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Effects of dopamine antagonists on the timing of two intervals

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Abstract

Rats were trained on a two-interval (12 and 36 s) temporal production task (the peak procedure). Test sessions were conducted in which either the D_1 antagonist SCH-23390 (SCH; 0.02, 0.04, 0.06 mg/kg) or the D_2 antagonist haloperidol (HAL; 0.05, 0.1, 0.2 mg/kg) were injected prior to testing. Both drugs affected the amount of responding, but only HAL affected timing. Under HAL, both intervals were overestimated, consistent with a HAL-induced decrease in clock speed. Drug-induced decreases in response output were more profound for the long interval than the short. In addition, there was evidence of HAL- and SCH-induced delays in response initiation that were more severe for the long interval, perhaps owing to its status as a weaker conditioned stimulus.

Keywords: Interval timing; Neuroleptic; Time perception; Time production; Conditioning

1. Introduction

Interval timing refers to the perception and production of durations in the seconds-to-minutes range. Interval timers are characterized by the capacity to start, stop, and reset arbitrarily. These capacities allow interval timers to time event durations and the intervals between events. Timing in this range is an integral part of many behaviors. For instance, in conditioning, the temporal relations between the conditioned stimulus and unconditioned stimulus affect many aspects of performance, including the form of the conditioned response (Holland, 1980), the speed of acquisition (Gibbon and Balsam, 1981), and the timing of the conditioned response (Gibbon, 1977). Interval timing may also be a integral aspect of coordinated movement (Ivry, 1993).

Interval timing is commonly assessed in humans and animals using variants of the peak procedure (Bitterman, 1964; Catania, 1970). In a peak procedure, subjects are presented with two types of trials employing a common cue (e.g., a tone or light). On learning trials, the cue is presented, and after a fixed amount of time (*T*), a reward is delivered. For example, a common procedure in the rat is to reward the first lever press occurring after the conclusion of the target interval (fixed interval schedule); lever presses occurring before the conclusion of the interval are not rewarded. On ''peak'' trials, the cue stays on for an extended period of time, and no rewards are delivered. This allows the experimenter to assess the subject's timing of the target interval in the absence of immediate feedback. The maximal rate of responding on peak trials tends to occur around *T*, indicating that subjects acquire accurate knowledge about the duration of the target interval.

The neural mechanisms of interval timing are not well understood, but several lines of evidence suggest a role of midbrain dopamine. Schultz and colleagues have found that the firing of midbrain dopamine neurons represents temporal expectations about reward (e.g., Hollerman and Schultz, 1998). When monkeys are trained to expect response-contingent reward, the nonpresentation of reward after a response will cause a decrease in the firing rate of DA neurons at the time at which the reward ought to have been delivered. Additionally, pharmacological manipulation

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of dopamine levels affects timing. If rats are trained on the peak procedure drug-free and then receive test sessions under the influence of a DA agonist or antagonist, expectations about the time of reward availability are altered (Buhusi and Meck, 2002; see also Meck, 1996). DA antagonists cause the peak in responding to occur later in the trial (as compared to drug-free rats), and agonists cause the peak to occur earlier in the trial. That is, antagonists cause overestimation of the interval, and agonists cause underestimation. Thus, DA antagonists and agonists produce behavior effects consistent with the slowing and speeding of an internal clock, respectively.

Because most work on the peak procedure has been conducted with animals trained on only one interval, it is not known how dopamine antagonists affect behavior when subjects must learn and reproduce multiple intervals. The clock speed hypothesis predicts that if subjects are trained on two target intervals, acute administration of dopamine antagonists will cause proportional overestimation of both intervals. However, a competing prediction can be derived from recent studies of timing in Parkinson's disease (PD), a disease characterized primarily by a loss of nigrostriatal dopamine (Dubois and Pillon, 1992). Malapani et al. (1998, 2002) found that when PD patients are trained on two intervals in the peak procedure while on dopamine replacement therapy (levodopa), but then tested while off medication, the patients overestimate the short interval and underestimate the long interval, a pattern that has been termed "migration." The specific neural mechanisms of the migration effect are not known, but because the effect is alleviated under dopamine replacement therapy, it is suspected that dopamine loss plays a role. In light of this finding, it is reasonable to wonder whether pharmacological blockade of dopamine receptors will produce a migration pattern. Such a finding would require significant revision of current views about the role of dopamine in interval timing.

The present experiments tested the effects of dopamine antagonist drugs in rats trained on two intervals (12 and 36 s) in the peak procedure. Rats were trained in a drug-free state, then tested under the influence of D_2 and D_1 antagonist drugs. If blockade of dopamine receptors slows clock speed, as previous single-interval studies suggest, then drug administration will cause proportional overestimation of the long and short intervals. If, however, the migration pattern is due to loss of D_2 or D_1 receptor activity, only the short interval will be overestimated, and the long interval will be underestimated.

2. Methods

2.1. Subjects

Eighteen male Sprague–Dawley rats (400–550 g) were housed on a 13–11 light–dark cycle (lights on at 8:00 a.m.). They were given 1 h access to food (Purina rat chow) per day and ad lib water, except on weekends when they were allowed free access to food until Sunday afternoon. The experimental protocol was approved by the Columbia University Institutional Animal Care and Use Committee.

2.2. Apparatus

The subjects were trained and tested in six identical modular test chambers (Med Associates, Georgia, VT; model ENV-008-VP) with dimensions of $30 \times 24 \times 21$ cm. The chambers were housed individually inside light- and sound-attenuating isolation boxes that were equipped with fans for ventilation. The floor of the chambers consisted of 19 metal rods placed 15 mm apart. A food trough (5×5 cm) was centered in the right side panel, 2 cm above the floor. The food trough was equipped with an infrared photocell that recorded head entries, the response of interest in this study. A response lever, not used in this experiment, was placed immediately to the left of the food trough, 6 cm above the floor and 3 cm from the back wall panel. The chambers were illuminated throughout the session by a red stimulus light, acting as a houselight. The light was located at the top left corner of the right wall panel, 8 cm above the floor and 2 cm from the back panel. The chambers were also equipped with a speaker that delivered an 80-dB white noise or tone (1000 Hz) serving as the conditioned stimuli. The speaker (6×7 cm) was mounted in the top right corner of the left wall panel.

2.3. Drugs

Haloperidol (dopamine D_2 receptor antagonist; Sigma, St. Louis, MO) and SCH-23390 (dopamine D_1 antagonist; Sigma, St. Louis, MO) were dissolved in saline solution with 0.2% lactic acid (w/w) (lactic acid was used to increase the solubility of haloperidol). Both were administered intraperitoneally 15 min prior to the test sessions in a volume of 1 ml/kg body weight. Doses were selected because previous work in our lab has shown them to produce approximately equivalent effects on response rate in this paradigm.

2.4. Procedure

Prior to training in the peak procedure, rats were given two daily feeder training sessions. Rats were placed in the test chambers with the houselight illuminated and five food pellets sitting in the food trough. After 15 min, they were removed. By the second session, all rats were eating from the trough.

Single-peak training commenced on the day following the last feeder training session. Each single-peak session consisted of 24 trials: 18 fixed time (FT) trials and 6 peak trials. The intertrial interval was variable with a mean of 90 s (range = 60 s). On FT trials, one pellet was delivered 12 s after onset of a 13-s white noise. No response was required. On peak trials, the white noise was presented for 96

s and no pellets were delivered. The order of trials was random. The houselight was illuminated throughout all sessions.

After 6 weeks of single-peak training (five sessions per week), rats received an additional 6 weeks of dual-peak training (Fig. 1). Dual-peak sessions consisted of 32 trials. Of the 24 FT trials, half were white noise trials (as above) and half were tone trials. On tone trials, one pellet was delivered 36 s after onset of a 39-s tone. Of the eight peak trials, four were white noise trials (as above) and four were tone trials, on which the tone was presented for 288 s and no pellets were delivered. The order of trials was random.

Following training, rats received dual-peak sessions under the influence of haloperidol (HAL), SCH-23390 (SCH), or the vehicle solution (VEH). The treatments were administered using a within-subject design in which each subject received each dose and type of drug as well as control injections of vehicle solution. There was one session per day, and each drug session was preceded by two vehicle sessions, for which rats were given intraperitoneal preinjections of VEH. HAL sessions were conducted first. Rats received doses of 0.05, 0.1, and 0.2 mg/kg, in that order. Each dose was administered once. Following the haloperidol sessions, rats received 1 week of drug-free training, and then SCH-23390 treatment began. The rats received doses of 0.06, 0.04, and 0.08 mg/kg, in that order.

2.5. Data analysis

Two behavioral indices were recorded: the number of head entries to the food trough per peak trial and the time of each peak trial head entry and exit. Using the latter information, we computed "peak" functions by subdividing each peak trial into 1-s bins, then assigning a "1" to each bin in which the head was present in the trough. The peak functions thus represent the probability of the head being in the trough during each second.

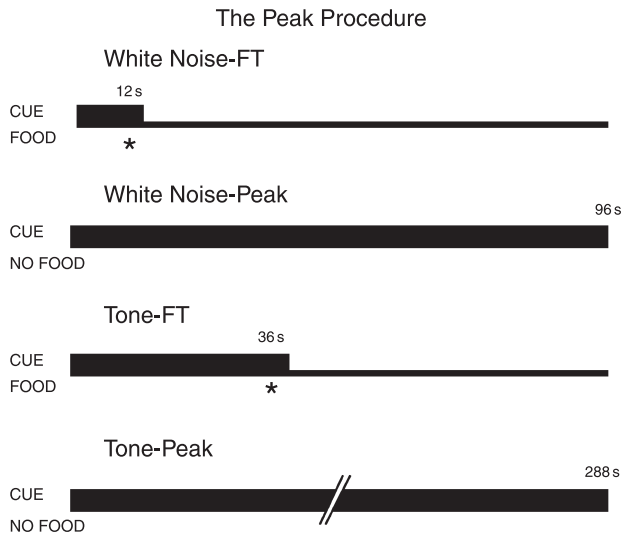

Fig. 1. Schematic diagram of the peak procedure. Fixed-time (FT) trials are either 13 (white noise trials) or 39 s (tone trials) in duration, with food delivered at 12 or 36 s after cue onset, respectively. Peak trials are either 96 (white noise) or 288 s (tone), with no food delivered. The tone peak schematic is broken to signify a compression of scale.

To quantitatively characterize the timing of head entries, we modeled the individual trial peak functions. The model is predicated on the fact that after some training, responding on peak trials typically takes on a break-run-break pattern, characterized by a low rate of responding at the beginning of the trial, giving way to a high rate of responding as the target time approaches, followed by a second low rate of responding after the target time has passed (Church et al., 1994). Since in our analysis the data are binary, the pattern is characterized by abrupt transitions (from 0 to 1) in the probability of the head being in the trough. To find the transition points between the high ($P=1$) and low ($P=0$) probability states, we implemented a computerized fitting program, similar to that used by Church et al. (1994), that conducted an exhaustive search of all possible transition points. The transition points that produced the best fitting low-high-low function (least squares criterion) were selected. Trials for which the low-high-low model produced a poorer fit than did the grand mean were excluded from further analysis (the number of trials from each subject included in the analyses is reported in Figs. 1 and 2).

From the transition points (S_{start} and S_{stop}), two additional measures of performance could be computed: middle time [$S_{start}+(S_{stop}-S_{start})/2$] and spread ($S_{stop}-S_{start}$). Middle time is used as a measure of the expected time of reinforcement (e.g., Church et al., 1994). Data analysis focuses on these measures obtained from the modeling, as well as response rate, calculated by dividing the number of head entries per peak trial by the peak trial duration. To simplify the statistical analyses, the vehicle session data were collapsed by taking the median across all six vehicle sessions. Separate VEH medians were computed for SCH and HAL.

The HAL and SCH data were analyzed separately. Each dependent variable was individually subject to a 2 (Target Interval: 12 or 36 s) $\times$ 4 (Dose: VEH, lowest, middle, highest) ANOVA, with both independent variables as repeated measures. To examine the effects of the drugs on each dependent measure, planned pairwise comparisons (t tests) between each dose and the corresponding vehicle score were conducted. Data for the short and long intervals were separately subjected to pairwise comparisons.

To test whether the drug effects were proportional across the two target intervals, each dependent measure for each subject was normalized by dividing by the vehicle median for that dependent measure. The resulting data are proportion-of-baseline scores. The normalized scores for each measure were then individually subject to a 2 (Interval) $\times$ 3

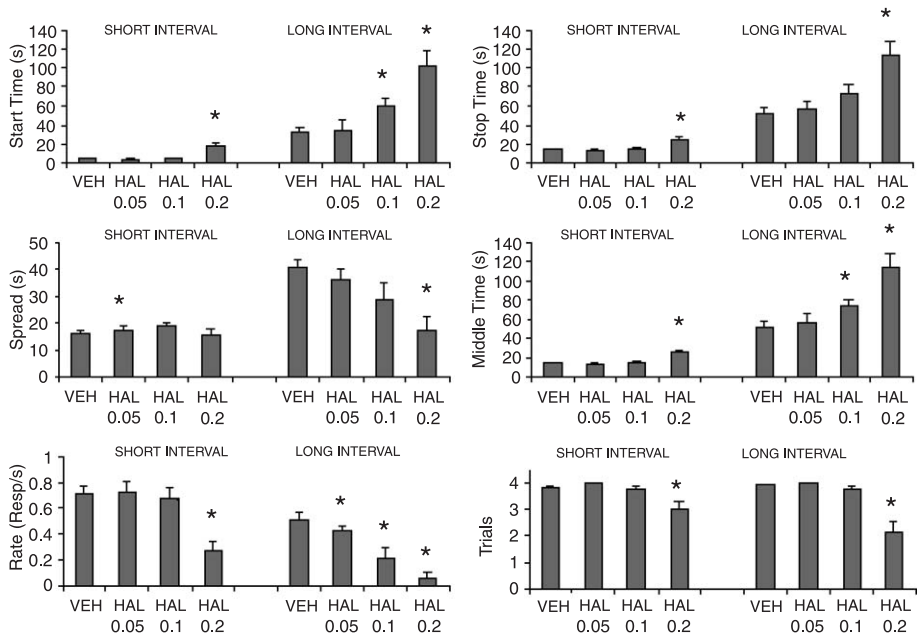

Fig. 2. HAL effects on start time, stop time, middle time, spread, response rate, and trials. The trials measure is the mean number of trials per subject per dose for which the low-high-low model provided a better fit to the data than did the grand mean (max = 4; see Data analysis for more details). VEH values are medians taken over the six VEH sessions. Error bars represent 1 S.E. Starred points (*) are significantly different from vehicle ($P < .05$).

(Dose) ANOVA. The criterion for rejecting the null hypothesis was set at $P < .05$ for all statistical tests.

3. Results

3.1. HAL

The results are shown in Fig. 2. There were significant effects of Interval [F's(1,14)>21.3, F(1,42)>21], Dose [F's(3,42)>5.6, F(3,42)>5], and the Dose×Interval interaction [F's(3,42)>3.8] on all behavioral measures. The middle time, start time, stop time, and spread were higher for the long interval than the short interval. Response rate was higher for the short interval than the long interval.

The drug effects can be summarized as follows. The highest dose of HAL produced significant increases in start time, stop time, and middle time for both the long and short intervals. Response rate during the long interval was decreased under all doses of HAL; the short interval response rate was decreased only under the high dose of HAL. Spread in the long interval was significantly decreased under the high dose of HAL. The short interval exhibited a very modest, but significant, increase in spread under the low dose of HAL. Under the highest dose of HAL, there were significant decreases, for both the long and short intervals, in the number of trials on which timing was evident (i.e., the number of trials for which the low-high-low model provided a better fit to the peak function than did the grand mean).

In the normalized HAL data (see Data analysis), there were significant effects of Interval and Dose on start time, middle time, spread, and response rate [Interval: F's(1,14)> 3.5; Dose: F's(2,28)>8.4]. The effect of Interval on stop time did not reach significance [$F(1,14) = 3.5$, P=.08]. Interval and Dose did not interact [F's(2,28) < 2]. The long interval response rate, start time, middle time, and spread were increased by a greater percentage under HAL than were the corresponding short interval measures. The long interval was thus more sensitive to the effects of HAL than was the short interval.

3.2. SCH-23390

The results are shown in Fig. 3. There were significant effects of Interval on all measures [F's(1,12)>34.3]. There were significant effects of Dose on spread and rate only [F's(3,36) = 3.3 and 11.4, respectively]. The effect of Dose on start time approached significance, $F(3,36) = 2.6$, P=.06. The Dose × Interval interaction reached significance only for the rate variable [$F(3,36) = 10.6$], but approached significance for the start time variable, $F(3,36) = 2.5$, P=.07 (other F's < 2.1, P's>.1). The significant interaction reflects that the long interval response rate was decreased more by SCH than was the short interval response rate.

As seen in Fig. 2, the most robust effect of SCH was a dose-dependent decrease in response rate across both intervals. The lack of a significant main effect of Dose on the timing measures urges caution in interpreting the effects of SCH on timing. The pairwise comparisons indicate that for

the long interval, the highest dose of SCH caused increases in start time, stop time, and middle time as well as a decrease in spread. The decrease in spread can be attributed to the fact that the SCH-induced increase in start time was somewhat greater than the increase in stop time (64% vs. 18%, respectively). For the short interval, there were no effects of SCH on start time, stop time, middle time, or spread.

Because there were no effects of SCH on the short interval timing measures, these measures were not normalized. Only the response rate data were normalized. There was a significant effect of Interval on the normalized rates, $F(1,12) = 28.9$. The effects of Dose and of the Interval × Dose interaction did not reach significance, $F(2,24) < 1$. The long interval was more sensitive to the response-suppressing effects of SCH.

4. Discussion

The purpose of this study was to evaluate the effects of dopamine D_1 and D_2 antagonist drugs in rats trained on two intervals in the peak procedure. The primary result is that the D_2 antagonist HAL caused an overestimation of both the long and short intervals consistent with a decrease in clock speed. This pattern is consistent with earlier studies of subjects trained on one interval in the peak procedure (e.g., Buhusi and Meck, 2002). Like HAL, the D_1 antagonist SCH dose-dependently suppressed response output, but SCH had negligible effects on timing, illustrating that impairments in response output can occur independently of changes in clock speed. There was no evidence that either drug produces the migration effect observed in PD patients tested in a similar procedure.

The HAL-induced overestimation of both intervals was evidenced by increases in start time and stop time (and thus, middle time). The effects on start and stop times were related to the target interval; that is, the drug-induced delays in start and stop times were greater in the long interval than in the short. This pattern is consistent with a HAL-induced decrease in clock speed (Meck, 1996) and cannot be attributed to the general motor slowing often produced by HAL and other neuroleptics (e.g., Fowler et al., 1986; Fowler and Liou, 1998). Because the motor response is the same for the long and short intervals, motor slowing would translate into a constant increase in start and stop time, invariant across target interval.

One curious result is that the HAL-induced increases in middle time were relatively greater for the long interval than the short. By contrast, a pure effect on clock speed would result in equivalent percentage overestimation of both intervals. That is, if HAL slowed clock speed by a given proportion (say, 1/4), then the short and long interval would be overestimated by the same proportion (1/4). Close analysis of the data reveals that the non-scalar (across target interval) effects of HAL on middle time and spread do not reflect a general non-scalar effect on timing. They are instead due to a disproportionate HAL-induced increase in start time. Although both the long- and short-interval start times were delayed by HAL, the long-interval start time was relatively more delayed than was the short-interval start time. The HAL-induced increases in stop time were proportional to the target interval, consistent with a clock speed effect. The overall pattern can be explained by assuming that, in addition to producing an overall rightward shift in the peak function consistent with a slowing of clock speed, HAL caused an exaggerated increase in start time that was specific to the long interval. The exaggerated increase in start time could be a manifestation of catalepsy, an impairment in response initiation known to be produced by HAL in the doses used here (Fowler and Liou, 1998; Undie and Friedman, 1988).

Effects of SCH on measures of response timing were evident only at the highest dose and only for the long interval. The long interval was overestimated, mainly due to an increase in start time. These SCH effects should not be interpreted as reflecting a slowing of clock speed, because any effect on clock speed would be evident at both intervals tested. The relative ineffectiveness of SCH in altering timing is consistent with earlier results indicating that drug potency in affecting clock speed is correlated with D_2 receptor affinity (Meck, 1986) (Fig. 3).

Both drugs exerted stronger effects on the response rate during the long interval than during the short. Under the highest dose of HAL, the response rate for the long cue was suppressed by 75%, but the rate during the short cue was suppressed by only 60%. Under the middle dose of SCH, the response rate for the long cue was decreased by 70%, while the response rate for the short cue was decreased by only 46%.

There are two variables that may account for the greater vulnerability of the long interval to the effects of HAL and SCH on start time and response rate. First, rats received considerably more training on the short interval than the long. There were about 60 sessions of training on the short interval and about 30 sessions of training on the long interval. Second, even in the absence of drug the long interval elicited less responding than did the short interval, as is common across many conditioning paradigms (Gibbon et al., 1977; Holland, 1980). Recent work suggests that the long interval's status as a weaker, more poorly trained cue may account for its increased sensitivity to the effects of dopamine antagonists on performance. Horvitz et al. (Horvitz, 2001; Horvitz and Eyny, 2000) have demonstrated that the effects of D_1 or D_2 antagonist drugs on the latency of a goal tracking response (retrieval of food pellets from a food trough) disappear when the response is overtrained. In Horvitz's paradigm, rats reach asymptotic response speed after about three training sessions. D_1 or D_2 antagonists administered in the third session increase response latency and decrease the number of "spontaneous" responses (i.e., responses in the absence of food). After 16 sessions of training, however, the drugs have no effect on latency of the goal tracking response but continue to suppress spontaneous responding. The finding recalls an anecdote about wheel-

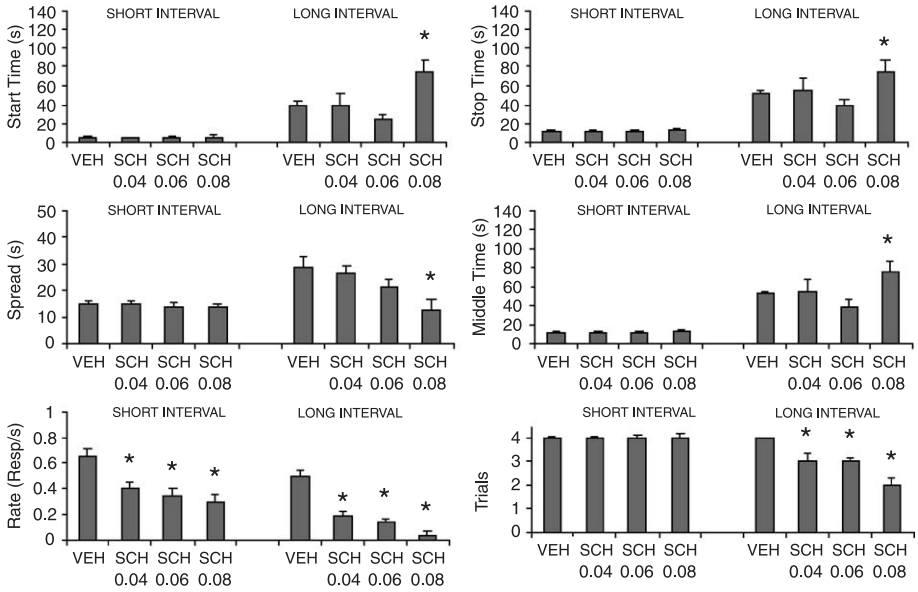

Fig. 3. SCH effects on start time, stop time, middle time, spread, response rate, and trials. The trials measure is the number of trials per subject per dose for which the low-high-low model provided a better fit to the data than did the grand mean. VEH values are medians taken over the six VEH sessions. Error bars represent 1 S.E. Starred points (*) are significantly different from vehicle ($P < .05$).

chair-bound PD patients being able to walk out of a building when a fire alarm sounds. The presence of a strong eliciting stimulus allowed patients to successfully execute complex movements that they were unable to initiate by themselves. Both HAL and SCH are known to produce catalepsy, a resistance to initiating movements not unlike that seen in PD (Ellenbroek et al., 1987; Undie and Friedman, 1988). It could be that the long cue's status as a weaker cue left it more vulnerable to these drug effects, and this translated into elevated start times and less responding as compared to the short interval.

The present data have two important implications for theories of interval timing. The first is that start and stop times can be manipulated independently of each other. Earlier work on interval timing stressed that start and stop times are positively correlated in non-drugged animals, and from this, it was inferred that animals use a single criterion for starting and stopping timed responding (Gibbon and Church, 1992). Our finding that HAL and SCH can differentially affect start and stop times favors independent start and stop criteria (Church et al., 1994), though one could also argue that the drugs instead add a time lag to the (start or stop) decision processes, without affecting the criteria themselves. The second important result is that drugs can cause overestimation of a single interval in animals trained on two intervals. SCH caused an overestimation of the long interval, but had no effect on timing of the short interval. Because the effect was limited to one of two intervals, it cannot be attributed to drug-induced changes in central interval timing processes, such as clock speed or response threshold. This result highlights the necessity of training animals on multiple intervals for identifying drug effects on central timing processes.

One shortcoming of the present experiments is that SCH dosing was conducted only after HAL dosing. As a result, there is the potential that the SCH effects were modulated by prior HAL exposure. Several factors argue against any contaminating order effects. First, autoradiographic studies are in agreement that chronic and subchronic HAL exposure does not affect SCH binding (Besret et al., 2000; Dean et al., 2001; Huang et al., 1997; Sanci et al., 2002; Tarazi et al., 1997). Second, exposure to HAL was relatively brief (a maximum of eight injections), and there was a 7-day washout period between HAL and SCH administration. In addition, the SCH-induced diminution in responding reported here is of a similar degree to that reported in another study using drug-naïve rats (Fowler and Liou, 1998).

The present results demonstrate that the primary effect of HAL on interval timing is a rightward displacement of the peak function that is consistent with a decrease in clock speed. D_2 blockade by HAL is not sufficient to produce the migration pattern seen in PD. SCH, in doses sufficient to produce up to a 75% decrement in responding, did not affect clock speed, but did cause an overestimation of the long interval, due mainly to an increase in start time. Both SCH and HAL decrease response output and delay response initiation, and these effects may be more pronounced in cues that are poorly trained or are weaker elicitors of responding.

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