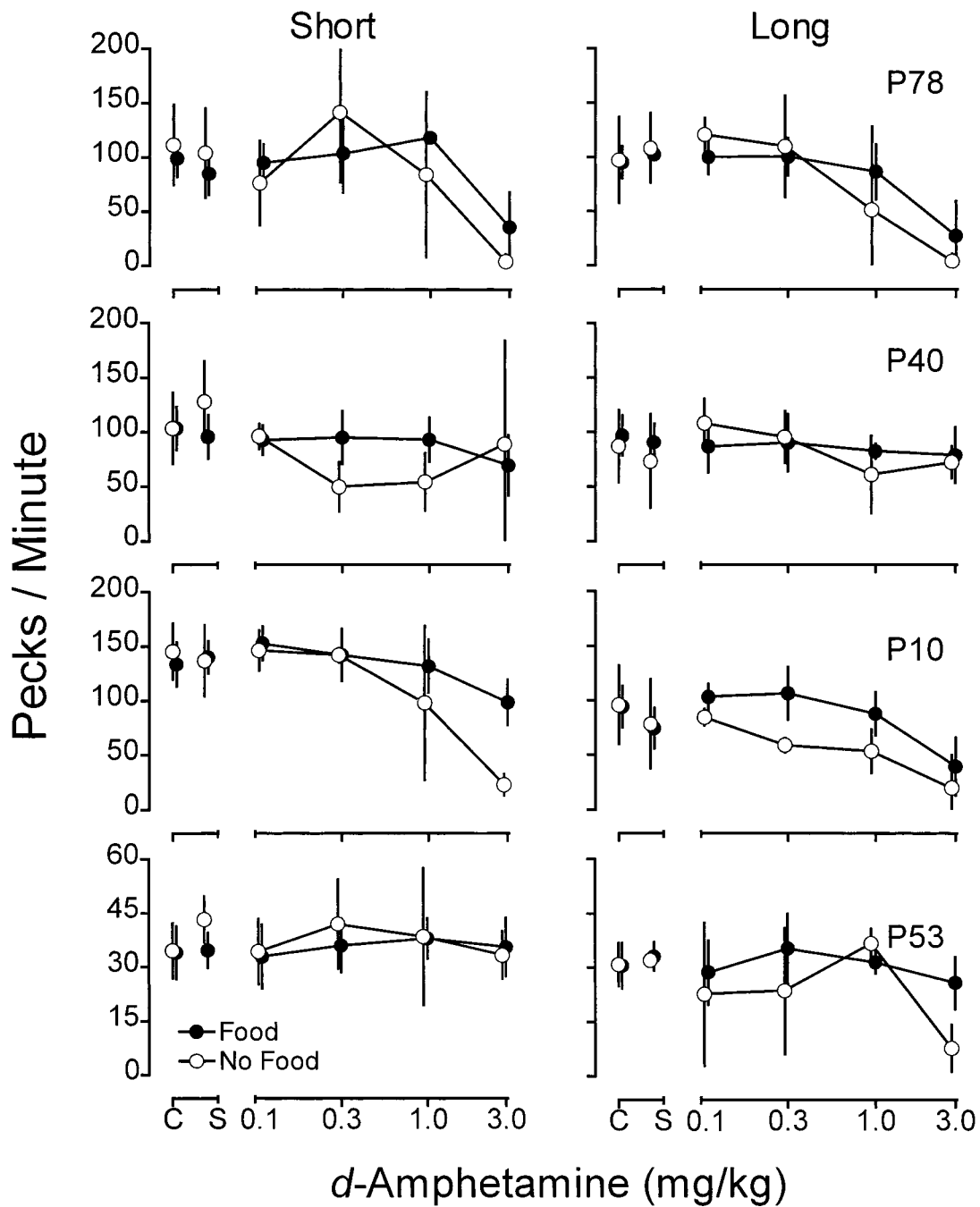


Fig. 5. Effects of injections of *d*-amphetamine on mean rates of key pecking for trials with food (filled circles) and trials without food (open circles) following the 5-s sample (short; left column) or 30-s sample (long; right column) for each pigeon. For clarity, y axes are scaled for individual pigeons and points are offset slightly. Other details are as in Figure 2.

arithmetic means of the temporal endpoints. This result indicates that the PSE was between the arithmetic and geometric mean, as found previously in different temporal discrimination procedures (e.g., Stubbs, 1968; see also Killeen, Fetterman, & Bizo, 1997).

Two lines of evidence suggest that the discrimination was in fact based on the sample duration, not on the presence or absence of food. First, under control conditions, the functions relating rate of key pecking to sample duration were graded: Rates increased gradually as a function of sample duration in the green component and decreased gradually as a function of sample duration in the blue component (Figure 3, top row). If the discrimination were based on the presence or absence of food, one would expect a step function: low equal rates after all S⁻ stimuli (i.e., stimuli following which food was never available) and high rates after S⁺ stimuli. Furthermore, under control conditions, rates of key pecking on S⁺ trials did not differ systematically on trials with food and trials without food (Figure 5).

The effects of *d*-amphetamine on overall response rates (Figure 2) were similar to those obtained previously for behavior maintained by interval schedules of positive reinforcement: At lower doses, amphetamine had no effect or increased the overall rate of key pecking, but at higher doses, amphetamine generally decreased the overall rate of key pecking (see van Haaren, 1993). Amphetamine did not, however, produce the shifts in the timing functions that are predicted by the neuropharmacological model of timing (Meck, 1996). Amphetamine increases levels of dopamine and should therefore shift the timing functions to the left, indicating overestimation of elapsed time. In the present experiment, however, amphetamine more commonly increased lower rates of key pecking and decreased higher rates of key pecking (Figure 4), thus flattening the timing functions rather than shifting them horizontally (Figure 3). The results thus indicate a general decrease in the control of behavior by time, rather than overestimation of the passage of time. Examining the effects of *d*-amphetamine on rates of key pecking during S⁺ trials only (Figure 5), to the extent that rates of key pecking differed on trials with food and trials without food, rates tended to be pre-

served at higher doses on trials with food. Thus, the flattening of the functions relating rates of key pecking to sample duration cannot be due to the presence of food on S⁺ trials, because the timing functions would tend to be even flatter if trials with food were excluded.

The present results are therefore inconsistent with the neuropharmacological model of timing proposed by Meck (1996). One possibility, however, is that the results do not reflect a disruption in temporal discrimination, but rather a disruption in stimulus control by the color of the response key. Temporal control could have been maintained, or changed in a way consistent with the neuropharmacological model, but once the sample ended, the bird could then not discriminate whether the key was lit blue or green. A failure to discriminate the color of the response key could plausibly produce a general flattening of the function relating the rate of key pecking to sample duration. Experiment 2 was conducted to examine this interpretation.

EXPERIMENT 2

To investigate the possibility that the results obtained in Experiment 1 reflected a breakdown in stimulus control by the color of the response key, rather than purely changes in temporal discrimination, this experiment arranged the components across conditions rather than within sessions. In one condition, the response key was lit red and pecks could be reinforced only after the shortest sample duration (5 s). In another condition, the response key was lit white and pecks could be reinforced only after the longest sample duration (30 s). This procedure therefore did not require the color of the response key to be discriminated within sessions, and any changes in response patterning could be more plausibly attributed to disruption of temporal control. Furthermore, because the lowest dose of *d*-amphetamine tested in Experiment 1 had no effect on behavior, the dose range was shifted to slightly higher doses.

METHOD

Subjects

The pigeons from Experiment 1 were transferred to the University of New Hamp-

shire to serve in Experiment 2. The pigeons were allowed free access to pelleted pigeon diet for 3 weeks following arrival; free-feeding weights were taken as the weight on the last day of free feeding. Over the course of 2 weeks, access to food was restricted until body weights were 80% of free-feeding levels. The pigeons were then maintained at this weight (± 15 g) through postsession feedings of pelleted pigeon diet as necessary. The absolute body weight for P40 was relatively low, and due to health concerns, after 3 weeks at 80% of free-feeding weight, this pigeon was maintained at 85% of free-feeding weight for the remainder of the experiment. Pigeons received no drugs for 13 to 17.5 weeks prior to tests of *d*-amphetamine in the current experiment. When not in experimental sessions, pigeons were individually housed in a temperature-controlled colony under a 12:12 hr light/dark cycle and were allowed free access to water and digestive grit. Sessions were conducted during the light portion of the cycle.

Apparatus

Four similar BRS/LVE sound-attenuating chambers, constructed of painted metal with aluminum front panels, were used. The chambers measured 35 cm across the front panel, 30.7 cm from the front panel to the back wall, and 35.8 cm from the floor to ceiling. Each of the panels had three plastic response keys that were 2.6 cm in diameter and 24.6 cm from the floor. The center key could be lit from behind with red or white light and required a force of at least 0.10 N to operate. The side keys were dark, and pecks to these keys had no programmed consequences. A lamp (28 V, 1.1 W) mounted 4.4 cm above the center key served as the houselight. A rectangular aperture 9 cm below the center key provided access to a solenoid-operated hopper filled with pelleted pigeon diet. White noise and chamber ventilation fans masked extraneous sounds. Contingencies were programmed and data collected by microcomputers located in an adjacent room with Med Associates interfacing and software.

Procedure

Experimental sessions were conducted daily at approximately the same time. Due to the pigeons' previous history, no key pecking or hopper pretraining was necessary. Reinforce-

ment consisted of 3-s access to the food hopper. During hopper presentations, the aperture was lit with white light, and the houselight and keylight were extinguished. Ten minutes after the pigeons were placed in the darkened chamber, the session began with the lighting of the houselight.

There were two conditions in this experiment. In both conditions, the houselight was turned on for 5, 10, 15, 20, 25, or 30 s (chosen randomly), and then the response key was lit for 30 s. After 30 s, the keylight was turned off and the next trial began with the lighting of the houselight. There were 10 trials with each sample duration, for a total of 60 trials per session. In one condition, the key was lit red and pecks could produce food on the same VI 20-s schedule from Experiment 1 after the 5-s sample. In another condition, the key was lit white and pecks could produce food on the same VI 20-s schedule after the 30-s sample. The time during hopper presentations was not included in the 30-s period of access to the lit key. During the first session of each condition, only the 5-s sample (red) or 30-s sample (white) was presented. Across the next four sessions, the other sample durations were added in ascending (red) or descending (white) order until on the sixth session all sample durations were present. Two pigeons (P10 and P53) completed the condition with the red key and the short S+ first and then the condition with the white key and the long S+. The other pigeons (P78 and P40) experienced the conditions in opposite order (long then short).

Drug Administration

Pigeons experienced at least 40 sessions with the final timing procedure in each condition (short: 40 to 42; long: 40 to 74) prior to administration of *d*-amphetamine. Drug testing generally occurred as in Experiment 1. A range of doses of *d*-amphetamine (0.56, 1.0, 3.0, and 5.6 mg/kg) and its vehicle (0.9% saline) were administered in a mixed order for each pigeon. Amphetamine (Sigma) was dissolved in saline and administered in a volume of 1.0 ml/kg of the body weight at 80% of free-feeding levels (85% for P40). The effects of each dose and the vehicle were determined two or three times.

RESULTS

Figure 6 shows the overall rate of key pecking (i.e., rates averaged across those obtained following all sample durations) as a function of dose of *d*-amphetamine for each pigeon separately for both conditions. Control rates of key pecking were higher in the long condition for 3 of 4 pigeons. The saline vehicle had little systematic effect on rates of key pecking in either condition. Lower doses of amphetamine produced moderate increases in rates of key pecking. Higher doses either did not change rates substantially (P78 and P40 in the long condition) or decreased rates. For P53, and to a lesser extent P78, rates in the short component remained elevated at the highest dose.

The top row of Figure 7 shows temporal discrimination functions during control sessions for each pigeon. In the short condition, in which food was available following the 5-s sample, mean rates of key pecking decreased as a function of sample duration. In the long condition, in which food was available following the 30-s sample, mean rates of key pecking increased as a function of sample duration. The function for P53 was flat at longer sample durations. Compared to the control functions (i.e., those functions obtained in the absence of drugs) from Experiment 1 (Figure 3), in which the long and short components were arranged within sessions, the timing functions were less precise (the point at which the functions crossed was shifted up) when the long and short components were arranged across conditions for each pigeon. For 2 pigeons (P78 and P10), the point at which the functions crossed was similar to that in Experiment 1. For the other 2 pigeons (P40 and P53), the point at which the functions crossed was to the left of that in Experiment 1. There were no systematic differences in the functions obtained for the pigeons that completed the long condition first (P78 and P40) and the functions obtained for the pigeons that completed the short condition first (P10 and P53).

The lower rows of Figure 7 show the temporal discrimination functions following increasing doses of amphetamine. Amphetamine increased lower rates of key pecking and decreased higher rates of key pecking for each pigeon (i.e., the functions relating rate

of key pecking to sample duration flattened). The point at which the long and short functions crossed, however, did not change systematically across pigeons. The PSE shifted consistently to the left for P40 and perhaps for P78, did not change substantially or consistently for P10, and shifted consistently to the right for P53.

Figure 8 allows assessment of the rate-dependent effects of amphetamine on key pecking by expressing the data from Figure 7 in another format, as in Figure 4 in Experiment 1. Mean rates for each sample duration following *d*-amphetamine administration were divided by control rates for those sample durations for each dose of *d*-amphetamine for each condition separately for each pigeon. The resulting number was then multiplied by 100 and plotted on logarithmic axes as a function of the mean control rate during the corresponding sample duration. Lower rates were generally increased by amphetamine, whereas higher rates were generally decreased. The rate increases were more prevalent at lower doses, whereas the rate decreases were more prevalent at higher doses. The effects were generally similar for rates in the long condition and rates in the short condition. The overall higher rates in the long condition shown in Figure 6 are reflected in Figure 8 by the restriction of the range of rates in the long condition compared to the short condition. In summary, *d*-amphetamine generally increased the rate of key pecking that usually occurred at a low rate, and decreased the rate of key pecking that usually occurred at a higher rate.

Figure 9 compares mean rates of key pecking per session on S+ trials only (5 s for the short condition and 30 s for the long condition) for trials during which food was delivered and for trials during which food was not delivered. There were fewer trials without food per session, and data from these trials were in some cases more variable than data from trials with food. For both the long and short conditions, during control and saline sessions rates of key pecking did not differ systematically across pigeons for trials with and without food. For P40, rates during trials without food decreased at lower doses of *d*-amphetamine than rates during trials with food. This effect also occurred to some extent for P78 and P10 in the long condition and for P53 in both con-

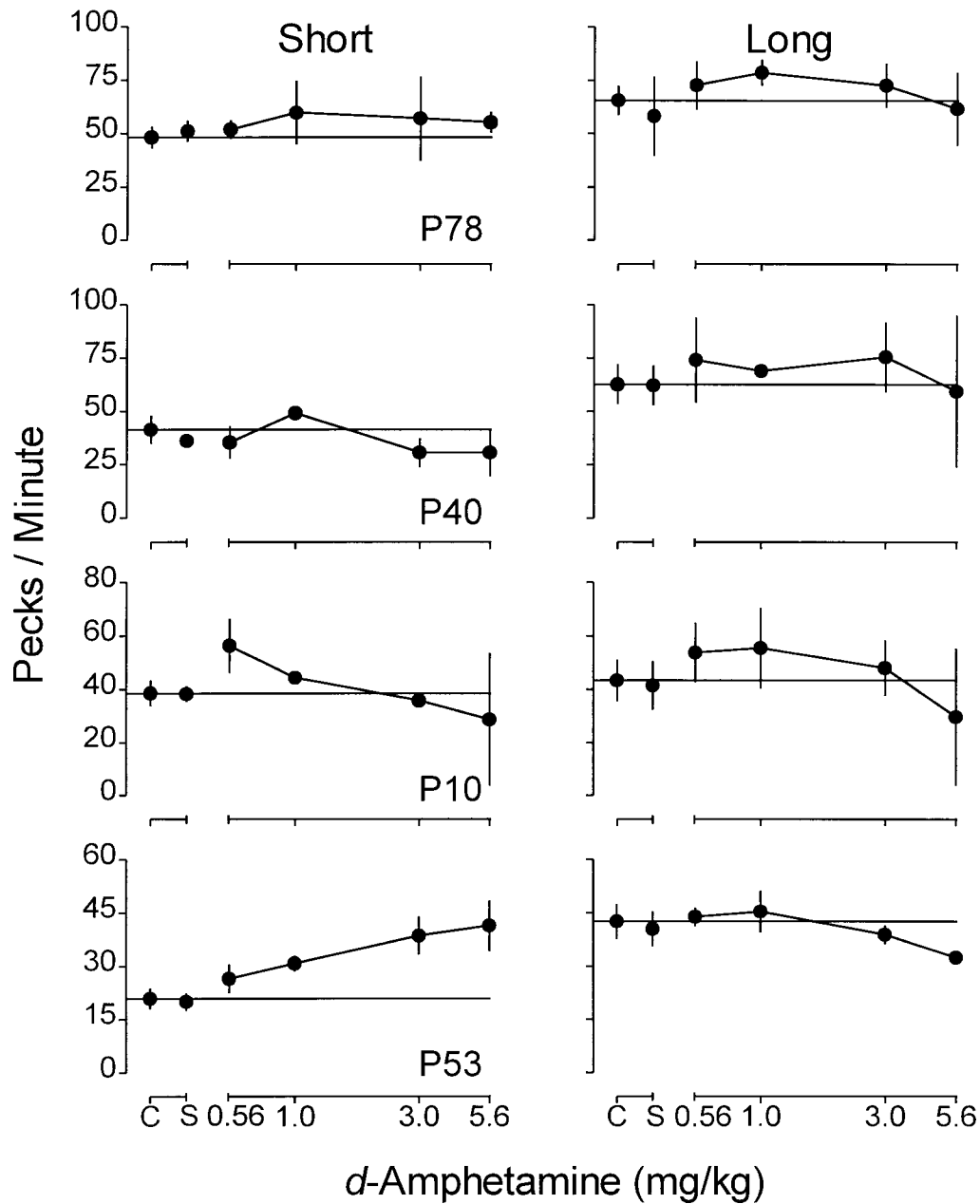


Fig. 6. Effects of injections of *d*-amphetamine on the mean rate of key pecking per session in the short condition (left panels) and the long condition (right panels) for each pigeon. Lines connect points showing mean rates for at least two determinations of the effects of each dose. For clarity, y axes are scaled for individual pigeons. Other details are as in Figure 2.

ditions. In some instances there was substantial variability across replications, however, and the effect was in some cases small or inconsistent across pigeons or doses. For P78 in the short condition, to the extent that *d*-amphetamine produced differential effects, it tended

to decrease rates at lower doses for trials with food.

DISCUSSION

In general, the results of this experiment, in which the key was only one color and food

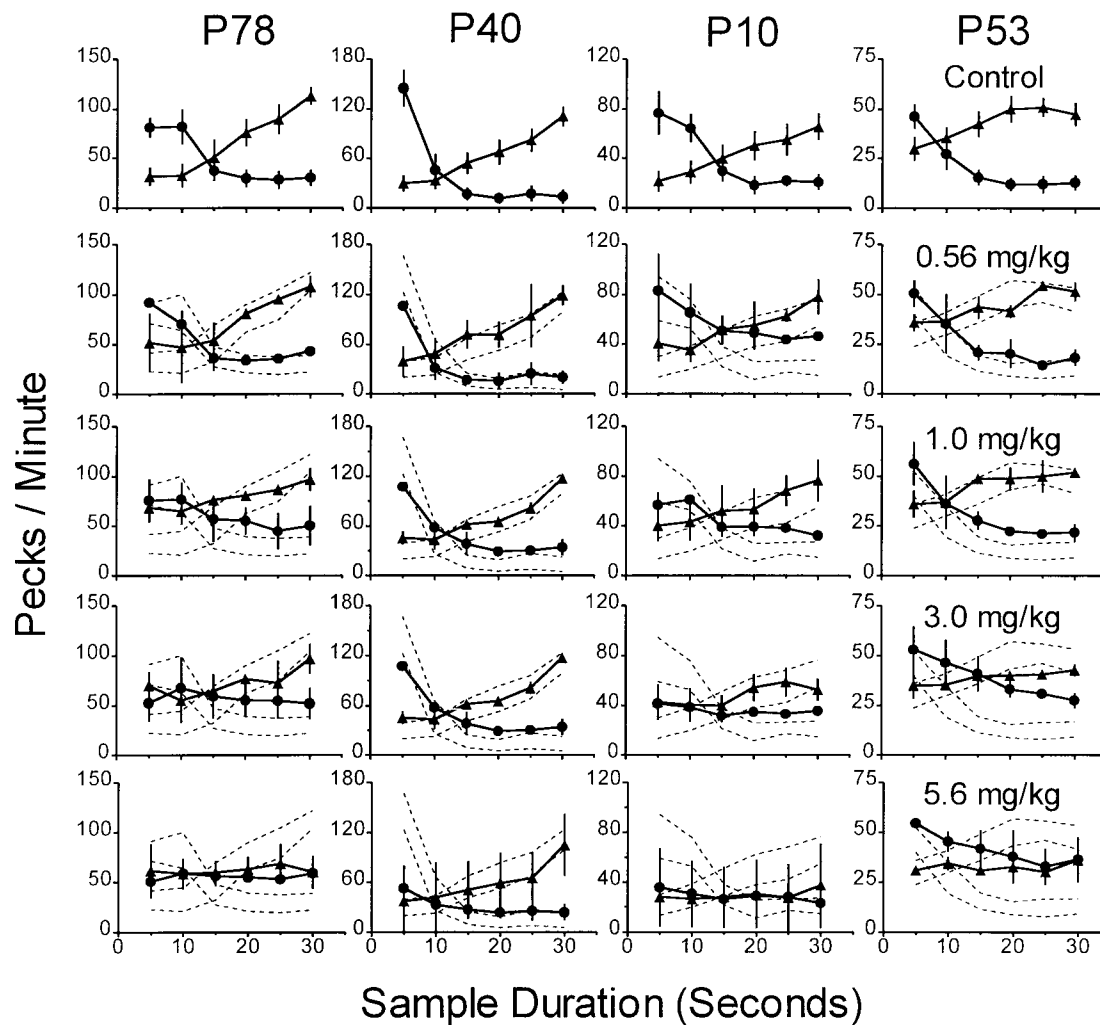


Fig. 7. Mean rates of key pecking as a function of sample duration in the long condition (white key; triangles) and short condition (red key; circles) for control sessions (top row) and following administration of at least two determinations of the effects of increasing doses of amphetamine (descending rows) for each pigeon (columns). In the short condition, control data are from 13 (P78), 10 (P40), and 12 (P10 and P53) sessions. In the long condition, control data are from 13 (P78 and P40), 15 (P10), and 10 (P53) sessions. For clarity, y axes are scaled for individual pigeons. Other details are as in Figure 3.

was available after only one sample duration during sessions, were similar to those of Experiment 1, in which the key was lit two different colors and food was available following either long or short sample durations across trials within sessions. The results of Experiment 1 therefore cannot be solely attributable to disruptions in stimulus control by the color of the response key. As in Experiment 1, the rate of key pecking as a function of sample duration under control conditions (Figure 7, top row) showed evidence of tem-

poral discrimination: Rates increased as a function of sample duration when food was available following the longest sample, and rates decreased as a function of sample duration when food was available following the shortest sample. Furthermore, the results were not attributable to the discrimination of the presence of food for key pecks during a trial rather than discrimination of the duration of samples. The functions relating the rate of key pecking to sample duration were graded (Figure 7, top row), and rates during

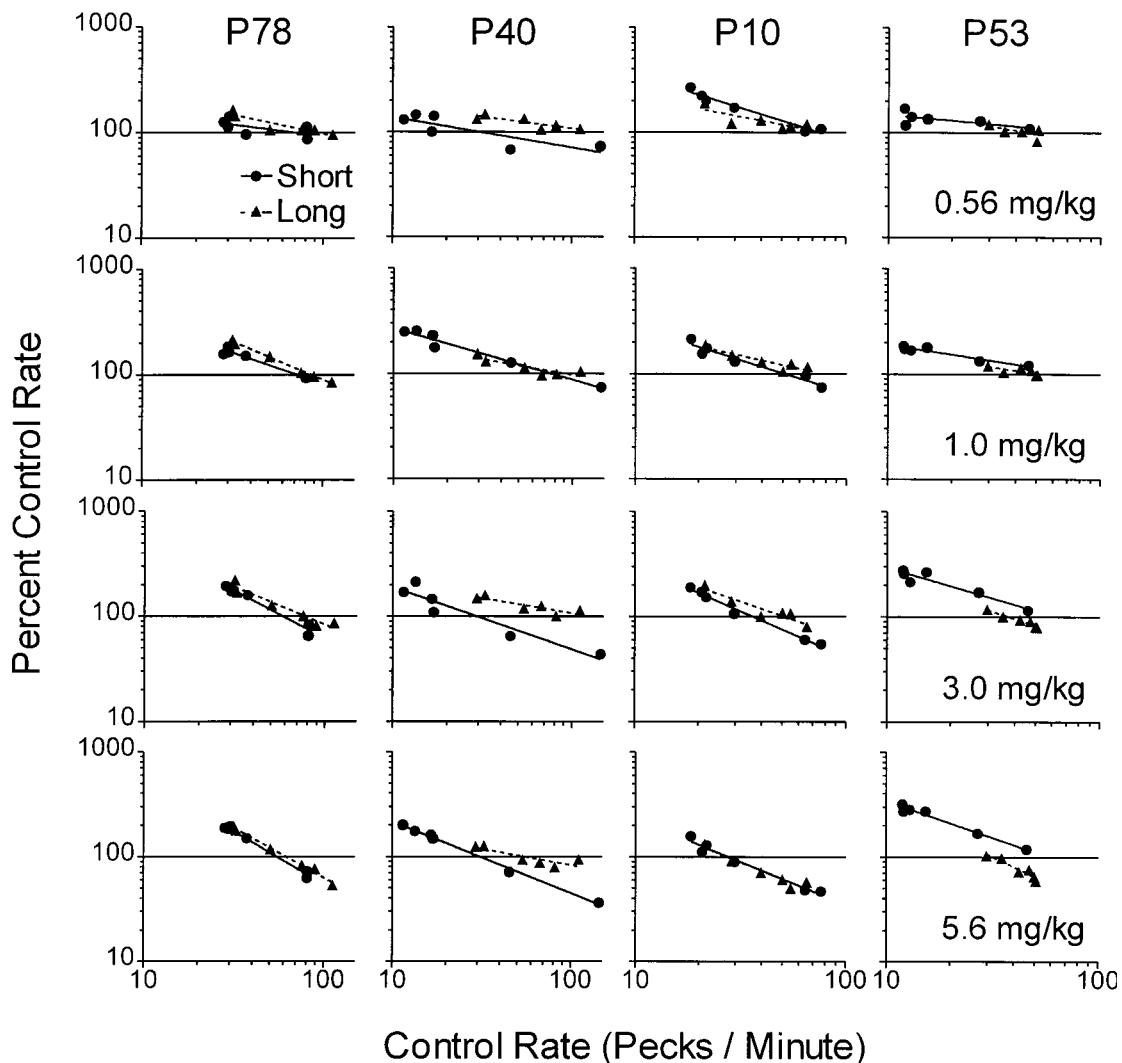


Fig. 8. Response rates during each sample duration following administration of *d*-amphetamine for each of 4 pigeons (columns) at four doses of amphetamine (rows). The x axis shows mean control rate during each sample duration, and the y axis shows percentage of that control rate during the same sample duration following amphetamine administration. The horizontal line indicates 100% of control rate (i.e., no change relative to control). Points above the line represent rate increases, and points below the line represent rate decreases, relative to control rates. Circles depict rates during the short condition, and triangles depict rates during the long condition. Linear regression lines were fit by the method of least squares. See text for details of calculations.

S+ trials did not differ systematically on trials with food and trials without food (Figure 9).

As in Experiment 1, lower doses of amphetamine moderately increased the overall rate of key pecking, and higher doses tended to decrease response rates (Figure 6). Most important, *d*-amphetamine did not produce the shifts in the timing functions that are predicted by the neuropharmacological model of timing (Meck, 1996). Across conditions,

amphetamine increased lower rates of key pecking and decreased higher rates of key pecking (Figure 8), thus flattening the timing functions rather than shifting them horizontally (Figure 7). The results thus indicate a general decrease in the control of behavior by time, rather than overestimation of the passage of time, when a disruption in stimulus control by the color of the response key is eliminated as a possible interpretation.

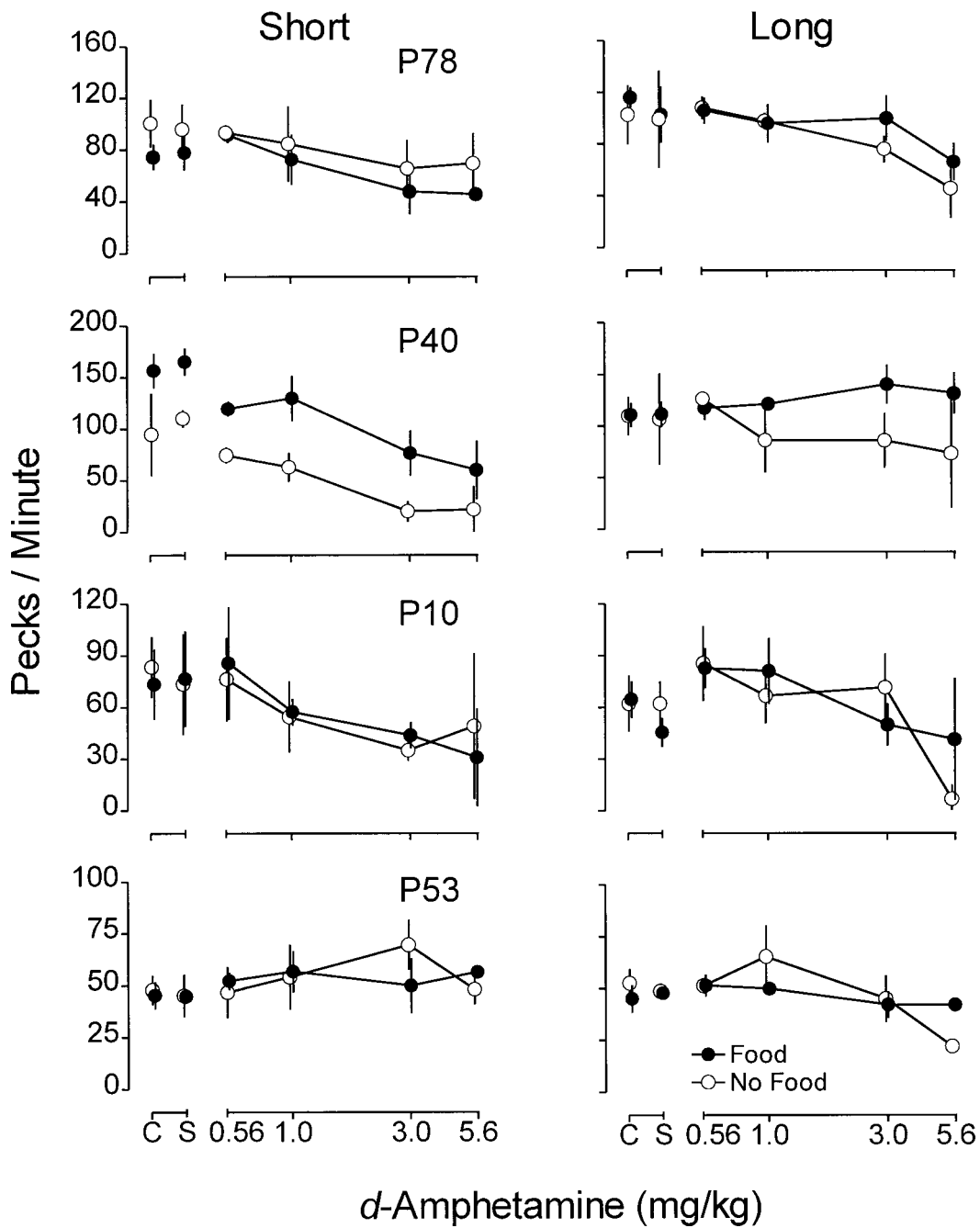


Fig. 9. Effects of injections of *d*-amphetamine on mean rates of key pecking for trials with food (filled circles) and trials without food (open circles) following the 5-s sample (short condition; left column) or 30-s sample (long condition; right column) for each pigeon. For clarity, y axes are scaled for individual pigeons. Other details are as in Figure 5.

GENERAL DISCUSSION

The present experiments used a novel procedure based on that of Reynolds and Catania (1962) to test the predictions of the neuropharmacological model of timing (Meck, 1996) and rate dependency (e.g., Dews & Wenger, 1977). The neuropharmacological model predicts that amphetamine, as a dopamine agonist, should increase the speed of a hypothesized internal clock and should therefore decrease the PSE (shift the timing functions to the left). Rate dependency, on the other hand, predicts no horizontal shifts in the timing functions, but suggests that lower rates of key pecking should increase and higher rates of key pecking should decrease. The results of the present experiments support a rate-dependent interpretation of the effects of *d*-amphetamine on timing.

Although behavior in the present experiments was sensitive to the effects of *d*-amphetamine, one possibility could be that the results obtained are somehow peculiar to this procedure. Manipulations known to affect timing in other procedures could be examined in the present procedure. For example, changing the rate of reinforcement in a situation changes the perception of time (e.g., Bizo & White, 1994). If the rate of reinforcement for pecking on S+ trials were changed in the present procedure, then estimates of the PSE arguably should change as well. Therefore, testing the effects of reinforcement rate could help to answer the question of whether this procedure is sensitive to other manipulations known to affect timing.

There is increasing evidence from other procedures, however, that the neuropharmacological model does not account well for data from multiple experiments on the effects of dopamine agonists on timing (see also Chiang et al., 2000; Stanford & Santi, 1998). For example, although some studies using versions of the interval bisection task (Catania, 1970; Stubbs, 1968) have found effects of dopamine agonists that support the neuropharmacological model (e.g., Maricq & Church, 1983; Maricq et al., 1981; Meck, 1983; Spetch & Treit, 1984), other studies have not (e.g., Chiang et al., 2000; Lejeune et al., 1995; Odum & Schaal, 2000; Rapp & Robbins, 1976; Santi, Weise, & Kuiper, 1995; Stanford & Santi, 1998; Stubbs & Thomas,

1974). Studies with dopamine antagonists using the interval bisection task have found supporting evidence (Maricq & Church, 1983; Meck, 1983, 1986). For the peak interval procedure (Catania, 1970), although some studies with drugs that increase dopamine levels have found results that support the model (e.g., Eckerman, Segbafia, Manning, & Breese, 1987; Frederick & Allen, 1996; Kraemer, Randall, Dose, & Brown, 1997; Maricq et al., 1981), other studies have not (e.g., Bayley, Bentley, & Dawson, 1998; Frederick & Allen, 1996; Knealing & Schaal, 2002). For dopamine antagonists, Frederick and Allen found results inconsistent with the model using the peak procedure.

The discrepancies in the literature on the effects of drugs on timing do not seem to be accounted for by several other factors either. For example, in the studies above with dopamine agonists and antagonists, both supporting and nonsupporting findings were obtained when the compounds were administered with one or more intervening sessions, as well when the compounds were administered for at least three consecutive training sessions. Similarly, in the studies cited in the paragraph above, supporting and nonsupporting evidence was found with drug-naïve and drug-experienced subjects. Finally, the species of the subject also does not appear to account for the discrepancies in the literature. For example, for dopamine agonists tested in the above studies, six studies with rats found supporting evidence, and six studies with rats found nonsupporting evidence. For pigeons, two studies found supporting evidence, and five found nonsupporting evidence.

Relatively fewer studies have been conducted to evaluate the effects of acetylcholine on timing. The neuropharmacological model maintains that drugs and other compounds that increase or decrease acetylcholine levels should produce gradual overestimation and underestimation of time, respectively. Although some studies have found support for the role of acetylcholine in timing (e.g., Meck, 1983; Meck & Angell, 1992; Meck & Church, 1987a, 1987b), a recent study did not (Odum, 2002).

In sum, different findings for the effects of drugs on timing do not appear to be explained by differences in the procedures used

to maintain behavior or by the history or species of the subjects. Perhaps an overlooked procedural difference may be discovered, but even so, the conditions under which drug effects conform to the model are clearly limited. The situation in the literature could be what one would expect if there were no reliable selective effect of drugs on timing. This view should not be interpreted to suggest that the effects of drugs on timing are unreliable or small. In fact, if one reorganizes the results described above for compounds that alter dopamine levels, there is remarkable consistency: All of the above studies either found results consistent with rate dependency (the present experiments; Bayley *et al.*, 1998; Chiang *et al.*, 2000; Eckerman *et al.*, 1987; Knealing & Schaal, 2002; Kraemer *et al.*, 1997; Lejeune *et al.*, 1995; Maricq & Church, 1983; Maricq *et al.*, 1981; Odum & Schaal, 2000; Rapp & Robbins, 1976; Santi *et al.*, 1995; Spetch & Treit, 1984; Stanford & Santi, 1998; Stubbs & Thomas, 1974), discarded data from trials with longer latencies that by the authors' description would render the results consistent with rate dependency (Maricq *et al.*, 1981; Meck, 1983, 1986), or did not report the data necessary to judge (Frederick & Allen, 1996).

To summarize the application of rate dependency to the data from the studies cited in the paragraph above, those using the peak procedure have generally found that lower doses of drugs, particularly those that increase dopamine levels, increase lower response rates. These low rates occur early in the interval, before food is available on FI trials, and later in the interval, after food is available on FI trials. The peaked function relating the rate of response to time in the interval is flatter. With higher doses of drugs, higher rates near the usual time of food availability are decreased, resulting in flattening of the function (e.g., Knealing & Schaal, 2002). For the interval bisection task, which is a discrete-trial procedure, the subject has one opportunity to make a response per trial. There is one response that is likely given short sample durations and another response that is likely given long sample durations. Consistent with rate dependency, drugs, particularly dopamine agonists, reduce the likelihood of the high-probability response and increase the likelihood of the low-probability

response. The result is flattening of the psychophysical function relating the probability of a long response to sample duration (e.g., Stubbs & Thomas, 1974).

The empirical generalization of rate dependency appears to account well for results from a variety of studies on the effects of drugs on timing. Drugs consistently produce large decreases in the control of behavior by time, but the changes often do not appear as selective horizontal shifts in the psychophysical functions. Rather, the most robust and consistent effect is that drugs flatten psychophysical functions. Gibbon and colleagues have also noted the reliable flattening of functions (Gibbon, Malapani, Dale, & Gallistel, 1997). Not only does rate dependency provide a reasonably accurate description of the present results and those from many other timing experiments, it also provides an account of results from many other experiments using a wide variety of procedures (see, e.g., Dews & Wenger, 1977; Kelleher & Morse, 1968; McKearney & Barrett, 1978; see Odum & Schaal, 1999, 2000, for discussion).

Dews (1958) is generally credited with the first description of rate-dependent effects. He maintained the behavior of pigeons on a variety of schedules of food delivery and found that methamphetamine increased the rate of behavior that customarily occurred at a low rate and decreased the rate of behavior that customarily occurred at a high rate. Intriguingly, Dews noted that the changes in responding maintained by an FI 15-min schedule produced by methamphetamine could be described as "making time seem to pass more quickly" (p. 146). He cautioned against this type of interpretation, however, arguing that it did not add to an understanding of the drug effect, and that it could in fact "interfere with recognition of a relatively simple and consistent effect of the drug" (p. 146).

Indeed, since Dews' (1958) initial description, a variety of drugs have been found to produce rate-dependent effects in a variety of situations. Rate dependency also has been found at several level of analysis, including that of local rates of response for individual subjects responding on a particular schedule of reinforcement. Rate dependency also has been found at the level of overall rates for individual subjects responding on different schedules of reinforcement, and at the level

of overall rates for different subjects responding under either the same or different schedules of reinforcement. There are, however, some exceptions to rate dependency (see, e.g., McKearney, 1981). In addition, rate dependency is most defensibly viewed as an empirical generalization (see Dews, 1981), and thus does not provide an explanatory behavioral mechanism of drug action (see Branch, 1984). That is, rate dependency describes a correlation between baseline response rate and drug effects, but does not describe why or how those different effects come about. On the other hand, the pharmacological model (Meck, 1996) attempts to provide an explanatory mechanism for the effects of drugs on timing, but it does not appear to account for a substantial portion of the existing data. The challenge remains to find a viable mechanism of action for this empirical generalization.

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