

THE EFFECTS OF MORPHINE ON THE PRODUCTION AND DISCRIMINATION OF INTERRESPONSE TIMES

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Recent experiments suggest that the effects of drugs of abuse on the discrimination of the passage of time may differ for experimenter-imposed and subject-produced events. The current experiment examined this suggestion by determining the effects of morphine on the discrimination of interresponse times (IRTs). Pigeons pecked a center key on a random-interval 20-s schedule of matching-to-sample trials. Once the interval had timed out, a choice trial randomly followed either a short (2- to 3-s) or long (6- to 9-s) IRT on the center key. Pecking the side key lit one color produced food after a short IRT, and pecking the side key lit the other color produced food after a long IRT. Two experimental phases differed in the functional role of the different key colors. Under control conditions, the IRT distributions had two modes, one at the lower bound of the short category and a smaller one at the lower bound of the long category. Pigeons accurately categorized the duration of the IRTs: One key color was pecked following short IRTs and the other key color was pecked following long IRTs. Morphine flattened the IRT distribution and reduced the accuracy of categorizing IRTs. Categorization of long IRTs was particularly disrupted. Morphine did not produce overestimation of time as assessed by the production or categorization of IRTs. These results are similar to those obtained previously for the effects of morphine on the discrimination of the duration of experimenter-imposed events.

Key words: morphine, timing, temporal discrimination, interresponse time, key peck, pigeons

Time is a fundamental variable in the experimental analysis of behavior. One category of temporally based schedules is a response-differentiating procedure, in which only responses with certain temporal spacing or patterning are reinforced (Catania, 1970). Another category of temporally based schedules is a temporal discrimination procedure, in which the temporal spacing or patterning of events indicates which of two or more responses will be reinforced (Catania, 1970). Together, these different types of temporal control are known as “timing” (Killeen, Fetterman, & Bizo, 1997).

Accurate timing is important for many everyday activities. Furthermore, distortions in perceived time have been noted in people with a variety of disorders, including chronic drug abuse (e.g., Petry, Bickel, & Arnett,

1998), attention-deficit/hyperactivity disorder (e.g., Toplak, Rucklidge, Hetherington, John, & Tannock, 2003), Parkinson’s disease (e.g., Malapani, Deweer, & Gibbon, 2002), and schizophrenia (e.g., Rammsayer, 1990). Thus understanding the neurological and environmental underpinnings of timing could have important implications and benefits (see Hinton & Meck, 1997). Accordingly, much recent interest has been focused on the effects of drugs of abuse and other compounds on timing (e.g., Meck, 1996).

There are a number of unresolved discrepancies in the literature on the effects of drugs on timing, however, which make general statements about the neuropharmacology of timing difficult (see e.g., Chiang et al., 2000; Odum, 2002; Odum, Lieving, & Schaal, 2002). For example, Chiang et al. found that *d*-amphetamine had different effects on behavior maintained by different timing procedures. In one procedure, the free operant psychophysical procedure (Stubbs, 1976), responses are intermittently reinforced on one of two operanda (e.g., the left lever) on a variable-interval schedule for the first half of a trial, then responses are reinforced on the second operandum (e.g., the right lever) for the last half of a trial. The psychophysical function describing the relation between the

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percentage of responses on the second operandum and the amount of time that has passed in the trial is taken as the measure of timing. Chiang et al. found that with this procedure, *d*-amphetamine flattened the psychophysical function relating responses to time and displaced it to the left. This result is interpreted as overestimation of time.

With the other procedure, however, *d*-amphetamine had a different effect. In the interval bisection procedure (Catania, 1970), a stimulus (e.g., a houselight) is presented for a particular duration. Responding on one operandum (e.g., the left lever) is reinforced if the duration was relatively short, and responding on the second operandum (e.g., the right lever) is reinforced if the duration was relatively long. The psychophysical function describing the relation between the percentage of responses on the second operandum and the duration of the stimulus is taken as the measure of timing. Chiang et al. (2000) found that with this procedure, *d*-amphetamine flattened the psychophysical function but did not shift it to the left. This result is interpreted as generalized disruption of timing without a particular distortion in perception (i.e., no overestimation or underestimation of time).

Based on these different outcomes for the effects of amphetamine on temporal discrimination, Chiang et al. (2000) suggested that some of the discrepancies in the literature on the effects of drugs of abuse on timing might be related to different procedures used. Specifically, they suggested that the effects of drugs of abuse on behavior might differ for the discrimination of experimenter-imposed events versus discriminations based on some aspect of the subjects' behavior. The present experiment examines this possibility.

In a previous experiment, Odum and Schaal (2000) investigated the effects of morphine, an opiate drug active primarily at μ receptors (see e.g., Jaffe & Martin, 1990), on the discrimination by pigeons of the duration of a key light in the context of a fixed-interval schedule. The center key was lit for either a relatively short or a long period of time (the sample), after which the center key was extinguished and the side keys were lit, each with a different color (the comparisons). A peck to the key lit one color produced food after relatively short samples, whereas a peck to the

key lit the other color produced food after relatively long samples. In the absence of morphine, choice of the comparison was well differentiated based on sample duration. The psychophysical function relating the proportion of pecks to the key color that corresponded to long samples ("long" choices) showed that few choices were long following short samples, but most choices were long following long samples. Morphine dose-dependently flattened the psychophysical timing function. An increasing proportion of long choices followed short samples, and a decreasing proportion of long choices followed long samples. The proportion of long choices was somewhat more disrupted following long samples, however. Because short samples were still categorized mainly as short, and long samples were also often categorized as short, this type of result is interpreted as underestimation of the passage of time (e.g., Meck, 1996).

In Odum and Schaal (2000), the stimulus to be discriminated was an external stimulus, the duration of a key light. The present study was undertaken to determine whether the results would differ if the stimulus to be discriminated were some temporal aspect of the subjects' behavior. We used a procedure developed by Shimp (1981, 1983) in which pigeons categorize the duration of their most recent interresponse times (IRTs). Short or long IRTs on the center key intermittently produced choice trials on the side keys. Pecks to the side key that corresponded to the most recent IRT produced food. If the effects of drugs of abuse differ for discrimination of subject-produced and experimenter-imposed events, then our results should differ from those obtained by Odum and Schaal (2000). We were also interested to determine whether morphine would have different effects on temporal response differentiation (IRT production) and temporal discrimination (accuracy of categorizing IRTs).

METHOD

Subjects

Three adult White Carneau pigeons served as subjects in Condition 1. A 4th pigeon died during initial training; data from this pigeon are not included. All pigeons had previous

histories with a variety of operant procedures. In addition, P53 had an extensive history of acute exposure to cocaine, morphine, and amphetamine. In Condition 2, the 3 pigeons from Condition 1 and 1 additional pigeon (P66) were used. Pigeon 66 had previous experience with a variety of operant procedures and no prior drug history. The pigeons were maintained at 80% (\pm 15 g) of free-feeding weights by postsession feeding as needed. Between sessions, pigeons were individually housed in the University of New Hampshire's temperature controlled colony under a 12:12 hr light/dark cycle and had free access to water and digestive grit.

Apparatus

Four BRS/LVE sound-attenuating chambers were used. Chambers were constructed of painted metal with aluminum front panels. The chambers measured 35 cm across, 30.7 cm deep, and 35.8 cm high. Each front panel had three translucent plastic keys that could be lit from behind with green, white, or red light and required a force of at least 0.10 N to record a response. Keys were 2.6 cm in diameter and 24.6 cm from the floor. A lamp (28 V, 1.1 W) mounted 4.4 cm above the center key served as a houselight. A rectangular opening 9 cm below the center key provided access to a solenoid-operated hopper filled with pelleted pigeon chow. During hopper presentations, the opening was lit with white light and the houselight and keylights were extinguished. White noise and chamber ventilation fans masked extraneous noise. Contingencies were programmed and data collected by a microcomputer located in an adjacent room using Med Associates® interfacing and software.

Procedure

Experimental sessions occurred 5 to 7 days a week at approximately the same time each day. Because of the pigeons' previous experimental history, no hopper or keypeck training was necessary. To allow time for drug absorption during selected sessions, all sessions began with a 10-min chamber blackout. Following the blackout, the houselight and center key were lit to begin the session.

The procedure was based on one developed by Shimp (1981) in which pigeons categorized the duration of their IRTs. Pigeons

made pecks to a center key. The amount of time between pecks (the IRT) was recorded. For the purposes of this experiment, IRTs between 2 and 3 s were classified as short and IRTs between 6 and 9 s were classified as long. These durations were chosen because Shimp (1983) found they produced differentiated IRT distributions and similar categorization accuracy for the short and long categories. A random-interval (RI) 20-s schedule was in effect on the center key. This schedule was programmed by arranging a choice trial with a probability of .0375 every 0.75 s. During the RI, pecks to the center key had no programmed consequences. When the RI timed out, the computer randomly selected whether a short or long IRT would result in a choice trial with the requirement that an equal number of trials follow short and long IRTs during each session. When the chosen IRT was produced, a choice trial began.

During choice trials, the center keylight was extinguished and the side keys were lit different colors. The location of each color (left or right key) varied randomly from trial to trial. Pecks made to the key that corresponded to the previously emitted IRT resulted in 3-s access to food. A peck to the other key resulted in a 3-s blackout. Following food or blackout, the center key was lit and the RI schedule again operated on that key. In Condition 1, the center key was lit white during the RI schedule. During choice trials, the side keys were lit green and red. For P76 and P53, during a trial following a short IRT, a peck to the green key resulted in food and a peck to the red key resulted in blackout. During a trial following a long IRT, a peck to the red key resulted in food and a peck to the green key resulted in a blackout. This color assignment was reversed for P84. In Condition 2, the procedure was the same except that the functional role of the particular key colors was changed. During the RI schedule, the key was lit red for all pigeons. During choice trials, the side keys were lit green and white. The key colors corresponding to short and long IRTs for P76 and P53 were green and white, respectively. For P84 and P66, the colors corresponding to short and long IRTs were white and green, respectively. For both conditions, daily sessions ended after 48 choice trials or 60 min, whichever occurred

Table 1

Mean responses per minute during the RI and mean accuracy for short and long interresponse time categories during control sessions for all pigeons. The average number of trials completed after 5.6 mg/kg morphine is also shown. Numbers in parentheses are standard deviations of the mean.

Condition	Pigeon	Responses per minute	IRT category	Control accuracy (%)	Trials completed (5.6 mg/kg)
1	53	19.2 (1.6)	Short	92.3 (6.4)	36.0 (24.0)
			Long	92.5 (4.9)	
	76	23.6 (2.2)	Short	96.5 (2.9)	23.8 (22.8)
			Long	90.4 (6.1)	
	84	15.7 (1.5)	Short	80.2 (6.2)	39.3 (17.5)
			Long	86.7 (7.3)	
2	53	15.9 (1.6)	Short	90.3 (6.4)	15.0 (22.4)
			Long	90.3 (5.5)	
	66	14.3 (2.2)	Short	95.8 (4.8)	32.0 (16.5)
			Long	88.3 (7.3)	
	76	16.8 (1.8)	Short	84.2 (6.5)	48.0 (0.0)
			Long	90.4 (5.4)	
	84	15.6 (0.8)	Short	88.4 (7.7)	30.7 (26.3)
			Long	88.4 (5.0)	

first. Sessions typically ended after 48 trials in about 45 min (including the 10-min blackout at the beginning of each session).

Correction procedure. Early during training, if matching accuracy was low because of a pronounced color or side bias, a correction procedure was instated (cf. Shimp, 1981). In this procedure, a peck to the incorrect key during a choice trial was followed by the darkening of the side keys for 3 s. The side keys were then relit with the same colors in the same positions. This process continued until a correct response produced food and ended the choice trial. All pigeons experienced the correction procedure at some point during initial training.

Morphine tests. Drug testing began for individual pigeons when the relative frequency of IRTs falling into 0.25 s bins and matching accuracy were stable and asymptotic (without any evident trend or unusual variability) as judged by visual inspection over the last 10 sessions. In addition, matching accuracy for both the long and short categories was required to be at least 80%. Performance met these criteria within 78 to 143 sessions (Condition 1), and 57 to 66 sessions (Condition 2) across pigeons.

Morphine sulfate (Sigma) was dissolved in 0.9% saline and administered in a volume of 1.0 ml/kg of the 80% free-feeding body weight. Morphine and vehicle were administered via intramuscular injections into the

breast of the pigeon immediately before it was placed in the experimental chamber. In order to accustom the pigeons to the injection procedure, they were given a preliminary injection of saline. Results of this injection were excluded from the analyses.

Following the preliminary injections, morphine and vehicle were given in the following order: 1.0 mg/kg, 3.0 mg/kg, 0.56 mg/kg, 5.6 mg/kg, and saline. Tests were separated by at least three consecutive baseline sessions not preceded by an injection. The effects of saline and each drug dose were determined in the order stated above at least three and a maximum of four times for both Condition 1 and Condition 2. This dosing regimen did not produce tolerance to the effects of morphine (i.e., the effects did not differ systematically across successive determinations).

RESULTS

The IRT discrimination procedure generated a moderate rate of key pecking during the RI schedule on the center key. Table 1 shows mean rates of key pecking during the RI from control sessions for each pigeon in each condition. Morphine did not substantially alter response rates except after 5.6 mg/kg morphine for some pigeons. Response rates on the center key (with standard deviations given in parentheses) in those cases were as follows: P76, Condition 1, 12.2 (8.6);

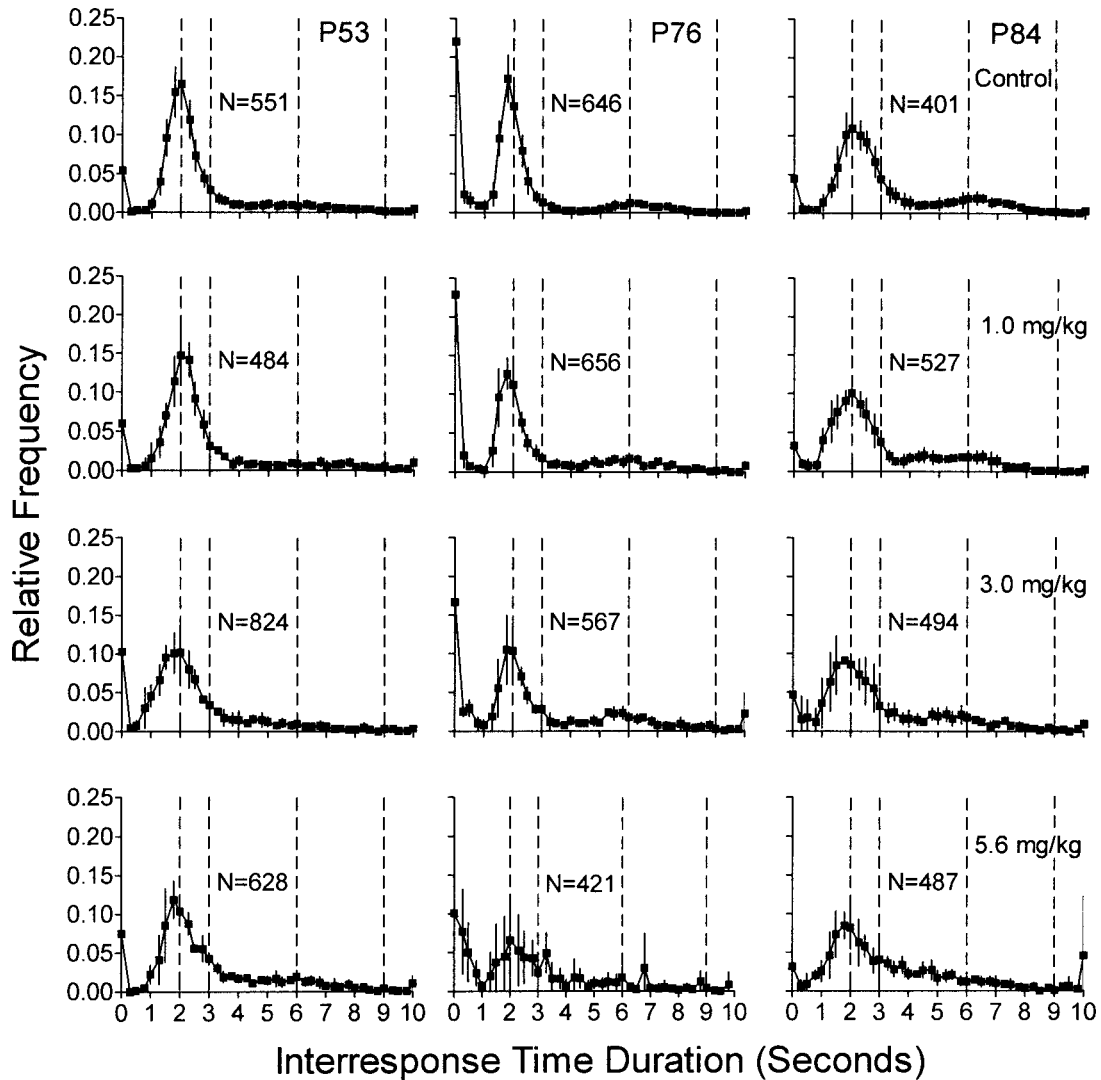


Fig. 1. Mean relative frequencies of interresponse times as a function of interresponse time duration in 0.25-s bins during control sessions (top row) and across doses of morphine (lower rows) for each pigeon during Condition 1. Dotted vertical lines indicate the boundaries of the short and long categories. Vertical bars represent one standard deviation above and below the mean. In some cases, the variability around a point is obscured by the point. The mean number of IRTs from which each distribution is constructed is shown in each panel.

P53, Condition 2, 11.2 (8.7), P66, Condition 2, 11.5 (5.6), and P84, Condition 2, 13.2 (2.0). Pigeons completed all 48 trials in control sessions and in sessions following administration of saline and all doses of morphine except 5.6 mg/kg. The average number of trials completed in Conditions 1 and 2 following 5.6 mg/kg morphine is given in Table 1. Data from sessions in which fewer than 10 trials were completed are not included in the following results.

During the first session of exposure to the IRT contingency, the majority of IRTs were shorter than 1 s. In contrast, following extended exposure to the procedure, the distributions were shifted to the right, toward longer IRTs. Figures 1 and 2 show the mean relative frequency distribution of IRTs as a function of IRT duration for each pigeon during control sessions (top row) and across increasing doses of morphine (lower rows) during Condition 1 (Figure 1), and Condi-

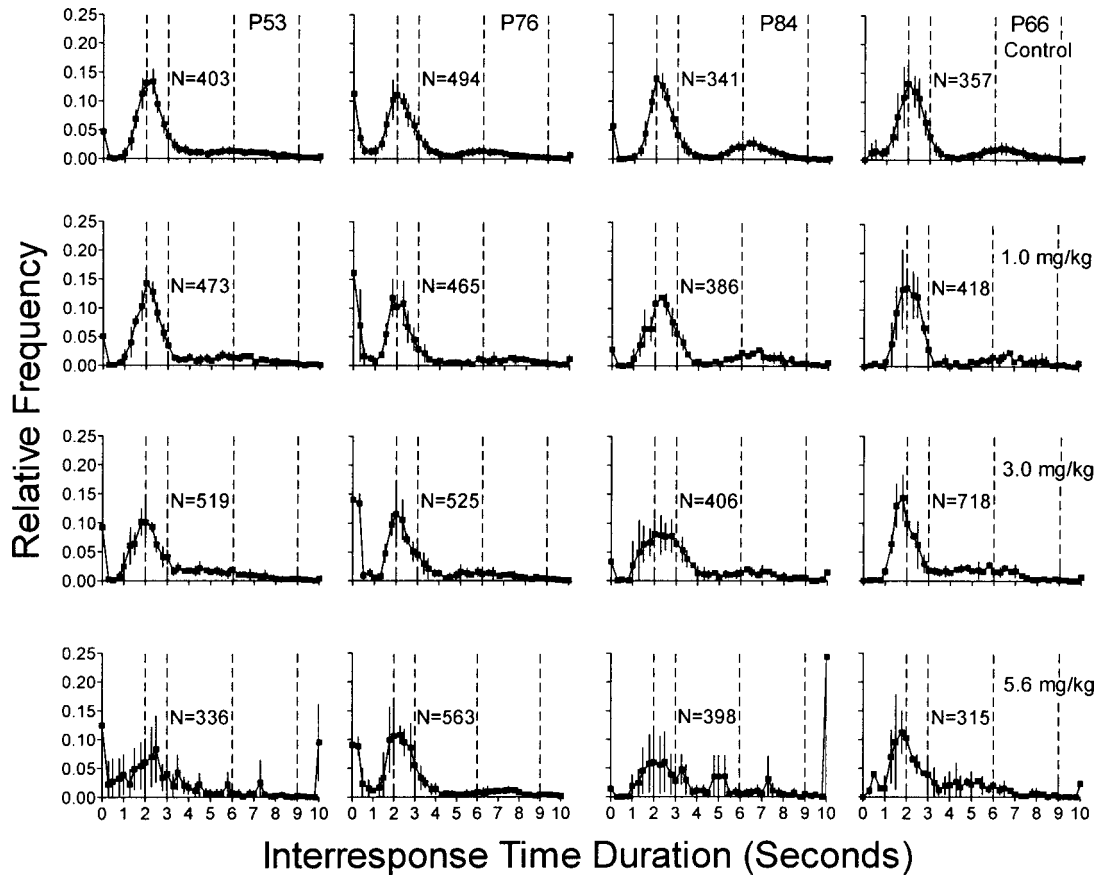


Fig. 2. Mean relative frequencies of interresponse times as a function of interresponse time duration in 0.25-s bins during control sessions and across doses of morphine for Condition 2. Other details as in Figure 1.

tion 2 (Figure 2). The control distributions (top row) show a burst of short IRTs (0 to 0.25 s). Aside from this burst, the distributions were roughly bimodal, with one mode at the lower bound of the short category and a less frequent mode at the lower bound of the long category. These results indicate that the procedure effectively shaped IRT production. Morphine produced a dose-dependent flattening of the IRT distributions (rows 2 through 4). At the highest dose, in particular, there was an increase in the proportion of the longest IRTs (all those greater than 10 s) for some pigeons. Morphine dose-dependently disrupted the temporal patterning of behavior and increased variability across determinations. There was no shift in the distribution toward shorter or longer IRTs. The mean number of IRTs emitted tended to increase

and then decrease as a function of morphine dose.

We conducted an IRTs per Opportunity analysis (IRTs/Op; Anger, 1956) to further examine the effects of morphine on the production of IRTs. This analysis gives the probability of an IRT conditional upon the number of opportunities to make the IRT. To calculate this probability, we divided the number of IRTs in each 0.25-s class by the number of IRTs in that class plus the number of all longer IRTs. Figure 3 shows the mean IRTs/Op as a function of IRT duration during control sessions and across morphine doses for Condition 1 (left panels) and Condition 2 (right panels). Because the effects of morphine on IRT production were similar across subjects (see Figures 1 and 2), mean data for each pigeon were averaged to produce the

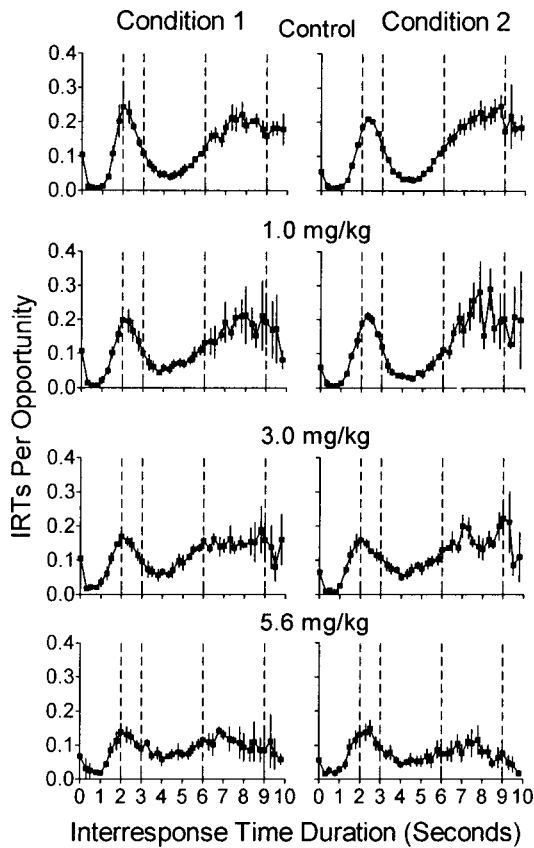


Fig. 3. Mean IRTs per opportunity as a function of IRT duration during control sessions (top row) and across doses of morphine (lower rows). Data shown are from Conditions 1 (left column) and 2 (right column). Vertical bars represent one standard error above and below the mean. Other details as in Figure 1.

data shown in this figure. During control sessions (top row), the distribution of IRTs/Op was bimodal, as were the IRT distributions shown in the top row of Figures 1 and 2, but the modes were similar in overall frequency. One mode was located within the bounds of the short category, and the other mode was located within the bounds of the long category. These results show that given the opportunity to make an IRT of a particular duration, the number of IRTs falling into the short and long categories was similar. Morphine produced a dose-dependent flattening of the distribution of IRTs/Op and an increase in the variability across subjects. For both categories of IRT, the IRTs/Op at the short and long modes decreased from about 0.25 under control conditions to about 0.15

at the highest dose of morphine. The IRT duration at which the mode occurred did not change systematically across doses of morphine, although there was variability in the mode duration and shape of the distribution, particularly for the long category of IRTs.

Figure 4 shows the mean proportion of IRTs falling into the short (2- to 3-s) and long (6- to 9-s) categories for each pigeon during control sessions and as a function of morphine dose for Condition 1 (left panels) and Condition 2 (right panels). The mean for all pigeons averaged across conditions is shown in the lower left panel. In both conditions, during control sessions the proportion of short IRTs was at least two times as great as the proportion of long IRTs for each pigeon. Saline had no systematic effect on the proportion of IRTs in each category. Across doses of morphine, the proportion of short IRTs decreased somewhat for all pigeons except P76. The proportion of long IRTs remained largely unchanged. This result shows that although morphine flattened the IRT distributions (as shown in Figures 1 through 3), the proportion of IRTs falling into the short and long categories remained relatively unchanged.

To assess whether the effects of morphine on the proportion of IRTs falling into the long and short categories were statistically significantly different, lines were fit using linear regression to the data relating the proportion of IRTs emitted in both categories to the dose of morphine. Data were pooled across pigeons separately for each condition. Control and saline data were not included in this analysis. In Condition 1, the slopes of the functions relating the proportion of short and long IRTs to the dose of morphine were -0.01 and -0.004 , respectively. These slopes were not significantly different, $F(1,82) = 1.04$, $p = .31$, when compared using analysis of covariance as described by Zar (1999). In Condition 2, the slope of the function relating the proportion of short IRTs to the dose of morphine was -0.02 , and the slope of the function for the proportion of long IRTs was -0.01 . These slopes also were not significantly different, $F(1,102) = 2.87$, $p = .09$. These results show that the morphine had little effect on the proportion of IRTs falling into the long and short categories. Furthermore, the

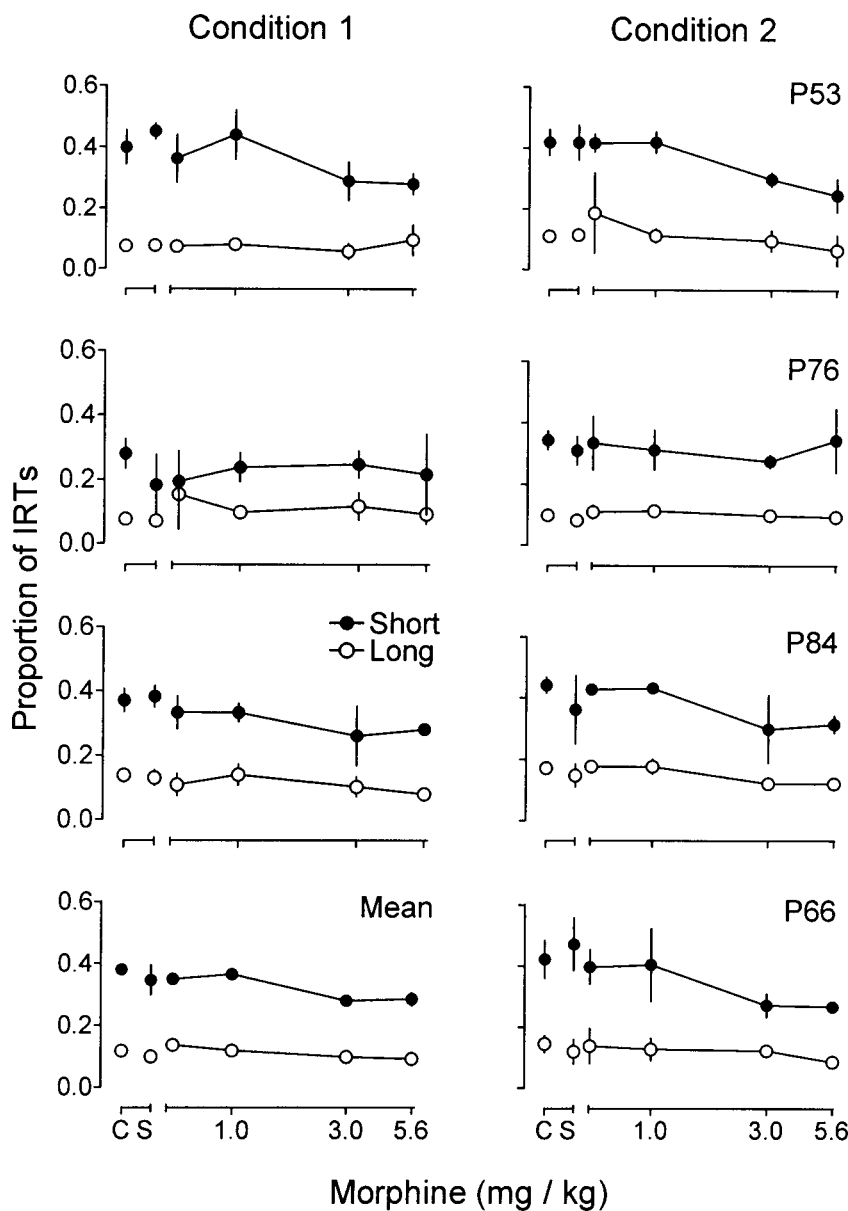


Fig. 4. Proportion of interresponse times in the short and long categories during control, saline, and morphine sessions for each pigeon during Conditions 1 (left panels) and 2 (right panels). Unconnected points show means for all control (C) and saline (S) sessions. Lines connect points showing mean proportion of interresponse times across doses of morphine. Open circles represent interresponse times falling into the long category and closed circles represent interresponse times falling into the short category. Vertical bars represent one standard deviation above and below the mean. The mean proportion of interresponse times across pigeons averaged across Conditions 1 and 2 is shown in the lower left panel. Vertical bars in the mean graph represent one standard error above and below the mean. In some cases, the variability around a point is obscured by the point.

effects were not substantially different for the two categories.

Mean accuracy of categorizing IRTs during control sessions in both conditions (shown in

Table 1) was between 80% and 97% for the short and long IRT categories. Across pigeons, there was no systematic difference in accuracy for the two categories. Figure 5

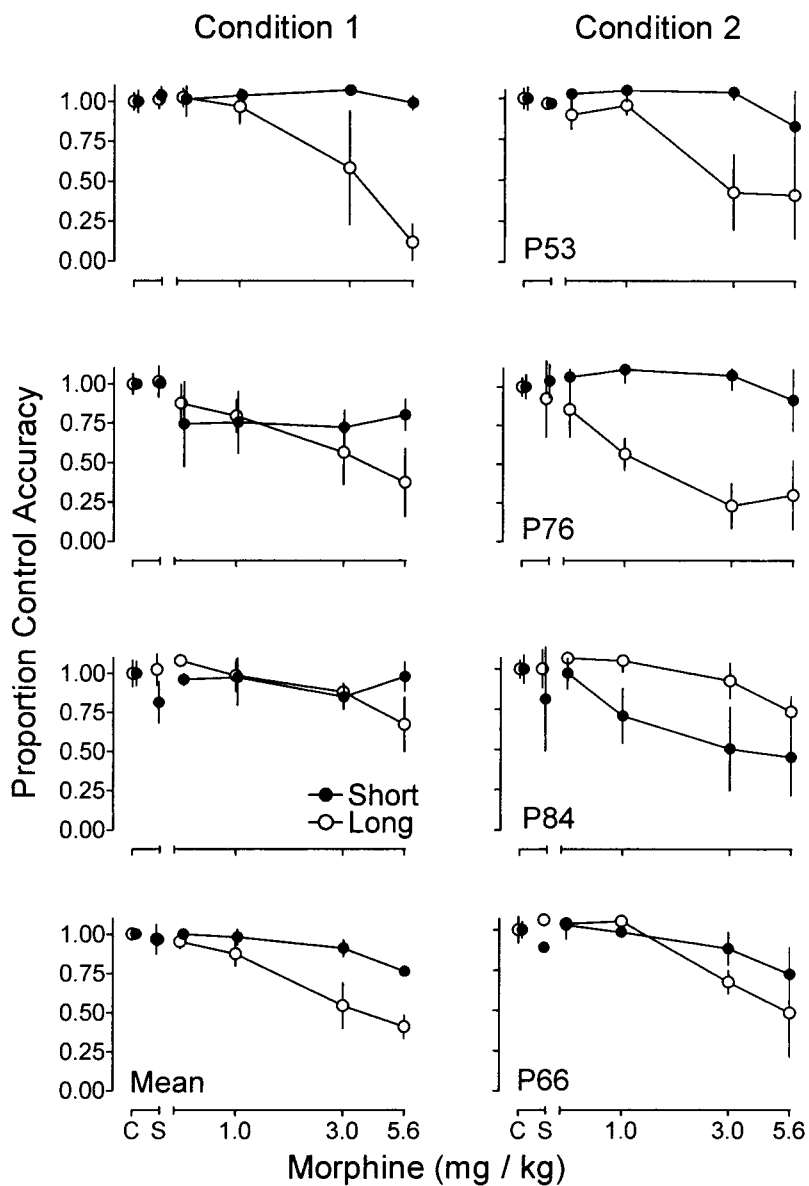


Fig. 5. Proportion control accuracy for categorization of short and long interresponse times for each pigeon during Conditions 1 (left panels) and 2 (right panels). See text for details of calculation. The mean accuracy across pigeons across Conditions 1 and 2 is shown in the lower left panel. Points for long and short interresponse times are offset slightly on the x-axis for clarity. Other details as in Figure 4.

shows the effects of morphine on the accuracy of categorization of short and long IRTs for all pigeons during both conditions. To accommodate unsystematic differences in accuracy under control conditions, data are expressed relative to control performance. Proportion of control performance was calculated by dividing the percentage correct for

the short and long categories by the mean corresponding percentage correct during control sessions. Mean proportion control accuracy across pigeons averaged across conditions is shown in the lower left panel. In both conditions, saline had no systematic effect on accuracy, although in some cases accuracy was lower than during control sessions. Overall,

morphine dose-dependently decreased the accuracy of categorizing long IRTs, whereas the categorization of short IRTs was less affected. In Condition 1 for P76, morphine also decreased overall accuracy for short categorizations, although the decrease was not dose dependent. In Condition 2 for P84, discrimination of long IRTs was less affected by morphine than discrimination of short IRTs.

To assess whether the effects of morphine were statistically significantly different for long and short IRT categorizations, lines were fit using linear regression to the data relating the proportion control accuracy and the dose of morphine separately for each category. Control and saline data were not included in the analysis. Data were pooled across pigeons for each condition. In Condition 1, the slope of the function relating proportion control performance for the short category to the dose of morphine was -0.001 , whereas the slope of the function for the long category was -0.12 . These slopes were significantly different, $F(1,82) = 30.63$, $p < 0.0001$, when compared using analysis of covariance as described by Zar (1999). In Condition 2, the slopes of the functions relating proportion control performance for the short and long categories were -0.06 and -0.11 , respectively. These slopes also were significantly different, $F(1,104) = 4.57$, $p = 0.035$. In summary, morphine decreased accuracy for categorization of long IRTs, whereas accuracy for categorization for short IRTs was relatively unaffected.

Although the previous analyses are consistent with the interpretation that side key choice responses were under the functional control of the immediately preceding IRT, another possibility is that responses on choice trials were based on the duration of the RI preceding the choice trial. Although there was considerable overlap in the distributions of obtained RI durations (the duration of the RI plus the time necessary for the chosen IRT to be emitted), for each pigeon in each condition the mean obtained RI duration was shorter for choice trials that were preceded by a short IRT than for choice trials that were preceded by a long IRT (data not shown). To assess whether this difference could account for accuracy on choice trials, Figures 6 and 7 present the proportion of long choices following long and short IRT samples as a func-

tion of the preceding obtained RI duration for Conditions 1 and 2, respectively. In these figures, on the one hand, exclusive control by the preceding RI duration is indicated by an increase in the proportion of long choices as a function of RI duration for trials following both short and long IRTs (i.e., functions with a positive slope). On the other hand, exclusive control by the preceding IRT is indicated by a relatively constant proportion of long choices as a function of RI duration for trials following both short and long IRTs (i.e., functions with a slope near zero).

Figures 6 and 7 show that under control conditions (top row), the proportion of long choices was high for trials following long IRTs and low for trials following short IRTs. Typically, the functions were relatively flat, indicating control by the preceding IRT duration. At the shortest RI durations, however, the proportion of long choices following long IRTs was below .5 in three of seven cases across conditions. In other words, at the shortest obtained RI durations, some long IRTs were categorized as short. At longer RI durations, there was also an increase in the proportion of long choices following short IRTs in some cases. These results indicate some influence of RI duration on choice responses under control conditions.

Morphine (lower rows) generally dose-dependently decreased the proportion of long choices following long IRTs. The proportion of long choices following short IRTs typically remained below .5, with an increase in the variability of the functions in some cases. The exception to this overall pattern is for P84, most notably in Condition 2, for which the proportion of long choices following long IRTs decreased, and the proportion of long choices following short IRTs increased, with increasing doses of morphine.

Typically, the functions remained relatively flat or irregular when morphine was administered, indicating little control by the preceding RI duration. There were important exceptions to this result, however, in which the slope of the functions relating the proportion of long choices to obtained RI duration increased, showing some control of choice responses by the preceding RI duration. This effect occurred following at least one dose of morphine for each pigeon. These results show that choice responses were largely con-

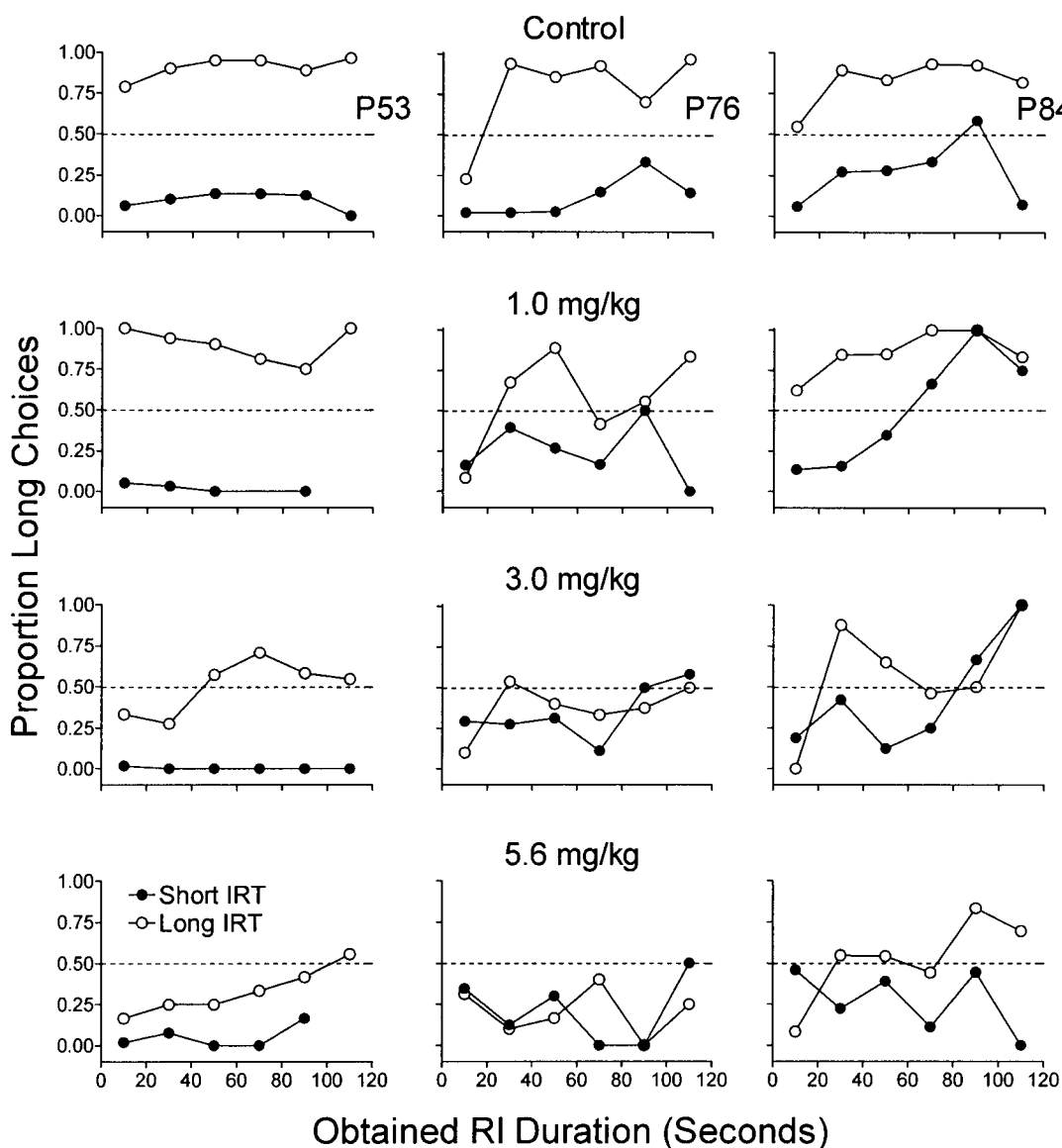


Fig. 6. Mean proportion of long choices following short (filled circles) and long (unfilled circles) IRTs as a function of obtained RI duration in 20-s bins during control sessions (top row) and across doses of morphine (lower rows) for each pigeon during Condition 1. The dashed line indicates a proportion of .5.

trolled by the preceding IRT duration, although in some cases administration of morphine was associated with increased control by the preceding RI duration.

DISCUSSION

The baseline performance generated by the IRT categorization procedure replicates that obtained by Shimp (1981, 1983). The

IRT distributions were roughly bimodal, with a more frequent mode at the lower bound of the shorter category, and a much smaller mode at the lower bound of the longer category. The IRTs/Op analysis showed that given the opportunity to make an IRT of a particular duration, the number of IRTs falling into the short and long categories was similar. Accuracy on choice trials following IRTs was high and similar following shorter (2- to 3-s)

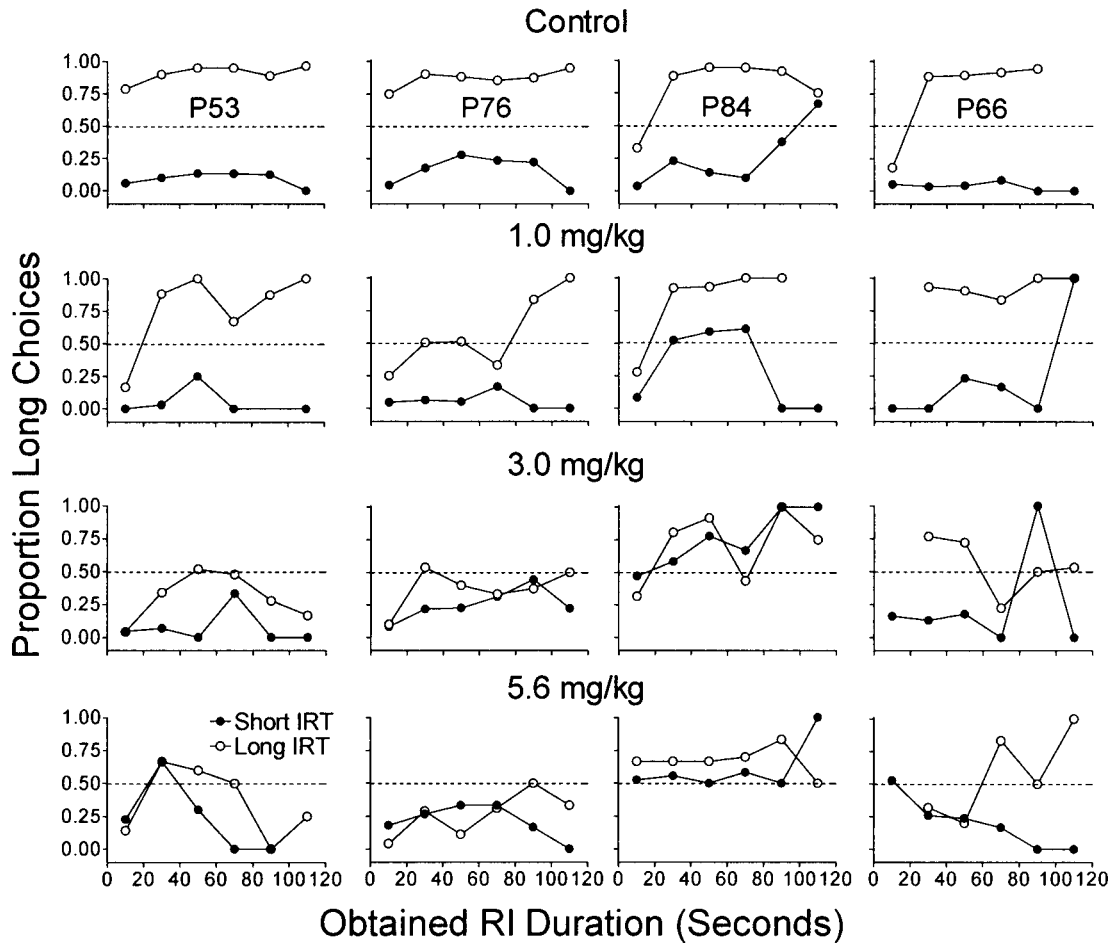


Fig. 7. Mean proportion of long choices following short (filled circles) and long (unfilled circles) IRTs as a function of obtained RI duration in 20-s bins during control sessions (top row) and across doses of morphine (lower rows) for each pigeon during Condition 2. The dashed line indicates a proportion of .5.

and longer (6- to 9-s) IRTs. The immediately preceding obtained RI duration generally had little influence on choice responses. At the shortest and at some longer RI durations, however, choice responses were in some cases influenced by the preceding obtained RI duration.

Morphine disrupted the production of IRTs. The IRT distribution was flattened in a dose-dependent manner, showing general disruption in the temporal patterning of behavior on the center key. There were no systematic shifts in the distribution to the left or right (i.e., morphine did not produce overestimation or underestimation of time in the production of IRTs). The proportion of IRTs falling into the long (6- to 9-s) and short (2-

to 3-s) categories was not substantially or differentially affected by morphine administration. Similar to previous studies (e.g., McMillan & Morse, 1967), in some cases morphine produced moderate increases in the overall number of responses at lower doses.

The effects of morphine on behavior during choice trials showed that, in general, most control over choice behavior was by the preceding IRT. In some cases, however, in the presence of morphine, choice responses were also influenced by the preceding obtained RI duration. Morphine selectively disrupted overall accuracy of choice responses following long IRTs. In other words, following administration of higher doses of morphine, the pigeons tended to choose the key color that

matched the short IRT category regardless of whether the IRT was short or long. The relatively specific disruption of accuracy following long IRTs was observed in both Conditions 1 and 2 with the key colors serving different functional roles. The selective disruption of the accuracy of categorizing long IRTs could be interpreted as underestimation of the duration of the IRT when it was categorized retrospectively (i.e., a choose-short bias). The results of the present experiment are similar to those of Odum and Schaal (2000), in which morphine produced generalized disruption of accuracy for short and long samples, accompanied by underestimation of time at the largest dose, when pigeons categorized the duration of experimenter-imposed events. Thus whether the programmed stimulus to be discriminated was some aspect of the subjects' behavior (present experiment), or the chamber stimuli (Odum & Schaal, 2000), morphine disrupted the categorization toward underestimation of time.

The one exception to this general result is for P84 in Condition 2. For this pigeon, the effects of morphine on the accuracy of discriminating long and short IRTs was different from that obtained for other pigeons in Conditions 1 and 2, as well as for this pigeon in Condition 1. For P84, the accuracy of discriminating long IRTs was less disrupted than for short IRTs (see Figures 5 and 7). In other words, rather than showing a choose-short bias, this pigeon tended to show a choose-long bias in Condition 2. Although there is no clear reason for this discrepancy, one possible explanation may be that for this pigeon, the key color associated with long IRT (green) remained constant across Conditions 1 and 2, and the key color associated with the short IRT changed. For P53 and P76, the key color associated with the short IRT (green) remained constant across Conditions 1 and 2, and the key color associated with the long IRT changed. Thus, in Condition 2, with higher doses of morphine pigeons may have shown a bias for the key color that did not change across conditions.

The overall results of the present experiment appear to be inconsistent with a model of the neuropharmacology of timing proposed by Meck (1996). In this model, there is an internal clock made up of a pacemaker that emits pulses that are stored in an accu-

mulator. The rate at which pulses are emitted from the pacemaker is suggested to be governed by activity within the central dopaminergic pathways. Compounds that increase dopaminergic activity are predicted to produce overestimation of time. Because morphine increases extracellular levels of dopamine (e.g., Rougé-Pont et al., 2002), Meck (1996) suggested that it should produce overestimation of time. The present results, however, may have been obtained because other effects of morphine interfere with or obscure the purported effects of dopaminergic activity on timing. Furthermore, morphine may not increase dopaminergic activity in the particular brain region that is related to timing (see e.g., Matell, Meck, & Nicolelis, 2003). Thus the current experiment does not provide a conclusive test of Meck's (1996) account.

The results of the present experiment and others highlight inconsistencies in the effects of drugs on different measures of timing as noted by Chiang et al. (2000). In the current experiment, morphine disrupted the production of IRTs in a nonspecific manner but disrupted the categorization of IRTs toward underestimation of duration. Popke, Mayorga, Fogle, and Paule (2000) had separate groups of rats respond under either a differential-reinforcement-of-low-rate—limited-hold (DRL-LH) schedule, in which lever presses produced food if the latency since the last response was between 10 and 14 s, or a temporal response differentiation (TRD) schedule, in which releasing the lever produced food if it had been held down between 10 and 14 s. Morphine tended to increase IRTs on the DRL-LH, but decreased response duration on the TRD schedule. Similarly, morphine produced different effects on two measures of timing with pigeons (Knealing & Schaal, 2002), and *d*-amphetamine (Chiang et al., 2000) and amineptine (Lejeune et al., 1995) produced different effects on two measures of timing with rats.

Taken together, however, the results of these studies do not lend support to Chiang et al.'s (2000) suggestion that inconsistencies in the literature on the effects of drugs on timing could be due to a particular aspect of the procedures employed. Specifically, they suggested that in procedures that involve temporal regulation of the subjects' behavior,

drug administration might produce different effects than in procedures in which the subject makes judgments about the duration of experimenter-imposed events. The present results and those of Popke et al. (2000) do not support this assertion. In Popke et al.'s experiment, both procedures involved the temporal regulation of behavior, not judgments about exteroceptive stimuli, yet morphine produced overestimation of time for one and general disruption of timing for the other. In the present experiments, the production of IRTs involved temporal regulation of behavior and the categorization of IRTs involved judgment about an aspect of behavior, rather than experimenter-imposed stimuli. Morphine produced generalized disruption of the temporal regulation of behavior, but underestimation of time for categorization of that behavior, similar to results obtained for categorization of exteroceptive stimuli (Odum & Schaal, 2000).

Çevik (2003) suggested the duration of experimental sessions might account for discrepancies in the effects of drugs on timing. She noted that several experiments in which amphetamine produced overestimation of time used relatively long sessions (2 hours or more), whereas several experiments in which amphetamine produced generalized disruption of timing used shorter sessions (less than an hour). In separate experiments using the interval bisection procedure, Çevik found that methamphetamine produced generalized disruption of timing when administered to rats 20 min prior to the start of an 80-min session, but produced overestimation of time when administered 100 min prior to the start of the session.

The present results in some aspects lend support to Çevik's (2003) session-duration explanation. Morphine produced generalized disruption of the production of IRTs when the effects were assessed about 10 to 45 min after administration. Other experiments, however, have reported results consistent with Meck's (1996) model of the neuropharmacology of timing with relatively short session durations with morphine (e.g., Knealing & Schaal, 2002; Popke et al., 2000; Schulze & Paule, 1991), *d*-amphetamine (e.g., Bizot, 1997; Chiang et al., 2000; Spetch & Treit, 1984) and the dopamine antagonist haloperidol (Bizot, 1997). Furthermore, results in-

consistent with the model have been reported with relatively long session durations with the dopamine antagonist pimozide (Ohyama et al., 2000).

Thus the duration of experimental sessions may explain some, but not all, of the discrepancies in the effects of drugs on timing. Previous analyses have suggested that other factors, including species, sex, route of administration, and variations in procedure cannot fully account for the variations in outcome (Çevik, 2003; Odum, 2002; Odum et al., 2002). A number of experiments, however, have reported underestimation of time in situations in which current models of the neuropharmacology of timing (e.g., Meck, 1996) predict overestimation of time (e.g., the present experiment; Odum & Schaal, 2000; Rapp & Robbins, 1976; Santi, Weise, & Kuiper, 1995; Stubbs & Thomas, 1974).

Interestingly, there may be a previously overlooked procedural difference between experiments reporting overestimation and underestimation of time with various drugs. In the terminology proposed by Killeen and Fetterman (1988), procedures in which the subject responds during an elapsing interval are immediate timing tasks, whereas procedures in which the subject judges the duration of an elapsed interval are retrospective timing tasks. In many interval bisection procedures, responding on one operandum produces food after a short sample, and responding on the other operandum produces food after a long sample (e.g., Catania, 1970). The operandum may or may not be present in the chamber during the interval to be timed, depending on the version of the procedure used. Although the interval-bisection procedure is typically classified as a retrospective timing task (e.g., Chiang et al., 2000), the subject can, by changing the position of its body during the stimulus, essentially behave as if the task were an immediate one. For example, at the start of a sample presentation, rats position themselves in front of one lever (which produces food after a short sample), then as the sample elapses, cross the chamber and position themselves in front of the other lever (which produces food after a long sample; e.g., Çevik, 2003; Lejeune et al., 1995).

Other interval-bisection procedures use symbolic matching to sample (SMTS), however. In SMTS, which operandum will pro-

duce food cannot be predicted during the sample presentation. Instead, for example, responding to the key lit one color produces food after short samples, and responding to the key lit another color produces food after long samples (e.g., Stubbs, 1968). The color that appears on each key varies unpredictably across trials. Experiments using SMTS (e.g., the present experiments; Odum & Schaal, 2000; Santi et al., 1995; Stubbs & Thomas, 1974) have reported that drugs that increase dopaminergic activity produce underestimation of time. Overestimation of time is typically reported with interval bisection tasks in which the operandum that will produce food is predictable during the sample presentation (e.g., Bizot, 1997; Çevik, 2003; Maricq & Church, 1983; Meck, 1983).

The differences in the effects of drugs on timing may thus depend partly on whether the task is functionally an immediate timing task or a truly retrospective one. The difference in the two procedures could lie in whether they require the subject to remember the sample. In interval bisection tasks in which the operandum that will produce food is predictable during the sample, the subject is not required to remember the sample duration. Instead, a rat, for example, need only press the lever it is standing in front of when the sample ends. In interval bisection tasks that use SMTS, however, the subject must remember the duration of the sample to choose the appropriate operandum when the sample ends. Future experiments will examine whether this possibility can account for some of the previously unexplained discrepancies in the literature on the effects of drugs on timing.

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