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Chronic treatment with haloperidol induces deficits in working memory and feedback effects of interval timing

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Abstract

Normal participants ($n = 5$) having no experience with antipsychotic drugs and medicated participants ($n = 5$) with clinical experience with chronic low doses of haloperidol (3–10 mg/day for 2–4 months) in the treatment of neuroses were evaluated for the effects of inter-trial interval (ITI) feedback on a discrete-trials peak-interval timing procedure. Feedback was presented during the ITI in the form of a histogram showing the distribution of the responses participants made on the previous trial plotted on a relative time scale. As feedback concerning the accuracy and precision of a reproduced duration (e.g., 7- and 14-s visual signals) became more remote in time, reproduced intervals gradually lengthened in duration. This rightward horizontal shift in peak time increased as a function of the probability of feedback and was enhanced by chronic treatment with haloperidol in a manner that was proportional to the duration of the signal. Our data suggest a gradual change in the underlying representation of the signal duration as a function of the remoteness of ITI feedback that is dependent upon both changes in working memory and the speed of the internal clock used to time durations in the seconds-to-minutes range.

1. Introduction

Timing short intervals in the seconds-to-minutes range relies on circuits in the frontal cortex and basal ganglia (see reviews by Gibbon, Malapani, Dale, & Gallistel, 1997; Harrington & Haaland, 1999; Harrington, Haaland, & Hermanowicz, 1998; Matell & Meck, 2004; Matell, Meck, & Nicolelis, 2003a; Matell, Meck, & Nicolelis, 2003b; Meck & Benson, 2002; Rao, Mayer, & Harrington, 2001). These circuits overlap heavily with those involved in other cognitive functions including attention, learning, and working memory (e.g., Desimone & Duncan, 1995; Lustig, Matell, & Meck, 2004; Posner & Dehaene, 1994; Smith & Jonides, 1999). In keeping with this shared circuitry, there are many behavioral connections between these different aspects of cognition. For example, accurate and precise timing requires attention (e.g., Brown, 1985; see reviews by Fortin, 2003; Pang & McAuley, 2003; Zakay & Block, 1996), timing is thought to be fundamental to learning and conditioning (Gallistel & Gibbon, 2000), and interval timing and working memory are intricately linked in a variety of situations, including serial recall and timing a signal with "gaps" or breaks (Buhusi, 2003; Lustig et al., 2004; Meck, Church, & Olton, 1984). Likewise, all of these functions are greatly influenced by dopamine's action in the cortex and basal ganglia (see reviews by Buhusi, 2003; MacDonald & Meck, 2004; Meck, 1996; Miller & Cohen, 2001; Rammsayer, 1997, 1999; Schultz, 1998). The present study examines the effects of behavioral feedback and dopamine manipulations on interval timing to examine their interactions.

Scalar expectancy theory (SET) has provided a framework for many behavioral and neuropsychological investigations of interval timing (Gibbon, 1977; Gibbon

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& Church, 1990; Gibbon, Church, & Meck, 1984). It has three main components or stages as illustrated in Fig. 1: first, the clock stage consists of a pacemaker with an attention mediated switch and an accumulator to store pacemaker pulses. When an organism pays attention to time, the switch closes, activating a circuit that allowing pulses to collect in the accumulator. During acquisition, the number of pulses that mark the durations of important events become associated with these events in the second stage of the model and are stored in reference memory. At test, samples from the accumulator and from reference memory are passed to the third stage of the model, the decision stage. Here, the samples from the accumulator and reference memory are compared in order to decide whether the current duration (as marked by accumulated pulses) matches the previously learned target duration as stored in reference memory.

Most research on SET has focused on the clock and memory stages of the model. These two stages appear dissociable both in terms of the brain circuitry that underlies them, and in the time course of their responsiveness to pharmacologic manipulations (Meck, 1983, 1996). In most pharmacologic investigations of interval timing, the target duration is first learned, or established in reference memory, prior to the drug's administration. The test trials occur after the drug is in effect. The drug's effects on interval timing are indicated by deviations from the target time reproduced during these test trials.

The clock stage relies primarily on frontal–basal ganglia circuitry. It is greatly influenced by dopamine function, perhaps especially at the D2 subtype of dopamine receptors (e.g., Meck, 1986). Dopamine antagonists typically lead to a "slow clock," as manifested by overproductions (waiting too long to respond) and underestimations (thinking less time has passed than actually has), whereas dopamine agonists typically have the opposite effect (Drew, Fairhurst, Malapani, Horvitz, & Balsam, 2003; Meck, 1983, 1996). These dopaminergic effects might occur either through modulation of the rate at which the pacemaker emits pulses, the efficiency of attention in keeping the switch closed to allow the accumulation of those pulses, or some combination of these factors (see Penney, 2003).

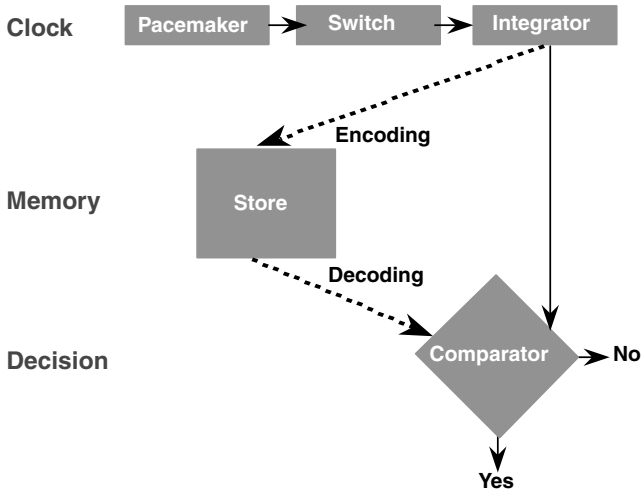

Fig. 1. Information-processing model of interval timing derived from the three stages (clock, memory, and decision) described by Gibbon et al. (1984).

Drugs that affect the clock stage lead to an immediate overestimation or underestimation of time. This distortion quickly reverses in the face of feedback about the inaccuracy of the timed responses. If the drug is then removed, the distortion reverses (Meck, 1996). These rapid, flexible effects are thought to occur because there is a discrepancy in the number of pulses associated with the target duration in reference memory during training, before the drug, versus the number of pulses accumulated during an equivalent amount of physical time during the test trials, when the drug is in effect. Feedback regarding the accuracy and precision of timing may alert the participant to this discrepancy, and allow the participant to make an adjustment to correct for it: for example, if the drug is one that leads to a faster clock, the participant may learn that more pulses must accumulate to match the target duration.

In contrast, the memory stage relies primarily on cortical and hippocampal cholinergic systems (e.g., Meck & Church, 1987; Meck, Church, Wenk, & Olton, 1987). Cholinergic agonists, such as physostigmine, cause animals to act as if their representation of the time in reference memory has been shortened, leading to underproductions of the target time and overestimations of current time relative to the target. Antagonists, such as atropine, have the opposite effect.

The time course of drugs that affect the memory stage is very different from those that affect the clock stage. As described above, drugs that affect the clock stage lead to an immediate distortion in timing that is quickly reversed by feedback. In contrast, drugs that affect the memory stage lead to a gradually developing distortion in time that is resistant to feedback (Meck, 1983, 1996).

Drugs that affect the memory stage are thought to have their effect by distorting accumulator values associated with the target time as they are passed into reference memory. At first, these distorted values will make up only a small portion of the distribution of values associated with time in the reference memory, and will thus have only a small effect on timing performance. As the number of trials for which the drug is in effect increases, an increasing number of distorted values will pass into reference memory. This gradual increase in the proportion of distorted versus veridical values in reference memory leads to a gradually increasing distortion of timing performance. Feedback does not correct the distortion because the values from subsequent trials are distorted as they enter into reference memory (see Meck,

2002a, 2002b). When the drug is removed, there is a gradual return to accurate timing as correct values are entered into reference memory across subsequent trials.

In the current study, we examined the effects of chronic administration of haloperidol, a dopamine antagonist used to treat various mental disturbance including schizophrenia, on interval timing performance in young adult college students. Based on previous findings with rats, it was expected that haloperidol administration would lead to a "clock" pattern of performance: An immediate overproduction of time that would be amenable to feedback. This pattern would also be consistent with the patterns of timing performance shown by patients with long-term dopamine dysfunctions. In particular, Parkinson's patients, whose disorder stems from an underproduction of dopamine, also show an overproduction of time under conditions in which they are presented with a single duration and not given feedback (e.g., Malapani & Rakitin, 2003; Malapani et al., 1998; Pastor, Artieda, Jahanshahi, & Obeso, 1992). Schizophrenic patients also exhibit deficits in temporal processing possibly related to abnormal dopaminergic activity in frontal–striatal circuits which contribute to faster clock speeds and underproduction of intervals (see Penney, Meck, Roberts, Gibbon, & Erlenmeyer-Kimling, 2004; Volz, Nenadic, Gaser, & Rammsayer, 2001).

We were also interested in closely characterizing the effects of feedback in general, and in particular the interactions between feedback and haloperidol administration (see Conners et al., 1996; Meck, 2003; Rammsayer, 1999; Wearden, Pilkington, & Carter, 1999). To that end, we manipulated the proportion of trials after which participants received feedback. This allowed us to look for changes in timing performance as a function of the number of trials since the last feedback event.

2. Methods

The main part of the study used a 2 (Drug condition: control, haloperidol) × 2 (Duration: 7, 14 s) × 3 (Feedback condition: 100, 50, 25%) design. Drug condition was a between subjects variable while duration and feedback were manipulated within subjects.

2.1. Participants

Two groups of participants were used. The control group (CON) consisted of five college students with no exposure to psychoactive drugs. The haloperidol group (HAL) consisted of five college students receiving low clinical doses (3–10 mg/day) of haloperidol 2–4 months prior to and during the experiment. There were 3 females and 2 males in each group and the age range was from 19 to 21 years.

2.2. Peak-interval procedures

Participants were tested on two target durations, 7 and 14 s, at the same time each day between 2 and 4 pm. Each signal duration was presented in a separate session. Sessions were separated by at least two days. The order in which durations were presented was counterbalanced across participants and drug condition.

Participants were tested using the peak-interval timing procedure (cf., Rakitin et al., 1998). This procedure is adapted from standard methods used in animal research on interval timing (e.g., Church, Meck, & Gibbon, 1994). Each experimental session began with five training trials, during which participants viewed a computer-presented blue square that changed color to magenta at the target time. The training trials were followed by the test trials, during which participants viewed the blue square and attempted to reproduce the target duration when they thought it was time for the square to change color. Participants were instructed to make multiple responses on each trial, attempting to bracket the target duration by starting slightly before the target and stopping slightly after.

After making their last spacebar response for that trial, participants could press the "Enter" key to terminate the trial. Otherwise, the trial would terminate automatically at three times the target duration. At the end of the trial, participants were either given feedback or began the next trial after a randomly varied inter-trial interval (ITI).

2.3. Feedback procedures

Three different feedback schedules were used within each session. Feedback consisted of a histogram, displayed on the computer monitor during the ITI, which showed the participant the distribution of his or her responses on the most recent trial, relative to the criterion time (see Rakitin et al., 1998 for additional details of the feedback histogram). After viewing the feedback histogram, participants pressed the "Enter" key to begin the next trial after a variable ITI. This feedback followed 100, 50, or 25% of the trials. Trials were randomly selected for feedback in those conditions with less than 100% feedback. The order of feedback conditions was counterbalanced across participants. Participants completed 60 trials for each Duration × Feedback condition, for a total of 360 trials.

3. Results

Participants' spacebar responses were analyzed using the method described by Church, Meck, and Gibbon (1994; see also Rakitin et al., 1998). In short, performance on each trial is first characterized in terms of

when the participant starts ($s1$) and stops ($s2$) their spacebar responses. The arithmetic mean of these two times (i.e., the duration in the middle between them; $(s1 + s2)/2$) is used as the index of the participant's remembered time for that trial, and is referred to as the "peak time." Peak times for trials within a condition are averaged together to determine the peak time for that condition.

The averaged peak times for participants across the different conditions are displayed in Fig. 2. These times were submitted to a Group (HAL & CON) × Duration (7 and 14 s) × Feedback (25, 50, and 100%) ANOVA. All three main effects were significant: Group, $[F(1,16) = 76.14, p < .001]$, Duration, $[F(1,16) = 2623.34, p < .001]$, and Feedback, $[F(2,16) = 173.17, p < .001]$. The three-way interaction was also significant, $[F(2,16) = 12.79, p < .0005]$. Examination of the means suggests that the HAL group was more affected by the feedback manipulation than was the CON group, and that this was especially true at the 14-s duration, $p < .05$.

The results of the two-way interactions were consistent with this interpretation. The HAL group was more sensitive to feedback than was the CON group as indicated by the Group × Feedback interaction, $[F(2,16) = 91.49, p < .0001]$. Feedback had a greater effect at the 14-s duration than at the 7-s duration as indicated by the significant Duration × Feedback interaction, $[F(2,16) = 20.32, p < .0001]$. Post hoc analyses indicated that the CON group showed a significant effect of feedback at both the 7-s $[F(2,4) = 7.79, p < .05]$ and 14-s $[F(2,4) = 8.65, p < .01]$ durations. The HAL group demonstrated very strong effects of feedback at the 7-s $[F(2,4) = 65.65, p < .0001]$ and 14-s $[F(2,4) = 73.58, p < .0001]$ durations.

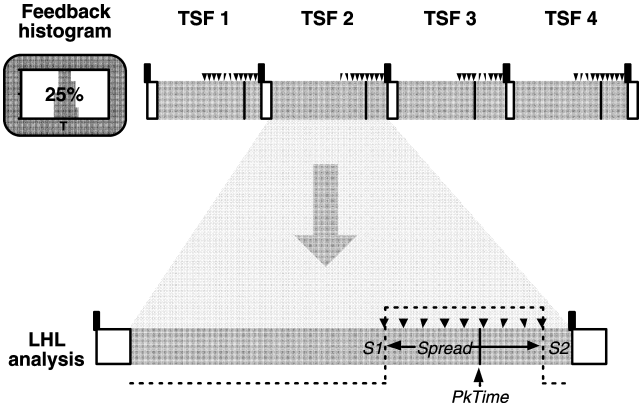

Fig. 2. Diagram of the 25% ITI feedback histogram condition in which responding on subsequent trials can be analyzed as a function of "trials since feedback" (e.g., TSF1…TSF2…TSF3…TSF4) as illustrated in the upper panel. In addition, the "low-high-low" (LHL) single-trials analysis for identifying the start ($s1$) and stop ($s2$) times for TSF responding as well as the spread and peak times (PkTime) for individual trials are illustrated in the lower panel.

We next examined the trial-by-trial data for the 25% feedback condition using methods described by Church et al. (1994). Trials are averaged together based on their distance from the feedback event. One can then compare the peak times for those trials that were the first to occur since a feedback event (Trial Since Feedback 1 = TSF1) to those that occurred two trials after the feedback even t (TSF2), and so on as illustrated in Fig. 3. This analysis was limited to TSF1 to TSF4 because there were too few trials occurring at a removal of five or more trials since a feedback event to provide reliable data.

The results of this analysis are displayed in Fig. 4. Feedback led to an immediate correction, as shown by accurate performance on the trial immediately following feedback (TSF1). This correction diminishes, and participants show an increasing tendency to overproduce the target duration, as distance from feedback increases as demonstrated by a significant effect of TSF, $[F(3,4) = 16.87, p < .0001]$. There was a main effect of Group, $[F(1,24) = 81.91, p < .0001]$, and the drift away from the target duration was significantly faster for HAL than for CON participants as indicated by a significant Group × TSF interaction, $[F(2,24) = 8.17, p < .001]$. No other main effects or interactions were significant, p's $> .05$.

The simplest interpretation of the results thus far is that chronic haloperidol led to a slowing of the clock in our participants, causing them to overproduce the

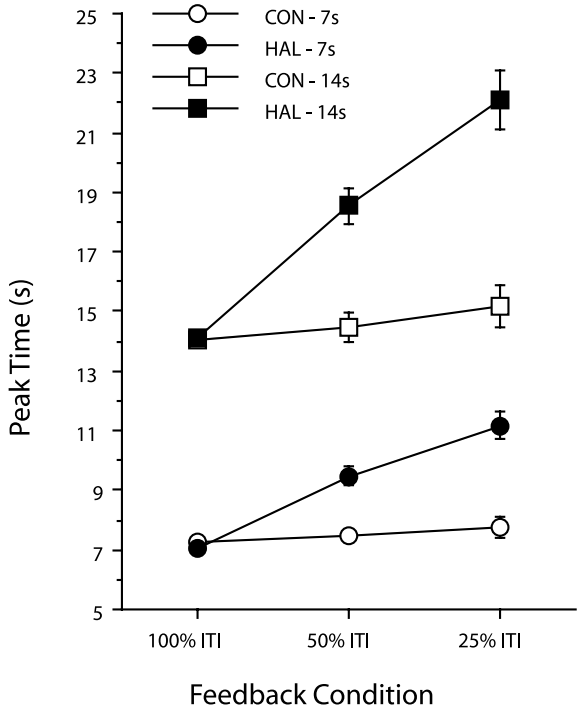

Fig. 3. Peak times (means ± SE) for participants in the control (CON) and haloperidol (HAL) conditions tested with 7- and 14-s signal durations as a function of the probability of ITI feedback (25, 50, and 100%).

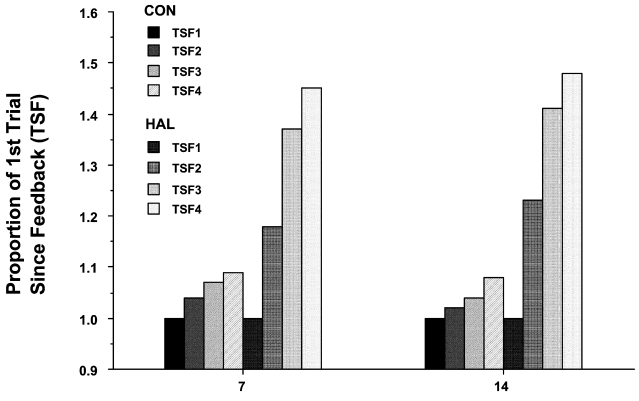

Fig. 4. Peak times normalized as a proportion of the first trial following ITI feedback for participants in the control (CON) and haloperidol (HAL) conditions tested with 7- and 14-s signal durations as a function of trials since feedback (TSF1–4). For each duration, CON values are on the left and HAL values are on the right.

target duration. At first glance, the results from the reduced-feedback conditions (50%, 25%) might seem to suggest that haloperidol was affecting memory, because the distortion was maintained despite intermittent feedback. However, the trial-by-trial analyses of the 25% feedback condition show that the effects of haloperidol were in fact very sensitive to feedback: on the first trial following feedback, both HAL and CON participants were very accurate. However, as the number of trials after the feedback event increased, so did participants' tendency to overproduce the interval, and the increase in overproduction was greater for the HAL group. This sensitivity to feedback is most consistent with the idea that haloperidol is affecting the functioning of the clock, not reference memory (cf., Meck, 1983, 1996).

4. Discussion

The results of this study can be summarized as follows: chronic haloperidol administration led to an overproduction of time in our college student participants, consistent with previous findings on haloperidol administration in animals and on the effects of neurological disorders that disrupt dopamine function (see reviews by Meck, 1996; Meck & Benson, 2002). A trial-by-trial analysis suggests that reproduction of the target interval becomes later in time as feedback becomes more remote. This effect occurs for both control and haloperidol participants, but the effect is exaggerated for those in the chronic haloperidol condition.

The first important point to be taken from these data is that under conditions of less than 100% feedback, apparent sustained distortions in timing cannot be unequivocally interpreted as the result of effects on reference memory. In the present study, the HAL group appeared to show a sustained distortion in the reduced-feedback conditions compared to controls, which would at first suggest that haloperidol was having an effect on reference memory. However, the analysis of individual trials clearly showed that this distortion was very sensitive to feedback, more consistent with an effect on the internal clock. Thus, if feedback is less than 100%, a trial-by-trial analysis is required to determine if overall distortions are more likely to be due to effects on the clock or memory stages of temporal processing. "Clock" effects should be sensitive to feedback, showing corrections on the trial immediately following feedback and drifting to increasing distortion as the number of trials since the last feedback effect increases. "Memory" effects should not show this same sensitivity and instead remain stable regardless of feedback.

Both CON and HAL participants showed an increasing distortion as the number of trials since the last feedback event increased. This pattern raises some interesting questions about the mechanisms by which feedback has its effects, and the interactions of those effects with dopaminergic function.

Feedback is often thought to have its effects by updating the representation of the target time in memory (see discussions by Meck, 1983, 1996; Meck & Benson, 2001). That is, feedback serves to alert the participant that the amount of time (number of accumulated pulses) they have associated with the target duration is incorrect, and on subsequent trials they change the amount of time (amount of pulse accumulation) before responding to adjust for the discrepancy (Meck, 2002a, 2002b). For example, in the current experiment, where haloperidol and distance from feedback led to an overproduction of time, the feedback event would alert participants that they were waiting too long (for too many pulses), and that on the next trial they should respond sooner.

One possible explanation for the pattern of results found here is that the representation of the target duration and/or the correction effects of feedback in working memory decay over time, and that this decay is exaggerated by chronic haloperidol. This interpretation would be consistent with previous findings that chronic haloperidol administration downregulates dopamine D1 receptors and impairs working memory (Castner, Williams, & Goldman-Rakic, 2000), and that dopamine is fundamental to the correction effects of feedback on many tasks (e.g., Schultz, 1998; Schultz, Dayan, & Montague, 1997).

Another possibility is that both feedback and the dopamine manipulations had direct effects on clock speed. In this regard, it is important to note a difference between the animal and human findings: In the animal timing literature, a lack of feedback is typically associated with a leftward shift of peak functions, i.e., responding too soon (e.g., Church et al., 1994). In contrast, for humans, a lack of feedback is associated with a rightward shift of temporal generalization and peak-interval functions, i.e., responding too late (e.g., Hinton,

Gibbon, Rakitin, & Meck, 1993; Wearden et al., 1999). The most likely reason for this divergence is the different reinforcement values of feedback in animal versus human studies. In animal studies, feedback consists of a appetitive reinforcement (i.e., food or juice reward). A failure to receive this feedback may result in agitation or frustration and therefore an increase in arousal and decrease in response inhibition, causing the animal to respond too soon. In contrast, for humans the most likely outcome of a lack of feedback is boredom and a drift of attention from the timing task.

In the current data, the feedback event could have led to a temporary increase in clock speed that would fade with increasing distance. The increase in clock speed could occur if feedback temporarily increased arousal and thus pacemaker firing (Matell & Meck, 2000, 2004). Another mechanism by which feedback could increase clock speed would be by temporarily increasing attention to time, so that the switch allowing pulses to pass from the pacemaker to accumulator would remain more efficiently closed, increasing the number of pulses that pass into the accumulator. As attention to time faded with increasing distance from feedback, the attentional switch would begin to "flicker", resulting in pulses being lost before reaching the accumulator.

The idea of a flickering mode switch described above was first used to explain over- and underestimations of time as a function of a stimulus's relative ability to capture and hold attention (Penney, 2003; Penney, Allan, Meck, & Gibbon, 1998, 2000). A similar idea has also been used to interpret the timing errors made by older adults, who often have deficits in controlled attention compared to young adults (Lustig, 2003; Lustig & Meck, 2001). In both cases, reduced attention to time is thought to lead to flickering of the switch and a loss of pulses, resulting in a slower clock. In the present case, exaggeration of the drift away from the correct time due to chronic haloperidol administration is also consistent with other work showing that haloperidol administration may reduce the ability to sustain attention (e.g., Levin, 1997; Levin, Wilson, Rose, & McEvoy, 1996). Haloperidol's effects on attention could have led to an increased flickering of the attentional switch for the HAL participants compared to controls, leading to a greater drift away from the target time as a function of the distance from feedback.

These different possibilities for the locus of haloperidol and feedback effects are by no means mutually exclusive. In fact, given the links between dopamine function and feedback effects, and the involvement of dopamine in many aspects of cognition, it is quite likely that feedback and haloperidol affect both clock speed and working memory. Arousal and attention effects of haloperidol and distance from feedback would lead to decreases in clock speed, leading to an overproduction of the target interval. Working memory decay of the correction effects of feedback due to increasing time from the feedback event, possibly exaggerated by haloperidol, would also lead to overproduction. Because both the clock speed effects and the working memory effects lead to parallel results—that is, overproduction—it is not possible to disentangle their separate contributions at this time.

The effects of haloperidol administration on peak-interval timing reported here are reminiscent of the effects of abstinence from tobacco smoking (Carrasco, Redolat, & Simón, 1998) and methylphenidate removal in attentional-deficit disorder (ADD) patients (Levin et al., 1996, 1998; Meck, 2003). When adults with ADD are removed from their medication and provided with ITI feedback on 100% of the peak-interval trials their peak functions are centered at the correct times showing excellent accuracy of the reproduced intervals. In contrast, when ITI feedback is provided on only 25% of the trials a proportional rightward shift is observed in the timing of 7- and 17-s intervals, reflecting a discrepancy in the accuracy of temporal reproductions that is not observed in normal participants. This rightward shift is accompanied by a broadening of the peak functions indicating a decrease in temporal precision with lower levels of feedback. Both of these findings are consistent with a slowing of the internal clock as a function of the probability of feedback and may be the result of an attentional deficit (e.g., flickering mode switch) as described by previous authors (e.g., Lustig, 2003; Meck & Benson, 2002; Penney, 2003). Interestingly, when ADD patients are given a stimulant drug (e.g., nicotine) the effects of 25% ITI feedback are enhanced and levels of temporal accuracy and precision are observed that are equivalent to the 100% ITI feedback condition. These results suggest an equivalence of the ITI feedback effects and the types of pharmacological stimulation provided to ADD patients by dopaminergic drugs such as methylphenidate or nicotine (see Conners et al., 1996; Levin et al., 1996, 1998). These findings also support the proposal that deficits in attention can lead to the underestimation of signal durations in a manner consistent with a slowing of an internal clock that is sensitive to dopaminergic manipulations whether they are produced by behavioral or pharmacological treatments.

An interesting possibility for future studies would be to include drug administrations (e.g., cocaine or methamphetamine) that increase clock speed and examine the effects of distance from feedback (e.g., Buhusi & Meck, 2002; Matell, King, & Meck, 2004). In this case, clock speed effects of drugs and/or feedback, whether due to arousal or increased attention to time, would lead to a faster clock, and thus underproduction of the target interval. In contrast, the correction or working memory effects of feedback should lead to compensation for the faster clock, and thus more accurate productions. Any dynamic change in timing performance as a function

of distance from the feedback event (in this case, an increasing tendency to underproduce the target interval) would thus be more directly attributable to working memory.

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