Differential Effects of Clozapine and Haloperidol on Interval Timing in the Supraseconds Range

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ORIGINAL INVESTIGATION

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Differential effects of clozapine and haloperidol on interval timing in the supraseconds range

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Abstract The effects of clozapine (0.6, 1.2, and 2.4 mg/kg) and haloperidol (0.03, 0.06, and 0.12 mg/kg) on the timing of 10, 30, and 90-s intervals were characterized in rats. Each drug's effect on timing behavior was assessed following intraperitoneal injections using a variant of the peak-interval procedure. Although haloperidol proportionately shifted peak times rightward in a manner consistent with a decrease in clock speed, clozapine exerted the opposite effect and proportionately shifted peak times leftward in a manner consistent with an increase in clock speed. These results support the proposal that typical antipsychotic drugs such as haloperidol and atypical antipsychotic drugs such as clozapine exert differential effects on dopaminergic, serotonergic, and glutamatergic systems within the cortex and striatum, two brain regions shown to be crucial for interval timing.

Keywords Timing and time perception · Temporal differentiation · Dopamine · Glutamate · Serotonin · Typical and atypical antipsychotic drugs · Corticostriatal circuits

Introduction

How timing and time perception are influenced by the regulation of dopamine (DA) receptors is of considerable interest, in part because treatment with DA agonists and antagonists has been shown to increase and decrease the speed of an internal clock, respectively (Buhusi 2003; Cevik 2003; Drew et al. 2003; Maricq and Church 1983; Matell et al. 2004; Meck 1983, 1986, 1996). In addition, DA antagonists have been shown to ameliorate the positive symptoms of schizophrenia, which include distortions in time perception (Brown et al. 2004; Elvevåg et al. 2004; Lustig and Meck 2005; Meck 2003, 2005; Rammsayer 1990, 1997, 1999; Penney et al. 2005). One of the major effects of the antipsychotic drugs used to treat schizophrenia is the up-regulation of striatal D_2-like receptors. Although previous studies have focused on the regulation of these striatal DA receptors, less is known about the pharmacological regulation of cortical DA receptors and their effects on cognition. Both traditional (e.g., haloperidol) and atypical (e.g., clozapine) antipsychotic drugs have been hypothesized to be effective in the treatment of schizophrenia due to their ability to block D_2 receptors in the dorsolateral striatum and extrastriatal brain regions, including the frontal and temporal cortex. A drug's efficacy in treating schizophrenia has been shown to correlate with its DA D_2 binding affinity (Creese et al. 1976). In addition, the ability of a drug to reduce the speed of a hypothetical internal clock is positively correlated with the drug's D_2 binding affinity and not its affinity to the D_1, D_3, the α-noradrenergic receptor, or the serotonin 5-HT_1 and 5-HT_2 receptors (Meck 1986, 1988).

In vivo studies in medicated schizophrenic patients have shown that treatments with traditional antipsychotic compounds such as haloperidol consistently induce 70–80% occupancy of striatal D_2 receptors (Nordstrom et al. 1993). Furthermore, high levels of D_2 receptor occupancy in the striatum are associated with a greater risk of extrapyramidal side-effects (Farde et al. 1992). More recent studies have shown that D_2 receptor blockade is high in the temporal cortex with both haloperidol and clozapine, whereas clozapine induced a significantly lower D_2 binding index than haloperidol in the thalamus and striatum (Xiberas et al. 2001). Damask et al. (1996) reported that haloperidol produces a modest up-regulation of DA receptor mRNAs in the striatum, whereas clozapine tended to down-regulate these mRNAs. Conversely, in the cortex, both drugs exerted strong effects on D_1 and D_2 mRNA levels. Cortical D_1 mRNA levels were up-regulated by haloperidol, but this effect was largely restricted to cingulate cortex; clozapine

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also up-regulated D_1 mRNA, but primarily in parietal regions. Haloperidol down-regulated D_2 mRNA in the majority of cortical regions, but most dramatically, in frontal and cingulate regions. In contrast, clozapine typically up-regulated D_2 mRNA, but primarily in regions other than frontal and cingulate cortex. These results indicate that clozapine and haloperidol each have regionally specific effects, and differentially regulate DA receptor mRNA expression in striatal and cortical regions of the rat brain.

A number of studies have shown that acute clozapine, but not haloperidol, increases extracellular concentrations of glutamate in the medial prefrontal cortex (mPFC) of freely moving rats (Daly and Moghaddam 1993; Yamamoto et al. 1994). It has also been demonstrated that clozapine preferentially potentiates *N*-methyl-D-aspartate (NMDA) receptor-mediated transmission in the mPFC, whereas haloperidol produces an overall inhibitory action on glutamate receptor-mediated neurotransmission (Arvanov et al. 1997). These neurochemical data have been used to support the proposal that D_2 receptor blockade in cortical regions may produce qualitatively different effects on behavior compared with D_2 receptor blockade in striatal regions (see Duncan et al. 1998). Because interval timing is dependent upon DA–glutamate interactions in corticostriatal circuits (Matell and Meck 2004; Meck 1996, 2005), these findings also suggest that clozapine and haloperidol may have differential effects on timing and time perception.

The DA system has long been thought to contribute to aspects of motivation, reinforcement, and reward prediction—umbrella terms that describe the process by which a biologically prepotent stimulus supports and organizes behavior that directs an organism to, or away from, the same stimulus in the future (e.g., Hernandez et al. 2002; Nicola et al. 2000; Pagnoni et al. 2002; Robbins 2003). Indeed, DA antagonists attenuate the reinforcing properties of brain stimulation reward, and this effect is correlated with the drug's D_2 binding affinity (Gallistel and Davis 1983). The differential effects of clozapine and haloperidol concerning reinforcement efficacy are evident during the performance of progressive ratio schedules of reinforcement by rats. In one experiment, the highest response ratio completed was reduced by haloperidol and increased by clozapine (Mobini et al. 2000). Although both drugs reduced the peak response rate, haloperidol reduced and clozapine increased the "motivational" parameter of the operant behavior in a manner similar to D-amphetamine. These findings are consistent with a reduction of reinforcer efficacy produced by haloperidol and an increase in reinforcer efficacy produced by clozapine (Cilia et al. 2001; Lara et al. 2001).

The relationship between DA receptor blockade and reinforcer efficacy as a function of a drug's binding affinity in different brain regions is interesting in light of the interval-timing system, whose association with DA transmission has been well-documented (Buhusi 2003; Buhusi and Meck 2002; Hinton and Meck 1997; Meck 1983, 1986, 1996; Matell and Meck 1999, 2004; Matell et al. 2003a,b). The extent to which an internal clock can be slowed is correlated with a drug's binding affinity to the D_2 receptor, and not its affinity to D_1, D_3, the α-noradrenergic receptor, or the serotonin 5-HT_1 and 5-HT_2 receptors (Meck 1986). One way to demonstrate this clock speed effect is with the use of the peak-interval (PI) procedure (Catania 1970; Church et al. 1994; Matell et al. 2004; Meck 1996). The PI procedure is a modified version of a discrete-trial fixed-interval (FI) procedure. The onset of a stimulus, such as a light or tone, signals the time-interval (i.e., the temporal criterion) after which a measured response (e.g., a lever press) is reinforced. Following extensive training, probe trials are introduced during which the stimulus remains on long past the trained criterion time. The mean response rate averaged across probe trials—the peak function—is observed to gradually increase from a low response rate at the beginning of the trial and peak approximately at the temporal criterion, only to gradually decrease to low levels of responding again. The peak function resembles a Gaussian-shaped distribution whose median is centered on the temporal criterion. The peak function also brings to light the *scalar property* of interval timing—a manifestation of Weber's law, such that the spread of the peak function is proportional to the interval being timed.

Following drug administration, a D_2 antagonist shifts the peak function rightward, and the degree of the shift is proportional to the temporal criterion, which excludes the possibility of this effect being purely motor in nature (Meck 1996). This effect is amenable to a predominant information-processing model of interval timing called scalar expectancy theory (SET). In this case, the interval-timing system is conceptualized as being composed of several modular domains. At the foundation of SET is an internal clock, the output of which is a value integrated over time after the onset of a signal. Responding is mediated by a comparison between the integrated output of the clock (T_1) and the internal clock value associated with the temporal criterion, drawn from memory (T_2). Specifically, the comparison follows a ratio response rule so that responding is a function of the ratio T_1/T_2. The response rule's "ratio-comparison" characteristic contributes to the scalar property (Gibbon et al. 1984; Church et al. 1994). Under this heuristic framework, haloperidol is believed to slow the speed at which the clock's output is integrated as time elapses in the trial thereby producing a proportional rightward shift of the PI function (Buhusi and Meck 2002; Lustig and Meck 2005; Meck 1996).

Alternatively, one may interpret the effects of dopaminergic manipulation on interval timing in the context of reinforcement mechanisms. The behavioral theory of timing (BeT, Killeen and Fetterman 1988) eschews an information processing explanation of interval timing, and instead adopts a relatively more behavioral perspective. In this theory, behavior serves as a discriminative stimulus for reinforcement, rather than a changing "internal" variable. The major proposal of BeT is that predictive signals for salient events, such as reinforcement, elicit a cascade of behavioral states whose ebb and flow are lawfully described over time at steady state conditions (Killeen 1975). A certain class of behavior(s) is emitted during each state, and the rate at which state transitions take place (i.e., the

"clock speed") is influenced by reinforcement density, which refers to the reinforcement's *value per unit time of the stimulus* (Bizo and White 1994; Killeen et al. 1997, 1999). In this context, haloperidol could exert its effects on interval timing by devaluing reinforcement (e.g., the food pellet), thereby lowering reinforcement density and shifting the PI function rightward.

Does temporally organized behavior reflect the output of a dedicated cognitive or neural subsystem or does a chain of behavioral states simply unfold across time at a rate that parallels reinforcement density? In support of the SET heuristic, there is evidence that neurons can encode *specific* durations (Matell et al. 2003a,b). Indeed, some dorsolateral striatal neurons modulate their activity with respect to one temporal criterion without exhibiting change in activity for an alternative temporal criterion. The heuristic framework of SET motivated the development of the striatal beat frequency (SBF) model, which provides a neurobiological instantiation for the aforesaid findings (Matell and Meck 2000, 2004). The SBF model posits that "duration encoding" in the dorsolateral striatum is a property of the anatomical, pharmacological, and electrophysiological properties of this area. There is converging evidence from human and animal studies to suggest that the frontal–striatal system, which is made up of functional "loops" comprising neurons in prefrontal cortex, striatum and thalamus, is fundamental to interval timing and working memory (Lustig et al. 2005; Malapani et al. 1998; Matell and Meck 2000, 2004; Matell et al. 2003a,b; Meck 1996, unpublished data; Meck and Benson 2002; Meck and N'Diaye 2005). Medium spiny neurons (MSNs) in the striatum are positioned to filter glutamatergic, corticostriatal input. The crux of SBF model is that the activation of MSN at the expected time of reinforcement reflects a trained sensitivity to a pattern of glutamatergic, corticostriatal afferents that are "tuned" to fire coincidentally around the temporal criterion. There is evidence that DA–in particular, D_2 receptors–contributes to this "perceptual filtering" mechanism by mediating the selection of relatively more active corticostriatal inputs (Bamford et al. 2004; Cepeda et al 1993, 2001).

Putting epistemological issues aside, one can reconcile aspects of BeT and SET by acknowledging that the speed of the hypothetical clock can be modulated by changes in feedback or reinforcement density (see Lustig and Meck 2005). A decrease in reinforcement density by nonpharmacological means (e.g., lowering the probability of reinforcement) can induce a rapid shift in temporally organized behavior (Fetterman and Killeen 1995) in a manner similar to the effects of dopaminergic antagonists (see Meck 2003). That striatal lesions profoundly influence interval timing (Gibbon et al. 1997; Meck 1996) provided an impetus for understanding the role of DA as it relates to interval timing and the development of the SBF model. However, there has been less emphasis placed on prefrontal cortical DA in the context of timing and time perception. For example, DA contributes to prefrontal cortical function by modulating glutamatergic transmission within the prelimbic cortex (PrL, e.g., Otani et al. 2003; Peters et al. 2004; Wang and O'Donnell 2001) and plays a role in the genesis of "delay-period" activity that is observed during classical "working memory" tasks (e.g., Sawaguchi and Goldman-Rakic 1991; Williams and Goldman-Rakic 1995). Given that clozapine and haloperidol exhibit seemingly opposite profiles of activity in the mPFC and dorsal striatum, and differing binding affinities for DA and 5-HT receptors, we wondered whether these drugs would differentially affect interval timing in the supraseconds range.

We chose to use a modified version of the PI procedure called the "tri-peak" procedure (Gallistel et al. 2004; Matell and Meck 1999; Matell et al. 2004). The tri-peak procedure is conceptually similar to the PI procedure, but there is one major difference. In the tri-peak procedure, the onset of a stimulus signals the beginning of a trial as usual. However, there are three response options, each of which is associated with a different temporal criterion in relation to the beginning of the trial, i.e., there is a "short," "medium," and "long" response option. One may characterize the three peak functions with respect to each response option across probe trials. The tri-peak response function looks trimodal, with each peak centered on the expected time of reinforcement associated with the response option. The tri-peak procedure is useful because it allows one to simultaneously evaluate interval timing in the context of three different time intervals. If clozapine increases the reinforcement efficacy and/or the speed of the internal clock, one would expect a leftward shift in the tri-peak function, and the degree of the shift would be proportional to each of the three temporal criteria (e.g., 10, 30, and 90 s). Conversely, if haloperidol decreases reinforcement efficacy and/or the speed of the internal clock, one would expect a proportional rightward shift for the entire tri-peak function. Alternatively, a nonspecific motor effect would lead to an absolute shift in the tri-peak function that would be independent of the intervals being timed.

Methods

Subjects

Twenty male Sprague–Dawley rats about 4 months of age weighing 200–300 g (Charles-River Laboratories, Raleigh, NC) at the beginning of the experiment were used as subjects. Rats were housed in pairs in a 12:12-h light/dark cycle with lights on from 7:00 AM. to 7:00 PM. Rats were given continuous access to water and maintained at 85% free-feeding weight by a daily ration of Purina rat chow given shortly after the daily sessions, which were conducted 7 days/week. All procedures were conducted in accordance with the policies of the Duke University Institutional Animal Care and Use Committee.

Apparatus

All experimental data were obtained in ten operant chambers (Coulbourn Instruments, Allentown, PA). A pellet dispenser (Coulbourn Instruments) delivered 45-mg food pellets (Noyes Precision, Formula A; P. J. Noyes, Lancaster, NH) to a food cup located halfway up the front wall. Two retractable response levers (Coulbourn Instruments), which were positioned 2 cm from each side wall, and one 4-cm nonretractable response lever (Coulbourn Instruments), which was positioned in the center of the chamber, were located horizontally across the front wall, 2.5 cm above the grid floor. A 2.5-cm Sonalert (P. R. Mallory & Co., Indianapolis, IN), calibrated to 93 dB with respect to background, was mounted in between the food cup and the center response lever. A 6-W house light was located on the ceiling and was illuminated throughout the session. Each operant chamber was housed inside a sealed wood sound- and light-attenuating box, and was equipped with a 10-cm ventilation fan and an eyepiece viewer for observation. An IBM-PC compatible computer attached to a custom-built electronic interface was used to control the experimental equipment and record the behavioral data.

Procedures

Pretraining (sessions 1–6)

All rats received six sessions of combined magazine and lever training. During these sessions, a food pellet was delivered once a min for 60 min. In addition, one of the side response levers was primed until 15 responses were made on that lever, at which point, the middle response lever was primed for 15 responses, and finally, the other side lever was primed for 15 responses. During the time that the side levers were primed, the primed lever was retracted for a 1-s period 2 s before free pellet delivery. The direction in which the levers were primed (e.g., left lever, middle lever, right lever) was based on the eventual direction of the short, medium, and long duration associated responses in the final procedure (see below). This procedure was repeated until the rat pressed each lever 30 times or 60 min had passed, thus, ending the session. The house light illuminated the chamber upon completion of the session.

FI training in increasing-duration order (sessions 7–12)

Sessions began with the illumination of the house light and onset of a 93-dB tone. A 10-s FI was scheduled upon either the right or left response lever (counterbalanced across rats). The first response after 10 s was reinforced with a 45-mg Noyes pellet, and the sound stimulus was turned off. After a 2-s delay, the sound stimulus was turned back on and a 30-s FI schedule was imposed upon the middle lever. Following reinforcement of this lever press, the sound stimulus was again turned off for 2 s. The sound stimulus was then turned on again and a 90-s FI was scheduled upon the remaining side lever. After reinforcement was earned for this lever, the sound was turned off and a random intertrial interval (ITI-55 s mean, range 40–70 s) began. This procedure was repeated for 95 min. The short within-trial break between the increasing duration FIs was used to "move" the rat from one side of the operant chamber to the other during the three FI trials. For each FI duration, the trial would self terminate if the rat did not make a response after the criterion time and before three times the criterion time plus a random 0–20% of the three times criterion time (e.g., a 30-s trial lasted anywhere from 90 to 108 s).

FI training in random order (sessions 13–18)

Sessions were identical to those described above with the exception that on any particular trial, the FI duration was randomly selected, and the full 55-s ITI was instituted after every trial. In these trials, no indication was given to the rat as to which duration (10, 30, or 90 s) would be selected for that trial's criterion. As a consequence, rats would begin each trial by orienting themselves in front of the short lever. If responding on this lever did not pay off, the rat would then switch to the "middle" lever. If reinforcement failed to be primed on this lever, the rat would switch to the long lever, for which responding would be reinforced following the 90-s criterion. All trials types were selected with equal probability.

PI baseline training (sessions 19–50)

These sessions were identical to the FIs in random order with the exception that a nonreinforced "probe" trial was added to the trial types randomly selected for each trial. These nonreinforced probe trials lasted for the same length of time as the self-terminating 90-s FI trials (270–330 s).

Drug treatment/testing regimen (sessions 51–77)

Rats were randomly divided into a clozapine (CLOZ) and a haloperidol (HAL) group with ten rats each. Individual rats received an intraperitoneal (i.p.) injection of either 0.9% saline or drug: clozapine (0.6, 1.2, and 2.4 mg/kg) and haloperidol (0.03, 0.06, and 0.12 mg/kg). Drug injections were randomly interspersed with saline injections with the constraint that at least one saline injection session separated drug injection sessions. Drug injections occurred (on average) every three test sessions. Drug dosages were randomized across drug injection sessions with the constraint that each dose was administered at least three times during the course of the experiment.

Drugs

Clozapine (Sigma/RBI, St. Louis, MO) was dissolved in a small amount of 10% lactic acid that was then brought up to volume with distilled water, sonicated, and then neutralized with 1 M NaOH (pH 6.0). Haloperidol (Sigma/RBI) was dissolved in a vehicle of 0.25% tartaric acid and adjusted as necessary for pH. All drugs were administered via the i.p. route (injection volume of 1 ml/kg) 30 min prior to the test sessions.

Data analysis

The time of each lever press was recorded and placed into time bins whose width was set at 10% of the criterion duration for each lever (e.g., 1-s bin width for the 10-s response lever and 9-s bin widths for the 90-s response lever). These data were then pooled over three sessions and plotted as a function of each lever's maximal response rate vs bin number multiplied by the scaling factor for each criterion duration. Statistical measures of the peak functions were derived by fitting each block of data with a Gaussian curve + linear ramp function, with the mean of the fitted Gaussian function being used as a measure of the peak time, and the standard deviation of the fitted Gaussian function being used as a measure of the spread. Temporal control was verified by calculating the ratio of the fit (variance accounted for) of a straight line to the fit of a Gaussian function for each duration and block. If this ratio exceeded 0.8, the rat's data for that criterion duration was dropped and replaced with the mean for all rats of that block of sessions. Data replacement occurred on less than 4% of the determinations.

A repeated-measures analysis of variance (ANOVA; 4×3) using dose and duration as within-subject variables was applied to the CLOZ and HAL groups separately for both peak time and peak rate. The alpha level was set at $p<0.05$ for all statistical analyses.

Results

Clozapine effects on peak time and peak rate

The effects of CLOZ on peak time with respect to each lever/temporal criterion (i.e., short, medium, and long) as a function of drug dose are shown in Fig. 1. The results of the repeated-measures ANOVA (dose×duration) revealed a main effect of duration [$F(2,18)=3{,}408.8$, $p<0.0001$] verifying the obvious difference in peak time with respect to each lever. The overall effect of CLOZ was to shift the tri-peak functions leftward (i.e., the peak time decreased). This conclusion is supported by a significant main effect of dose [$F(3,27)=855.6$, $p<0.0001$]. Moreover, the timing functions plotted in Fig. 1 suggest that CLOZ induced a leftward shift that was proportional to the duration being timed. This observation is confirmed by a significant duration×dose interaction [$F(6,54)=259.6$, $p<0.0001$]. The previous analyses applied to spread revealed no significant effects.

The mean peak rate data for each temporal criterion as a function of CLOZ dose are presented in Fig. 2. A repeated-measures ANOVA (dose×duration) showed a significant effect of duration [$F(2,18)=10.20$, $p<0.01$] but a non-significant effect of dose [$F(3,27)=1.85$, ns] as well as a nonsignificant duration×dose interaction [$F(6,54)=0.78$, ns]. Consequently, although CLOZ had no reliable effect on peak rate, the effect of duration was to decrease peak rate as a function of increases in the temporal criteria. This dissociation between the effect of CLOZ on peak time and peak rate supports the proposal that these response measures can be independently manipulated (Matell et al. 2004; Roberts 1981).

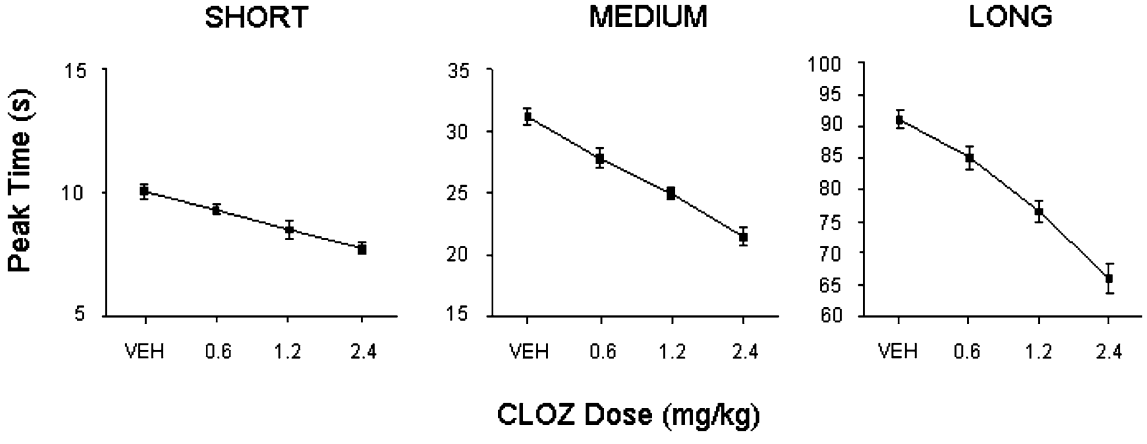


Fig. 1 The effects of clozapine (CLOZ) on peak time. Peak time was shifted leftward following systemic CLOZ injections. The *left*, *center*, and *right panel* display the CLOZ effects on the 10-s (*short*), 30-s (*medium*), and 90-s (*long*) durations, respectively. Each panel describes the peak time as a function of CLOZ dose. Note that the *Y*-axis for each panel is scaled differently to account for the greater change at longer durations. There were significant effects of duration ($p<0.0001$), dose ($p<0.0001$), and the duration×dose interaction ($p<0.0001$), which is consistent with the observation that the leftward shifts in peak time are proportional to the durations being timed. The data are expressed as means±SEM

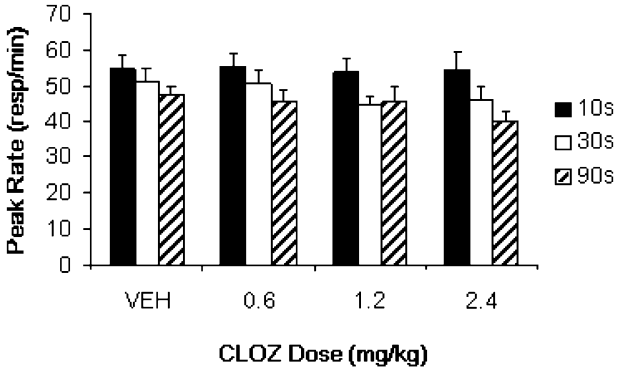


Fig. 2 The effects of clozapine (CLOZ) on peak rate. The *X*-axis contains the dose of CLOZ that was administered with respect to 10-, 30-, and 90-s temporal criteria whereas the *Y*-axis expresses the mean peak rate±SEM. There was a significant effect of duration ($p<0.01$) but no reliable effect of dose or the duration×dose interaction

Tri-peak response functions for vehicle control and CLOZ sessions (highest dose, 2.4 mg/kg) are presented in Fig. 3 in order to illustrate the horizontal leftward shifts produced by CLOZ administration as well as the symmetry of the Gaussian-shaped functions plotted on a linear time scale. The slopes of the regression of produced times against reinforced times decreased from 1.01 under vehicle to 0.73 under the highest dose of CLOZ (proportional regressions, with intercept=0.08) as illustrated in Fig. 4.

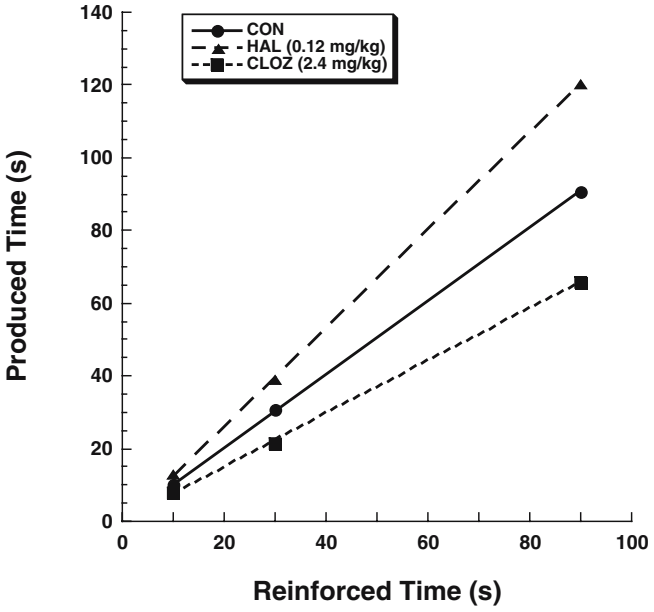
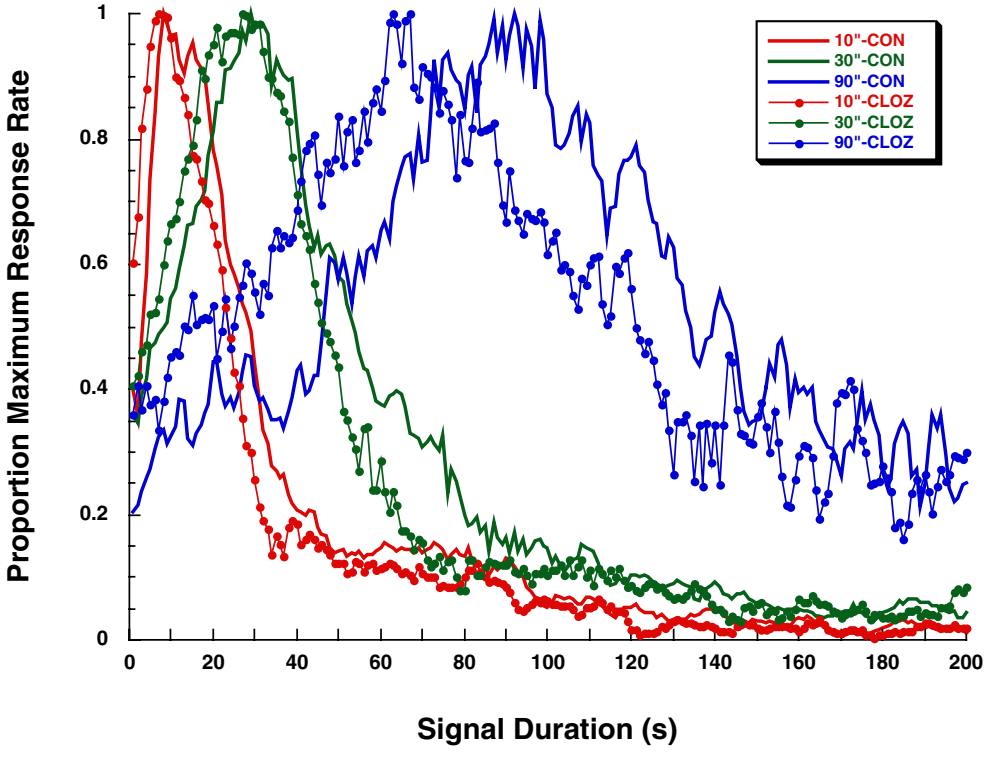


Fig. 4 Mean produced peak times plotted as a function of the programmed times of reinforcement (10, 30, and 90 s) for vehicle control, clozapine (CLOZ, 2.4 mg/kg i.p.) and haloperidol (HAL, 0.12 mg/kg i.p.) sessions. Linear regression lines are fit to each treatment condition

Haloperidol effects on peak time and peak rate

The effects of HAL on peak time with respect to each lever/temporal criterion (i.e., short, medium, and long) is shown in Fig. 5. The results of the repeated-measures ANOVA (dose×duration) revealed a main effect of duration [$F(2,18)$

Fig. 3 Mean proportion of maximum response rate plotted as a function of signal duration for vehicle control and clozapine (CLOZ) sessions for the highest drug dose (2.4 mg/kg i.p.)



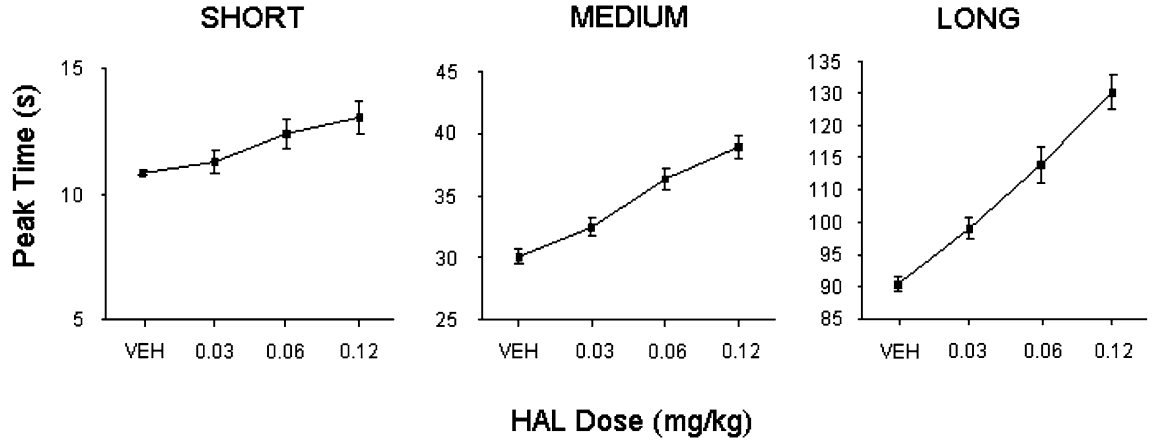


Fig. 5 The effects of haloperidol (HAL) on peak time. Peak time was shifted rightward following systemic HAL injections. The *left*, *center*, and *right panel* display the HAL effects on the 10-s (*short*), 30-s (*medium*), and 90-s (*long*) durations, respectively. Each panel describes the peak time as a function of HAL dose. Note that the *Y*-axis for each panel is scaled differently to account for the greater change at longer durations. There were significant effects of duration ($p<0.0001$), dose ($p<0.0001$), and the duration×dose interaction ($p<0.0001$), which is consistent with the observation that the rightward shifts in peak time are proportional to the durations being timed. The data are expressed as means±SEM

=2,110.2, $p<0.0001$] confirming the three different peak times observed in the tri-peak function. The overall effect of HAL was to shift the tri-peak functions rightward (i.e., the peak time increased). This conclusion is supported by a significant main effect of dose [$F(3,27)=1,018.4$, $p<0.0001$]. Moreover, the response functions plotted in Fig. 5 suggest that HAL induced a rightward shift that was proportional to the duration being timed. This observation is confirmed by a significant duration×dose interaction [$F(6, 54)=367.1$, $p<0.0001$]. The previous analyses applied to spread revealed no significant effects.

The mean peak rate data for each temporal criterion as a function of HAL dose are presented in Fig. 6. A repeated-measures ANOVA (dose×duration) showed a significant effect of duration [$F(2,18)=7.64$, $p<0.01$] but a nonsignificant effect of dose [$F(3,27)=1.02$, ns] as well as a nonsignificant duration×dose interaction [$F(6,54)=0.70$, ns]. Consequently, although HAL had no reliable effect on peak rate, the effect of duration was to decrease peak rate as a function of increases in the temporal criteria. This dissociation between the effect of HAL on peak time and peak rate provides further support for independent processes (e.g., timing and motivation).

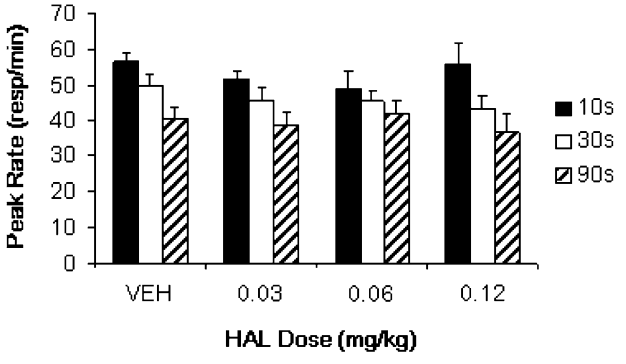


Fig. 6 The effects of haloperidol (HAL) on peak rate. The *X*-axis contains the dose of HAL that was administered with respect to 10-, 30-, and 90-s temporal criteria whereas the *Y*-axis expresses the mean peak rate±SEM. There was a significant effect of duration ($p<0.01$) but no reliable effect of dose or the duration×dose interaction

Tri-peak response functions for vehicle control and HAL sessions (highest dose, 0.12 mg/kg) are presented in Fig. 7 in order to illustrate the horizontal rightward shifts produced by HAL administration as well as the symmetry of the Gaussian-shaped functions plotted on a linear time scale. The slopes of the regression of produced times against reinforced times increased from 1.01 under vehicle to 1.34 under the highest dose of HAL (proportional regressions, with intercept=−0.8) as illustrated in Fig. 4.

Discussion

The atypical pharmacological profile of clozapine is usually attributed to its receptor binding affinities. Although the drug has a somewhat lower affinity for D_2 receptors than "classical" antipsychotics, it has high affinities for a number of 5-HT receptors (5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_6, 5-HT_7), muscarinic, H_1 histamine receptors, and for α_1- and α_2-adrenoceptors (Futton and Goa 1997). On the other hand, the "classical" antipsychotic haloperidol is generally regarded as a relatively selective D_2 receptor antagonist, although it also has relatively high affinities for D_3, D_4, and α_1-adrenoceptors. In contrast to clozapine, haloperidol is rather ineffective at most 5-HT receptor subtypes (with the exception of 5-HT_{2A}), α_2-adrenoceptors, all muscarinic receptor subtypes, and H_1 histamine receptors (Futton and Goa 1997; Scatton and Sanger 2000).

On the basis of their different receptor binding profiles, we anticipated that clozapine and haloperidol would have different effects on interval timing. To this end, clozapine induced a leftward shift of the tri-peak function that was proportional to the interval being timed, and haloperidol induced the opposite pattern—a proportional rightward

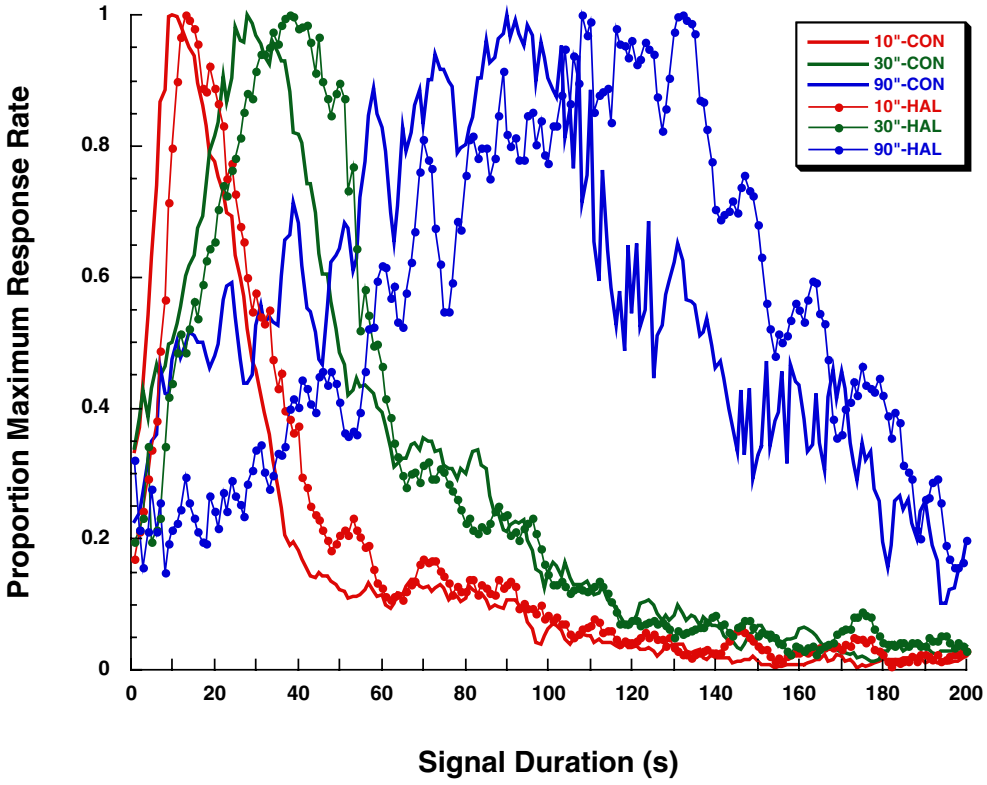


Fig. 7 Mean proportion of maximum response rate plotted as a function of signal duration for vehicle control and haloperidol (HAL) sessions for the highest drug dose (0.12 mg/kg i.p.)

shift of the tri-peak function. This pattern of results is consistent with a clock speed effect, which has previously been demonstrated with a range of DA-specific agonists and antagonists (Maricq and Church 1983; Matell et al. 2004; Meck 1986, 1996). Conversely, both clozapine and haloperidol produced modest and unreliable effects on peak rate, which is generally interpreted as a measurement of motivation (Maricq and Church 1983; Matell et al. 2004; Meck 1986, 1996). On the basis of systemic drug injections alone, it is difficult to isolate the neurobiological mechanisms that mediate the effects of clozapine and haloperidol on interval timing. However, the breadth of literature devoted to understanding the pharmacological profiles of clozapine and haloperidol is large enough to allow for reasonable speculation given the proposed neural circuits involved in timing and time perception as depicted in Fig. 8.

There is considerable evidence to suggest that the prefrontal cortex may impart flexibility on the interval-timing system by supporting rapid adjustments in the temporal organization of behavior under novel conditions (see Gibbon et al. 1997; Meck 1996; Meck et al. 1987; Olton et al. 1988). For example, the modulation of clock speed that arises following systemic haloperidol administration is eliminated following lesions to the prefrontal cortex (Matell and Meck 2004; Meck 1996, unpublished data). This role is also supported by a study that elucidated the contribution of the lateral agranular cortex to interval timing [i.e., precentral cortex (PrC), Olton et al. 1988]. PrC lesions do not disrupt timing behavior during the presentation of one of either two different stimuli (e.g., light or tone), each of which holds a different relationship to the time of reinforcement delivery. However, interval-timing behavior in PrC-lesioned rats is severely compromised when the same two stimuli are presented simultaneously during probe trials. Under these conditions—referred to as simultaneous temporal processing—normal rats can accurately time each stimulus independently and concurrently (Meck and Church 1984; Pang and McAuley 2003; Pang et al. 2001).

Serotonergic manipulations have provided another productive avenue toward understanding the neuropharmacology of interval timing (e.g., Body et al. 2003, 2004). Indeed, the rodent PrL contains 5-HT_{1A} and 5-HT_{2A} receptors in abundance (Pazos et al. 1985; Pompeiano et al. 1992). Serotonergic 5-HT_{1A} and 5-HT_{2A} receptors may inhibit prefrontal output and facilitate glutamatergic prefrontal input, respectively, in pyramidal neurons (Aghajanian and Marek 1997; Czyrak et al. 2003; Marek and Aghajanian 1999; Santana et al. 2004). However, the role of 5-HT as it relates to interval timing is somewhat obscured in that 5-HT manipulations induce behavioral changes that are task dependent (e.g., Ho et al. 2002). For example, lesions of the raphe nucleus, which deplete 5-HT, appear to flatten the PI function, suggesting a change in the Weber fraction but do not reliably change the peak time when a single temporal criterion is used (Morrissey et al. 1994). On the other hand, 5-HT depletion has little or no effect on tasks that require the animal to allocate responding to different response options, the choice of which depends on a temporal discrimination (Al-Zahrani et al. 1996; Ho et al. 1995). Given the somewhat ambiguous relationship between 5-HT and interval timing, the burden of proof for such a connection may depend on more specific phar-

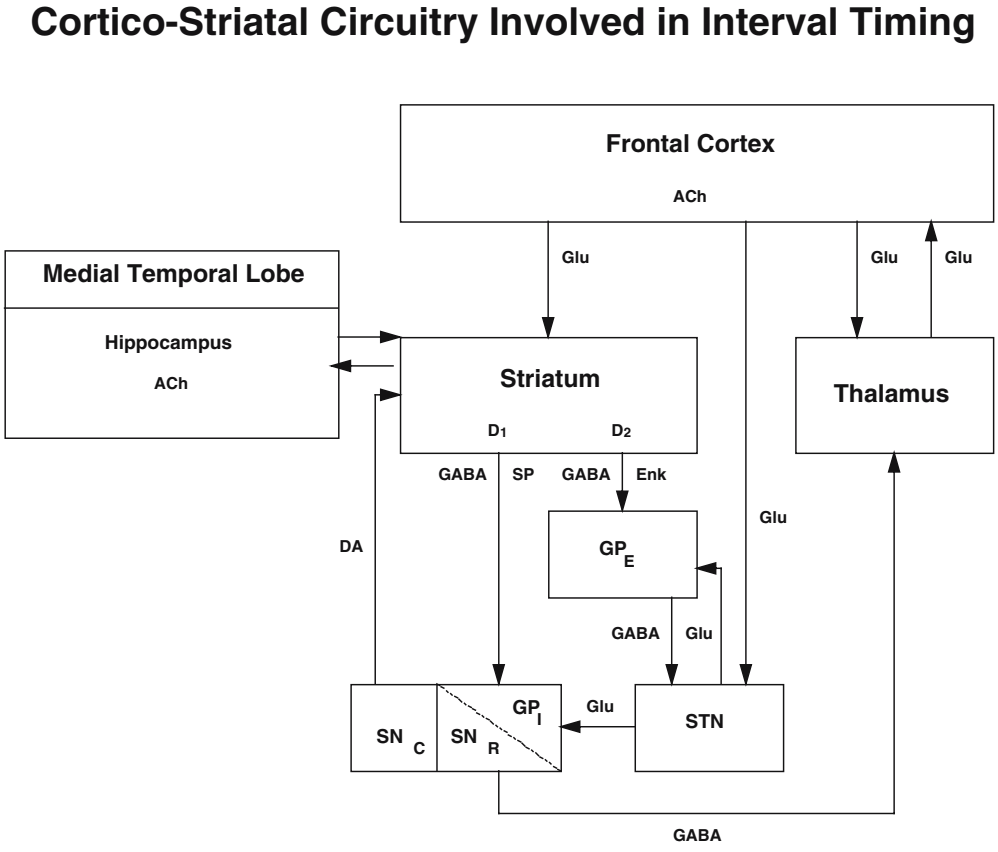


Fig. 8 Outline of the neurotransmitter systems and corticostriatal/hippocampal circuitry proposed to mediate interval timing in the seconds-to-minutes range. Descriptions of these anatomical connections and how corticostriatal coincidence detection and resulting thalamocortical feedback results in the temporal control of behavior are provided by Xiao and Barbas (2004) and Matell and Meck (2000, 2004), respectively. *Ach* acetylcholine, *Glu* glutamate, *SP* substance P, *Enk* enkephalin, *GABA* gamma aminobutyric acid, *DA* dopamine, D_1 dopamine D_1 receptor subtype, D_2 dopamine D_2 receptor subtype, GP_E globus pallidus external capsule, GP_I globus pallidus internal capsule, SN_C substantia nigra pars compacta, SN_R substantia nigra pars reticulata, *STN* subthalamic nucleus. Adapted from Meck 2005

macological manipulations such as those that target 5-HT receptor subtypes (Body et al., personal communication).

It is tempting to attribute clozapine and haloperidol's differential effects on interval timing to differences in their impact on excitability in the mPFC. Glutamate concentrations do increase in mPFC following acute injections of clozapine, but not haloperidol, whereas both drugs increase glutamate in the striatum (Daly and Moghaddam 1993; Yamamoto et al. 1994). Moreover, acute clozapine treatment leads to an overall increase in evoked excitatory postsynaptic potential (EPSP) and facilitates long-term potentiation (LTP), whereas haloperidol leads to an overall decrease in evoked EPSPs and no effect on LTP in PrL brain slices (Arvanov et al. 1997; Gemperle et al. 2003). The potentiation of evoked EPSPs is dependent on D_1 receptor activation in the prefrontal cortex (Chen and Yang 2002). In addition, there is reason to believe that 5-HT contributes to the clinical efficacy of atypical neuroleptics —perhaps by means of the 5-HT_{2A} receptor subtype (e.g., Aghajanian and Marek 1997; Marek and Aghajanian 1999; Tyson et al. 2004). Interestingly, large quantities of 5-HT receptors have been reported in the mPFC of rats (Pazos et al. 1985; Pompeiano et al. 1992). Moreover, the observed glutamatergic changes within the rodent mPFC following antipsychotic administration appear to hold some relationship with 5-HT_{2A} receptors (Arvanov and Wang 1998, 1999; Marek and Aghajanian 1999). Although the precise mechanism by which clozapine acts to facilitate glutamate release in the mPFC remains to be determined, it should be noted that fenfluramine, a 5-HT_{2A} agonist, brings about an effect on interval timing that is consistent with an increase in clock speed (Body et al. 2004).

Another possible explanation for the current findings is that a shift in reinforcement and/or feedback density, as is the case after clozapine or haloperidol administration, influences the speed of an internal clock (see Lustig and Meck 2005). The PrL may be a candidate prefrontal cortical area to mediate such a change through a serotonergic (i.e., 5-HT_{2A}) mechanism. The rat PrL, but not the infralimbic area (IL), plays a role in modulating behavior with respect to changes in the contingency of reinforcement (Balleine and Dickinson 1998). Moreover, PrL also contributes to integrating changes in the incentive value of a specific reinforcement type with behavior supported by that reinforcement type (Killcross and Coutureau 2003). Finally, the PrL sends rich projections to the nucleus accumbens core (e.g., Groenewegen et al. 1999), another brain area that is critical for detecting changes in incentive value (Corbit et al. 2002).

The ventral striatum is believed to play an important role in reinforcement and neuroeconomics (Berridge and Robinson 1998; Robbins and Everitt 1996; Schultz 1998; Wise 1982). Moreover, the neural architecture of the ventral striatum suggests that it is incorporated into parallel and functionally segregated frontal–striatal loops (Alexander et al. 1986; Groenewegen et al. 1999), which provide a means by which complex computations can take place (Beiser and Houk 1998). Although the properties of fron-

tal–striatal circuits provide a neural substrate by which interval timing may be mediated (Hinton and Meck 2004; Matell and Meck 2000, 2004; Meck and Benson 2002; Meck and Malapani 2004), there has been less focus on the interaction between dorsal and ventral striatal circuits during temporal processing (but see MacDonald and Meck 2003, 2004; Matell and Meck 2004; Rammsayer 1997). There is ample evidence to suggest that coincident input into the ventral striatum potentiates information flow thorough this area (Goto and O'Donnell 2002), providing a mechanism by which changes in reinforcement density may interact with frontal–striatal circuits comprising the dorsal striatum. Perhaps the differing influences of clozapine and haloperidol on PrL activity may provide a basis by which one would characterize this interaction. Alternatively, the neural locus of action may be different with respect to each drug. For example, clozapine exerts its effect at the PrL whereas the haloperidol effect is acting primarily through D_2 sites in the dorsal striatum, owing to differences in D_2 receptor binding at the doses used in the current study (Xiberas et al. 2001). This possibility suggests that one may be able to separate direct clock speed effects from indirect "reinforcement density" effects on interval timing.

Although the regulatory role of DA as it relates to corticostriatal plasticity is decidedly complex, e.g., defining the functional distinction between pre- and postsynaptic D_2 receptors (Centonze et al. 2004; Usiello et al. 2001), interval-timing tasks may be helpful to characterize DA's role at the behavioral level (e.g., Paule et al. 1999). Given the functionally heterogeneous nature of the mPFC, the subdivisions of this brain region need to be characterized with reference to their contributions to interval timing and temporal memory. It has been proposed that the higher clinical effectiveness, including the "cognitive enhancement" that characterizes atypical antipsychotics, depends on the facilitation of glutamatergic activity and differential gene expression in the mPFC (e.g., Goldberg and Weinberger 1994; Hoff et al. 1996; Lahti et al. 2003; Leveque et al. 2000; Merchant et al. 1996; Ninan et al. 2003; Nguyen et al. 1992; Weinberger and Lipska 1995). Consequently, we propose that the differential effects of clozapine and haloperidol on interval timing are a direct reflection of the degree of glutamatergic activity in corticostriatal circuits impacting on the coincidence detection of patterns of oscillatory activity by medium spiny neurons in the striatum (Matell and Meck 2004).

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