Published in final edited form as:
Behav Processes. 2014 January ; 101: 123–134. doi:10.1016/j.beproc.2013.09.013.

Dissociations between interval timing and intertemporal choice following administration of fluoxetine, cocaine, or methamphetamine

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Abstract

The goal of our study was to characterize the relationship between intertemporal choice and interval timing, including determining how drugs that modulate brain serotonin and dopamine levels influence these two processes. In Experiment 1, rats were tested on a standard 40-s peak-interval procedure following administration of fluoxetine (3, 5, or 8 mg/kg) or vehicle to assess basic effects on interval timing. In Experiment 2, rats were tested in a novel behavioral paradigm intended to simultaneously examine interval timing and impulsivity. Rats performed a variant of the bi-peak procedure using 10-s and 40-s target durations with an additional "defection" lever that provided the possibility of a small, immediate reward. Timing functions remained relatively intact, and 'patience' across subjects correlated with peak times, indicating a negative relationship between 'patience' and clock speed. We next examined the effects of fluoxetine (5 mg/kg), cocaine (15 mg/kg), or methamphetamine (1 mg/kg) on task performance. Fluoxetine reduced impulsivity as measured by defection time without corresponding changes in clock speed. In contrast, cocaine and methamphetamine both increased impulsivity and clock speed. Thus, variations in timing may mediate intertemporal choice via dopaminergic inputs. However, a separate, serotonergic system can affect intertemporal choice without affecting interval timing directly.

Keywords

Clock speed; Impulsivity; Self control; Temporal discounting; Dopamine; Serotonin

1. Introduction

Intertemporal choice features prominently in decision-making for all animals, including humans (Ainslie and Haslam, 1992; Evenden, 1999b; Meck et al., 2012a,b; Rachlin and Green, 1972). The trade-off between small, immediately available rewards and large rewards only available after a delay is key to understanding decisions about diet, exercise,

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studying, and investing, to name a few. Mischel and colleagues (Mischel and Metzner, 1962; Mischel et al., 1989) provided early insight into how choice behavior is affected by delays by offering children the opportunity to resist eating one treat (a smaller, sooner option) in order to obtain a more desirable one in the future (a larger, later option). Children who were more patient in this type of delay of gratification task gained a host of advantages over the course of their lifetimes. They achieved greater academic success (Mischel et al., 1989), were better able to cope with rejection and frustration (Shoda et al., 1990), and were less likely to use cocaine according to self-reports (Ayduk et al., 2000). Impulsivity in intertemporal choice tasks more broadly has been linked to gambling (Alessi and Petry, 2003), cigarette smoking (Reynolds et al., 2004), obesity (Seeyave et al., 2009), violent crime (Cherek et al., 1997), and alcohol addiction (Petry, 2001). Decades of research have showed that ability to delay gratification is one of the most useful predictors in a psychologist's toolbox (Bickel and Marsch, 2001). Thus, understanding the nature of self-control and impulsivity is an important goal of behavioral studies (Carlson and Moses, 2001; Crockett et al., 2010; Garcia and Kirkpatrick, 2013; Fantino et al., 1979).

Recent studies have been directed toward elucidating the neural mechanisms governing intertemporal choice across species (e.g., Broos et al., 2012; Kim et al., 2008; Louie and Glimcher, 2010; Mobini et al., 2002; Peters and Büchel, 2011; Samanez-Larkin et al., 2011; Sellitto et al., 2011; Winstanley et al., 2004). Choices made about options displaced through time are governed by a variety of brain regions implicated in decision-making, delay and reward representation, and impulsivity more broadly. Serotonin (5-HT) is thought to mediate impulsive decision-making. Decreases in 5-HT levels increase impulsivity in both rodents and humans (e.g., Mobini et al., 2000; Schweighofer et al., 2008; Winstanley et al., 2004; Wogar et al., 1993). Dopamine (DA) levels may also mediate impulsivity and intertemporal choice; however, its effects are inconsistent depending on the behavioral paradigm (Gu et al., 2011; Harrison et al., 1997; Kayser et al., 2012; Winstanley et al., 2003), and may depend on an intact serotonergic system (Harrison et al., 1997; Winstanley et al., 2006).

Time discrimination, especially as it relates to reward delivery, is obviously an important component of intertemporal choice (Galtress et al., 2012a,b; Kirkpatrick, 2013). In order for organisms to make appropriate decisions about options displaced through time, they must have an intact representation of the relevant time intervals. In addition, they should be able to update their estimation of those intervals according to experience. Interval timing in the seconds-to-minutes range adheres closely to Weber's law, meaning the normal distribution of temporal estimates has a width that scales with the length of the target duration (Allman et al., 2014; Buhusi and Meck, 2005; Oprisan and Buhusi, 2013 – see Killeen, 2013 for a more nuianced analysis of time). Numerical and most sensory estimations also adhere to this rule, often referred to as the scalar property of interval timing (Brannon et al., 2008; Buhusi et al., 2009; Gibbon, 1977; Gibbon et al., 1984; Meck and Malapani, 2004; Treisman, 1964). Several duration perception/production procedures have been developed to assess interval timing in nonhuman animals. The peak-interval (PI) procedure, for example, rewards the first press on a primed lever following a fixed interval, but only on a subset of trials. The unrewarded trials allow investigators to probe time estimations without interruption. Previous studies using the PI procedure in humans and other animals (e.g., Agostino et al., 2011b; Buhusi et al., 2009, 2013; Buhusi and Meck, 2007; Cheng and Meck, 2007; Church

et al., 1994; Lake and Meck, 2013; MacDonald et al., 2007; Matell and Meck, 1999; Meck and Williams, 1997; Rakitin et al., 1998) have reliably obtained Gaussian response curves whose peak times and variances fit well with Weber's law.

Unlike the related processes of millisecond timing and circadian timing, which depend mainly on an intact cerebellum and hypothalamus, respectively, interval timing relies most heavily on corticostriatal circuits (Buhusi and Meck, 2005; Galtress and Kirkpatrick, 2010; Hinton and Meck, 1997, 2004; Matell et al., 2003, 2011; Meck, 2006a,b,c; Meck et al., 2008; Merchant et al., 2013). In particular, the projections of midbrain DA neurons to the dorsal striatum are crucial for interval timing (Coull et al., 2011; Meck, 2006b; Williamson et al., 2008). Patients with Parkinson's disease, characterized by degraded DA neurons in the substantia nigra pars compacta that would normally project heavily to the striatum, exhibit impaired interval timing (Allman and Meck, 2012; Jahanshahi et al., 2010; Jones and Jahanshahi, 2013; Malapani et al., 1998a, b, 2002). Ensemble recordings have revealed that striatal neurons may indeed have some of the necessary properties to conduct interval timing: approximately 20% of neurons are sensitive to time of reward, firing at different rates for the different times being directly investigated (Matell et al., 2003). While the dorsal striatum is clearly important for interval timing, it is at present unknown how this information is transferred to mechanisms of decision-making and what roles DA and glutamate may play in intertemporal choice (Agostino et al., 2011a, 2013; Cheng et al., 2006b; Cheng and Liao, 2007; Coull et al., 2013; Hata, 2011; Jones and Jahanshahi, 2011; Kayser et al., 2012; Kelm and Boettiger, 2013; MacDonald et al., 2012; Merchant et al., 2013).

In addition to interval timing affecting intertemporal choice, the discounted value of a reward based on delay to acquisition may have an impact on the process of interval timing. Presumably, an interval is timed more effectively when decisions will be made with the temporal information gathered. Valuation will thus alter the interval-timing process. The importance of DA projections to the striatum for value-based learning, temporal discounting, and control of impulsivity only underscores the linked nature of interval timing and reward (Asgari et al., 2006; Body et al., 2004, 2005, 2006, 2013; Ho, 1996; Kurti and Matell, 2011; MacDonald et al., 2012; Schultz et al., 1997; Wiener et al., 2008; Willuhn et al., 2010). Surprisingly, the relationship between hyperbolic discounting and timing remains almost wholly unstudied – but see Cui (2011) and Galtress et al. (2012a, b) for recent initiatives. Our goal in the present experiment was to develop a novel version of the PI procedure using two different target durations (e.g., bi-peak procedure) in order to allow us to investigate the relationship between intertemporal choice and interval timing in rats (MacDonald and Meck, 2004, 2005, 2006; Matell et al., 2006; Meck et al., 2012a,b). By adjusting the bi-peak procedure to allow for "defection" with the possibility of immediate reward, we were able to determine an animal's estimate of time and valuation of rewards displaced through time. The addition of the defection lever effectively mixes a bi-peak procedure with a delay of gratification procedure, in which the smaller sooner option is available throughout the delay (Reynolds et al., 2002). We then used this hybrid procedure to measure the effects of a selective 5-HT reuptake inhibitor (fluoxetine) and indirect DA agonists (cocaine and methamphetamine) on both interval timing and intertemporal choice because of their known

impact on time perception and prediction (Ardayfio et al., 2008; Barr et al., 2004; Coull et al., 2011; Daw et al., 2002; Sysoeva et al., 2010; Wiener et al., 2011).

2. Materials and methods

2.1. Subjects

The temporal control of behavior was studied in eight (Experiment 1) and fifteen (Experiment 2) male Sprague-Dawley rats weighing 250–400 g (Charles-River Laboratories, Raleigh, NC, USA) and approximately 3 months of age when the experiments began. Rats were housed in pairs in a 12:12 light/dark (LD) cycle with lights on from 7:00 A.M. to 7:00 P.M. Rats were given continuous access to water and were maintained at 85% free-feeding weight. They were fed a ration of Purina chow after each daily session conducted during the light phase of the LD cycle. Experiments were conducted in accordance with procedures approved by the Institutional Animal Care and Use Committee of Duke University.

2.2. Apparatus

All experimental data were obtained in eight identical lever boxes (Model ENV-007, MED Associates, St. Albans, VT) housed in ventilated cubicles designed to provide light and sound isolation (Model ENV-019, MED Associates, St. Albans, VT). Lever boxes had dimensions of 24 cm × 31 cm × 31 cm. Tops, sidewalls, and doors were constructed of clear acrylic plastic; front and back walls were constructed of aluminum. The floor consisted of 19 parallel stainless steel bars. A pellet dispenser (Model ENV-203, MED Associates, St. Albans, VT) delivered 45 mg food pellets (Research Diets, New Brunswick, NJ) to a food cup located 1 cm above the floor on the front wall. Each lever box was equipped with two retractable response levers (Model ENV-112, MED Associates, St. Albans, VT) situated on the front wall of the lever box to the left and right of the food cup. In addition, each lever box contained one non-retractable response lever situated in the middle of the front wall, centered, above the food cup. A 28-V house light was mounted at the center of the top of the front wall. A speaker system (Model ENV-225, MED Associates, St. Albans, VT) was mounted on the opposite wall from the levers and was used to present white-noise signals at 75-dB. An IBM-PC compatible computer running MED-PC Version IV Research Control & Data Acquisition System software (MED Associates, St. Albans, VT) was attached to an electronic interface (Models DIG-700 and SG-215, MED Associates, St. Albans, VT) used to control the experimental equipment and record the data. The time of each lever press was recorded to an accuracy of 10 ms and placed into 1-s time bins for further analysis of individual trials and mean response functions.

2.3. Drugs

Fluoxetine hydrochloride (FLX; Sigma/Aldrich) at doses of 3.0, 5.0, and 8.0 mg/kg (Experiment 1) or 5.0 mg/kg solely (Experiment 2) was dissolved in bacteriostatic water (VEH). Injections were given intraperitoneally (i.p.) as a fixed proportion of body weight (1.0 ml/kg) approximately 20 min before the start of each experimental session. Rats received 3 rounds per dose of VEH-FLX treatment (Experiment 1) or 5 rounds of SAL-FLX treatment (.9% saline) (Experiment 2) and the FLX doses were selected based upon previous studies of its effect on incentive motivation for food reward (Sanabria et al., 2008).

Cocaine hydrochloride (COC; Sigma Chemical Co., St. Louis, MO) at a dose of 15.0 mg/kg was dissolved in 0.9% saline (VEH). All injections were given i.p. as a fixed proportion of body weight (1.0 ml/kg) approximately 10 min before the start of each experimental session. Rats received 3 rounds of VEH-COC treatment and the COC dose was selected based upon previous studies of its effect on interval timing (Matell et al., 2004; Cheng et al., 2006a, 2007a).

Methamphetamine hydrochloride (MAP; Sigma/RBI, Saint Louis, MO, USA) at a dose of 1.0 mg/kg was dissolved in 0.9% saline (VEH). All injections were given i.p. as a fixed proportion of body weight (1.0 ml/kg) approximately 10 min before the start of each experimental session. Rats received 3 rounds of VEH-MAP treatment and the MAP dose was selected based upon previous studies of its effect on interval timing (Matell et al., 2006; Cheng et al., 2007b,c).

2.4. Experiment 1 – Behavioral training

2.4.1. Pretraining: Sessions 1 and 2—All rats received two sessions of combined magazine and lever training. During these sessions a pellet of food was delivered once every 30 s, and in addition, each lever press produced food. The session began with the insertion of the left lever and continued until the rat had pressed the lever 60 times or until 30 min had passed, whichever came first. The houselight was off during the pretraining sessions.

2.4.2. Peak-interval (PI) training: Sessions 1–30—Each rat was trained for 5 daily sessions on a discrete-trials fixed-interval (FI) 40-s procedure in which food was primed after the white-noise signal had been present for 40 s – after which the rat's first response on the left or right lever (counterbalanced across rats) terminated the signal and activated the pellet dispenser. This was followed by 25 sessions of peak-interval (PI) 40-s training during which a random half of the trials were FI 40-s trials identical to those described above. The remaining trials were probe trials during which no food was made available and the white-noise signal continued uninterrupted for a total of 90 s. All trials were separated by a random duration intertrial interval (ITI) with a minimum of 50 s and a mean of 130 s. In the PI procedure data are collected exclusively from the probe trials for which peak time and peak rate measures are calculated (see Buhusi and Meck (2010) and Section 2.6).

2.4.3. Peak-interval (PI) fluoxetine testing: Sessions 31–65—Administration of FLX (3.0, 5.0, or 8.0 mg/kg ip) or a VEH injection was given every third session in a counterbalanced design in order to control for day effects. Injections of each FLX dose were given in a pseudo-random order for a total of three times each with the only constraint being that each dose had to be given in each round before the same dose could be repeated.

2.5. Experiment 2 – Behavioral training

2.5.1. Pretraining: Session 1—All rats were given 1 session of pretraining in which every 30 s the 2 side levers were retracted and then reinserted for 1 s before the delivery of food reinforcement. In addition, all levers were primed for reinforcement on a continuous reinforcement (CRF) schedule, until 20 responses were made on each lever, or 60 min had passed.

2.5.2. Fixed-interval (FI) training: Sessions 2–14—Following completion of pretraining training, rats spent 14 daily sessions performing fixed-interval (FI) training. Trials began with the onset of white-noise signal. A 10-s FI trial was scheduled for either the right or the left response lever (counter-balanced across rats) and the first response after 10-s was reinforced with 4 food pellets. A 40-s FI trial was scheduled for whichever lever was not assigned to the 10-s target duration. The first response after 40-s was reinforced with 4 food pellets and at that point, the white-noise signal was turned off. The inter-trial interval (ITI) was 120 s, but could increase if the rat chose to defect during the trial. Thus, if a rat defected at 20 s into the trial, the ITI became 140 s. In this way, trial lengths were kept equal regardless of decisions to defect (Ainslie, 1974; Rachlin and Green, 1972). During FI training, the middle lever was also available. If pressed, the middle lever ended the trial, with a 20% probability of receiving 1 food pellet, but an 80% chance of receiving 0 pellets.

2.5.3. Peak-interval (PI) procedure: Sessions 15–135—Once FI training was completed, rats were transitioned to the peak-interval (PI) procedure. During the most common type of session (and the only type on which analyses reported below were performed), the 10-s and 40-s levers were associated with a 50% probability of receiving 4 food pellets but a 50% probability of receiving 0 pellets. Probe lengths were 65, 75, and 85 s. The middle lever (defection lever), if pressed once, ended the trial, with a 20% probability of receiving 1 food pellet, but an 80% chance of receiving 0 pellets. The ITI was 100 s, but could increase if the subject defected on a given trial. The ITI decreased based on the length of the probe such that trial length was kept approximately constant.

For occasional 2–7 day intervals, rats were placed on a non-defection PI procedure, meaning the defection option was no longer available, but reinforcement was primed for the 10-s and 40-s levers as described above. This was done to ensure that timing of the 10-s and 40-s target durations remained largely intact. During the sessions in which defecting was not an option, the center lever was inactivated. Individual rats experienced slightly different numbers of sessions of each type. The two-day interval analyzed here is drawn from the range of Sessions 25–35, prior to drug injections. The three sample PI sessions analyzed here come from within Sessions 35–40, prior to drug injections. Fluoxetine injection sets were given within Sessions 45–65. Cocaine injection sets were given within Sessions 85–100. MAP injection sets were given within Sessions 120–135. Five days of normal PI training always separated any given injection pairing. Vehicle injections were always given 1 day prior to drug injections. There were five separate FLX-vehicle injection pairs, and three each of cocaine and MAP.

2.6. Data analysis

For each probe trial the number of responses in each 1-s time bin during the signal was recorded for each rat. These functions were summed over trials and the mean response rate as a function of time since signal onset was calculated for each rat. In the PI procedure the time of the rat’s maximal response rate during a probe trial is called the peak time and the response rate at that time is called the peak rate. Peak time serves as a measure of accuracy as it reflects the time point during a signal presentation that the rat maximally expects reinforcement to occur. Changes in peak time have been used to evaluate clock speed as

well as the content of temporal memory (Meck, 1996, 2002). Peak spread, defined as the standard deviation of the fitted Gaussian distribution, is used to assess timing precision and peak rate is used to assess motivational levels (Cheng and Meck, 2007; Meck, 2006a,b,c; Meck et al., 2012a,b; Paule et al., 1999; Penney et al., 1996).

Lever presses were analyzed using custom Matlab 7.1 (Math-works, Natick, MA) programs. To calculate peak times, peak rates, and spreads, the data were fitted with a Gaussian function with a linear ramp (see Matell et al., 2003). All drug and saline conditions include data from multiple treatment sessions. For these analyses, responses were pooled across sessions because the probability of defection could increase or decrease the number of possibilities for lever presses on any given session. Importantly, if the rat defected on any given trial, all time points following the defection were not coded as having zero responses on the 10 or 40 s target levers; instead, these post-defection time points did not contribute at all to the overall peak curves. Thus, the curves described here represent lever presses per opportunity. A subject was only contributed a particular target duration curve if any trials lasted until the target. That is, a 10-s peak only qualified if the rat did not defect before 10-s on all relevant probe trials; likewise with a 40-s peak. Finally, for the purpose of data presentation, a point within an average peak function is only displayed if 3 or more subjects contributed trials to that point.

3. Results

3.1. Experiment 1

3.1.1. Dose–response effects of fluoxetine on peak time and peak ratex—Mean (±SEM) peak time and peak rate measures for 40-s PI testing as a function of FLX dose are illustrated in Fig. 1 in the left and right panels, respectively. A repeated measures ANOVA indicated that there were no significant effects of drug dose on either of these measures, $F(3,21) = 1.94$, $p > 0.05$. The mean proportion maximum response rate functions for the baseline and 5 mg/kg FLX conditions are plotted in Fig. 2. No significant differences in peak time, peak rate, or spread were observed between these two conditions, $p > 0.05$.

3.2. Experiment 2

3.2.1. Characterization of defection points—Despite the presence of a defection option on the middle lever, all rats showed characteristic peak functions as illustrated in Fig. 3. In order to characterize intertemporal choice we first looked at the probability of defection across trials. We observed very high levels of defection with some inter-individual variability, as shown in Table 1. Because the mean (±SEM) probability of defection on any given trial was 0.89 ± 0.03, nearly ceiling, we looked next at what specific times within a trial subjects were defecting. Here, we observed far more variation, with the average defection time at 20.1 s ± 2.41 (see Table 1), between the 10-s target duration and the 40-s target duration. We looked more closely at when rats were defecting as shown in Fig. 4 – which displays the mean percentage of maximum defection rate as a function of the time since signal onset (panel A) and the mean conditional probability of defection if a specific time point is reached (i.e., if the trial has not already ended due to prior defection or 40-s FI reinforcement. As one can see from both graphs, defections are clustered in peaks below 10

s, between 10 and 40 s, and following 40 s. The second and third time-point clusters for defection are especially noteworthy as they potentially reflect the subjective time that is equidistant between the two target durations as well as the “giving in time” which reflects the time at which the subject behaves as if the longer target duration has passed (Brunner et al., 1996; Kacelnik and Brunner, 2002), respectively. We also noted a relationship between defection time and overall probability of defection, with higher probabilities associated with earlier defection times, $r = -0.73$, $p < 0.01$.

In order to assess whether clock speed (as measured by horizontal shifts in peak time) was related to our measures of impulsivity, we regressed defection time and probability on peak times for the 10-s lever. We found a significant relationship with defection probability, whereby lower defection probabilities were associated with later peak times, possibly the result of slower clock speeds ($r = -0.39$, $p < 0.05$).

We were also concerned that estimates of peak time may be inaccurate, given the new defection procedure. Temporary removal of the middle lever allowed us to probe more fully the relationship between interval timing and accuracy on the defection version of the task (Fig. 5). We found that, for the 10 s lever, peak times correlate across the defection-absent and defection-present conditions ($r = 0.56$, $p < 0.05$); the same was true for peak widths ($r = 0.55$, $p < 0.05$). We replicated the regression results reported above for the defection-present condition: later peak times in the defection-absent condition are associated with lower defection probabilities in the defection-present condition ($r = -0.69$, $p < 0.01$). As would be expected, later peak times in the defection-absent condition were associated with increased rewards from the 10-s and 40-s levers in defection-present trials ($r = 0.63$, $p < 0.01$), as well as increased rewards overall, $r = 0.62$, $p < 0.01$, suggesting this may be an advantageous strategy (see Fig. 6). Importantly, this means that clock speeds in one set of sessions (defection-absent) correlates with defection probability in another set (defection-present), and eliminates the possibility that these results are simply an artifact of high defection rates. None of these effects were observed for the 40-s peak times, likely because rats were much less likely to experience the 40-s reward due to early defections. Later peak times are typically credited to slowed clock speeds (Lustig and Meck, 2005; Matell et al., 2006; Meck, 1986, 1996). Thus, we can conclude that, across individuals, later peak times (i.e., slower clock speeds) are associated with fewer defections, which may reflect increased self-control in this procedure. Although peak *times* were relatively accurate in the no-defection condition, (10 s: $M = 9.65 \pm 0.56$; 40 s: $M = 43.11 \pm 1.14$), peak spreads were somewhat abnormal (10 s: $M = 7.76 \pm 0.60$; 40 s: 15.84 ± 1.14). As expected, peak spread was higher for the 40-s target duration than for the 10-s target duration, $t(14) = 6.51$, $p < 0.0001$, but was closer to a 2:1 ratio than the 4:1 ratio predicted by the scalar property of interval timing (Cheng and Meck, 2007; Gibbon et al., 1984). This may be because of the continued presence of the 10-s lever, whether reward was delivered or not or other procedural differences from the standard PI procedure (see Buhusi et al., 2009; Matell et al., 2004; Matell and Meck, 1999).

3.2.2. Fluoxetine alters the time of defection, but not peak times—To avoid floor effects in defection times, only the 10 rats demonstrating the most ‘patience’ (defined as highest average defection times) were included in the subsequent pharmacological

experiments. FLX injections (5 mg/kg) did not affect the probability of defection. Specifically, defection probability following VEH injections (0.92 ± 0.04) matched defection probability following FLX injections (0.91 ± 0.03), $p > 0.5$, 2-tailed paired-samples *t* test. We assessed how FLX altered defection times for each of the three defection ranges (0–10 s, 10–40 s, 40+ s) as illustrated in Fig. 7. There was no overall change in how the defection points were distributed across these time ranges ($\chi^2 = 2.61$, df = 2, $p > 0.05$, see Table 2). Moreover, we did not observe any difference in defection time for the 0–10 s range (SAL = 3.99 s ± 0.61; FLX = 3.83 s ± 0.38), or the 40+ s time range (SAL = 48.4 s ± 1.54; FLX = 48.0 s ± 1.44). However, the 10–40 s range did show a significant increase in defection time (SAL = 19.87 s ± 1.57; FLX = 20.93 s ± 1.08, $t(9) = 2.57$, $p < 0.05$). This rightward shift in the distribution of defection points occurring between 10 and 40 s can be seen in Fig. 7. This may simply reflect an increased latency to make the defection response or indicate a greater tendency to wait for the 40-s reward under the influence of FLX.

The response rate data for the 10-s and 40-s target durations were analyzed to determine whether a change in the accuracy (peak time), peak rate, and precision (spread) of the PI functions could account for the observed difference in defection times (see Fig. 8). There were no significant differences in peak time (10-s: SAL = 9.32 s ± 1.48 FLX = 7.97 s ± 1.71; 40-s: SAL = 48.64 s ± 0.54, FLX = 46.91 s ± 0.64; see Fig. 8). There were no significant differences in peak rate (10-s: SAL = 38.0 resp/min ± 3.9, FLX = 39.0 resp/min ± 4.1; 40-s: SAL = 33.0 resp/min ± 6.4, FLX = 39.5 resp/min ± 8.3).

We observed no significant changes in peak spread for the 10-s target duration (10-s: SAL = 7.64 s ± 0.85, FLX = 10.22 s ± 2.22). For the 40-s duration, only 5 rats showed peak functions based on our analysis criteria (see above). However, these five rats did show a difference in peak spread, $t(4) = -4.05$, $p < 0.05$ (SAL: 15.61 ± 1.19; FLU: $M = 9.63 \pm 1.87$), with narrower peaks under FLX. This effect seems to be distinct from the shift in defection times described above. The five rats with 40-s peaks showed no change in 10–40-s defection times, $t(4) = 0.60$, $p > 0.5$; however, the five rats lacking 40-s peaks *did* show a change in 10–40-s defection times, $t(4) = 4.3$, $p < 0.01$. They are primarily responsible for the change in the group mean value.

During the saline condition, the width of the 40-s peak was still greater than the width of the 10-s peak, $t(4) = 2.98$, $p < 0.05$. However, this difference disappeared with the narrower 40-s peak spreads following FLX administration (the 10-s peak was unaffected). These results confirm those reported in Experiment 1 which indicated that FLX (3, 5, & 8 mg/kg) does not affect the basic parameters used to assess the accuracy and motivational levels associated with interval timing; however, in this case, precision was affected, but only for the later criterion time. The five rats demonstrating this effect also did not show a change in defection times, suggesting multiple differentiable effects of FLX.

Although the group effect on defection times for the 10–40 s range was relatively small (albeit statistically significant), FLX did cause the times of defection to shift dramatically for some rats, as illustrated in Fig. 9. Following SAL injections, this rat defected too early and too often to demonstrate a full peak function for the 40-s target duration. In contrast, following FLX injections, defection times had shifted sufficiently to the right for the 40-s

peak function to fully appear. This rat went from defecting at a mean of 18.4 s to 23.1 s under FLX. The distribution of defection times is significantly changed $\chi^2 = 16.83$, df = 2, $p < 0.001$. Following vehicle injection, 18% of this rat's defections occurred before the 10-s mark; 82% between 10 and 40, and none after 40-s. Following FLX, these changed to 11%, 85%, and 5%, respectively. These results are consistent with prior reports of considerable inter-individual differences in sensitivity to FLX (Baker et al., 2001; Homberg et al., 2004; Sanabria et al., 2008). Such observations highlight the importance of examining defection parameters for individual subjects in future studies as a function of drug dose and relevant genetic markers.

3.2.3. Cocaine and methamphetamine affect impulsive choices and interval timing—Both COC and MAP are known to alter interval timing, producing immediate proportional leftward shifts in response curves during PI timing procedures similar to those used in the current study (Cheng et al., 2007a,c; Matell et al., 2004). Consequently, we hypothesized that defection times would be shifted in accordance with the new time estimations obtained under COC and MAP. Under COC, we saw significantly earlier defection (VEH = 20.10-s ± 2.00; COC = 14.68 s ± 2.27, $t(9) = 3.28$, $p < 0.01$), but we observed no significant shifts within each of the defection time ranges. The same was true of MAP (VEH = 14.67 ± 2.82; MAP = 9.69 s ± 2.52, $t(9) = 2.36$, $p < 0.05$). Instead, defections were more likely to occur in earlier time ranges. MAP caused a drastic shift to higher probability of defection in the first 0–10 s, χ^2 (2) = 162.3, $p < 0.0001$, as did COC χ^2 (2) = 234.33, $p < 0.0001$ (see Table 2 and Fig. 10). We did not observe a significant overall change in defection probability, although both COC and MAP trended toward increasing defections, COC: $t(9) = 1.85$, $p < 0.1$; MAP: $t(9) < 1.84$, $p < 0.1$.

With such high defection rates in both the COC and MAP conditions, assessing peak times was difficult. Though we did not observe a clear leftward shift in peak times for all rats, some rats did show substantial disruption in timing that may have been the result of a combination of increased peak width and a leftward shift in the 10-s and 40-s PI functions, as illustrated in Fig. 11 (see Balci et al., 2008, 2009; Cheng et al., 2007c). By collapsing across COC and MAP sessions, we saw a strong trend toward an increase in the peak width for the 10-s target duration which is quite evident in Fig. 12, indicating a substantial disruption in timing (VEH = 7.4 ± 0.70; COC + MAP = 15.39 s ± 3.63, $t(9) = 2.22$, $p < 0.05$). In addition, previous results are indicative of an increase in clock speed caused by the DA up-regulators COC and MAP across a range of signal durations (Buhusi and Meck, 2002; Matell et al., 2004, 2006; Meck, 1983, 1996). Thus, it seems likely that part of how COC and MAP affected behavior was by shifting the psycho-metric functions leftward, although the issue of how impulsivity and clock speed interact in this case to control performance is unclear.

4. Discussion

The relationships among interval timing, associative learning, computational learning, temporal discounting, and decisions about options displaced through time are vastly understudied (Balsam et al., 2010; Galtress et al., 2012a,b; Jozefowiez and Machado, 2013; Jozefowiez et al., 2013; Ray and Bossaerts, 2011). At present, we have scant understanding

of how much of the variation in impulsivity is due to differences in the manner in which the subject forms representations of the relevant time intervals and makes decisions based upon a comparison of these time values (cognitive model –Gallistel and Gibbon, 2001) versus the subject learning associations among the representations of these same time intervals and the relevant stimuli and responses – with the strength of these associations changing according to the principals of classical conditioning (associative model – Miller and Witnauer, 2012). Here, we present a novel procedure for studying the relationship between interval timing and time-based decisions. We have combined a traditional psychophysical procedure for examining interval timing, the PI procedure, with a delay of gratification procedure, in which there is a constant possibility of choosing a smaller, more immediate reward over a larger, delayed reward. We found that some of the variation in impulsivity (probability of defection) may be attributable to variations in clock speed—subjects with later peak times (indicating slower clock speeds) were less likely to defect. The use of such 'cognitive constructs' such as clock speed and delay of gratification are typically considered to be more suitable to a 'cognitive model' of interval timing, but are also consistent with some recent associative interpretations in which links between arousal and time perception have been proposed (Killeen and Fetterman, 1988; Machado, 1997).

Although we have connected the effects of dopamine agonists to increases in both impulsivity and clock speed, it should be noted that amphetamine has been shown to reduce impulsivity and improve performance on the stop task in both rodents and humans, but only in those subjects demonstrating relatively poor baseline inhibitory performance (de Wit et al., 2000; Feloa et al., 2000). Following amphetamine administration, decreases in impulsive choice have been observed on delay-discounting tasks in humans at low doses (de Wit et al., 2002; Feola et al., 2000), but both increases, decreases, and no effect on impulsive responding have been observed in rats (Cardinal et al., 2000; Evenden and Ko, 2005; Evenden and Ryan, 1996; Richards et al., 1999; Wade et al., 2000; Wooters and Bardo, 2011) depending on the behavioral task, strain of rat, chemical formulation of the psychostimulant, etc. Nevertheless, the overall finding is that increases in impulsivity predominate following amphetamine administration at the doses typically studied (Cardinal et al., 2000; Dalley et al., 2011; Winstanley et al., 2003). Even those investigators reporting decreases in impulsivity following amphetamine administration have recognized that special factors are likely involved, e.g., low drug doses, specific subject populations, as well as the careful selection of the time course involving the interaction of pharmaco-dynamics and the behavioral task (Rivalan et al., 2007). Moreover, these investigators have argued that impulsivity is most likely to be observed in instances where time estimation is a major component of the behavioral task due to the enhanced clock-speed effects of amphetamine (e.g., Hayton et al., 2012; Rivalan et al., 2007). The conclusion being that one has to take a variety of factors into account and attempt to develop a set of behavioral tasks that address different dimensions of self control and impulsivity.

Part of the challenge in understanding this relationship is to determine those neural structures that are shared between intertemporal choice and interval timing, and those that contribute exclusively to one or the other. Here, we present evidence that 5-HT up-regulation through acute FLX administration can affect decisions about time, while leaving interval timing itself unchanged. However, some rats also showed the reverse pattern, with

FLX affecting timing precision, highlighting the role of individual differences in the effects of FLX. Previous studies in both humans and nonhuman animals have suggested that increases in 5-HT can decrease impulsivity, while 5-HT depletion enhances ‘patience’ (Evenden, 1999a; Schweighofer et al., 2008; Winstanley et al., 2004). However, it was not clear whether these results could be attributed entirely to changes in time estimation. One previous study using mice also found no influence of FLX on interval timing using the PI procedure (Cordes et al., 2008). Unlike FLX, however, the indirect DA agonists COC and MAP likely affected intertemporal choice by altering the speed of the internal clock, although other interpretations involving memory and attention are possible (Buhusi and Meck, 2009; Coull et al., 2011; Meck, 2003, 2007).

These results are consistent with earlier accounts of the effects of FLX. Acute FLX administration reduces food intake in free-feeding rats and 5-HT antagonists tend to have the reverse effect (Feldman and Smith, 1978; Sanabria et al., 2008). Our results, along with those from other timing studies (Ho et al., 1996), suggest that the effects of FLX and other 5-HT manipulators are not attributable to an altered clock speed in the timing of food rewards. Instead, FLX may directly affect motivation for rewards (Sanabria et al., 2008), including rewards that don’t involve food (Ciccocioppo, 1999). In the context of an intertemporal choice task, this may mean a decreased desire for an immediate reward, and an increased ability to maximize long-term food intake. In our task, because of the adjusting ITI, delays between rewards were approximately equal whether the rat chose to end the trial or not. 5-HT manipulations do not seem to affect sensitivity to reward size (Brunner and Hen, 1997; Mobini et al., 2000). A recent study by Miyazaki et al. (2011) demonstrated that 5-HT neurons in the dorsal raphe nucleus had high, sustained firing rates when a rat was successfully able to delay gratification. DA agonists may do the opposite, i.e., increase relative motivation for an immediately available reward (Wise, 2004), at the cost of delayed rewards losing their salience. Thus, impulsivity may also directly affect the interval timing process, reducing the representation of the target duration as its subjective reward value declines.

The current implementation of our hybrid timing/intertemporal choice task may not be entirely ideal for probing the relationship between intertemporal choice and interval timing; however, adjustments can be made in future studies to make it more suitable. One major drawback is the relatively high level of early defection observed in many rats; presumably, this could be mitigated with shorter target durations and larger rewards. With later defection times, more accurate interval timing curves can be assessed across pharmacological manipulations.

One simple alteration to our hybrid timing/intertemporal choice task could switch it from a delay-of-gratification paradigm, in which the smaller, sooner option is always available, to a delay-discounting paradigm, in which a binding choice is made at the start of each trial (Reynolds et al., 2002). By allowing defection only within the first few seconds of each trial or by restricting possibilities within the trial based on the first levers pressed, the task described here could easily become a delay-discounting paradigm. Some of the pharmacological results obtained here may be unique to the delay-of-gratification routine, which requires constant decisions about whether to defect, and combines the current

experience and estimation of time with projections about future delays in making a choice. Consequently, directly comparing the two versions of this task may prove useful for distinguishing the neural mechanisms of these two different paradigms, both of which are highly relevant to naturalistic decisions (Kacelnik and Brunner, 2002; Ray and Bossaerts, 2011; Stephens et al., 2002).

In summary, we have observed clear individual differences in intertemporal choice and timing, with many of these patterns linked. Clock speed (as measured by peak times) was related to willingness to abstain from a small, immediate option in favor of later, larger options. This suggests that clock speed may (at least in part) underlie the dramatic differences observed across individuals, including in humans, in intertemporal choice paradigms (Alessi and Petry, 2003; Myerson and Green, 1995). As inter-individual differences in impulsivity predict a variety of personality traits and life patterns (Ayduk et al., 2000; Jupp et al., 2013; Mischel and Metzner, 1962; Mischel et al., 1989; Shoda et al., 1990), it is essential to uncover the mechanisms of such variation. The selective 5-HT reuptake inhibitor FLX reduced impulsivity, as measured by reduced choices to ‘opt out’ of the timing procedure. However, we observed no changes in peak times, indicating that clock speed was preserved. In contrast, indirect DA agonists enhanced impulsivity, as shown by increased preference for smaller, earlier rewards. We conclude that variations in timing ability may mediate changes in impulsivity via dopaminergic inputs, and that a separate serotonergic mechanism may affect intertemporal choice and decision-making. Such serotonergic-related processes appear to operate without altering clock speed or memory translation constants, although patterns of variance and co-variance may be modified (Gibbon and Church, 1990, 1992; Gibbon et al., 1984; Matell and Meck, 2000, 2004; Meck, 1983, 2002; Meck and Yin, 2011).

Acknowledgments

This work was supported, in part, by NIH grant F31-DA-028133 (SRH). The authors would like to thank to Victoria Burgos, Ruey Cheng, and Lauren Williamson for help with data collection and analysis.

References

Agostino PV, Cheng RK, Williams CL, West AE, Meck WH. Acquisition of response thresholds for timed performance is regulated by a calcium-responsive transcription factor, CaRF. Genes Brain Behav. 2013; 12:633–644. [PubMed: 23848551]

Agostino PV, Golombek DA, Meck WH. Unwinding the molecular basis of interval and circadian timing. Front Integr Neurosci. 2011a; 5:64. [PubMed: 22022309]

Agostino PV, do Nascimento M, Bussi IL, Eguia MC, Golombek DA. Circadian modulation of interval timing in mice. Brain Res. 2011b; 1370:154–163. [PubMed: 21078306]

Ainslie, G.; Haslam, N. Hyperbolic discounting. In: Loewenstein, G.; Elster, J., editors. Choice Over Time. Russell Sage Foundation; New York, NY: 1992. p. 177-209.

Ainslie GW. Impulse control in pigeons. J Exp Anal Behav. 1974; 21:485–489. [PubMed: 16811760]

Alessi SM, Petry NM. Pathological gambling severity is associated with impulsivity in a delay discounting procedure. Behav Process. 2003; 64:345–354.

Allman MJ, Meck WH. Pathophysiological distortions in time perception and timed performance. Brain. 2012; 135:656–677. [PubMed: 21921020]

Allman, MJ.; Teki, S.; Griffiths, TD.; Meck, WH. Properties of the internal clock: first- and second-order principles of subjective time; Ann Rev Psychol. 2014. p. 65http://dx.doi.org/10.1146/annurev-psych-010213-115117 (in press)

Ardayfio PA, Benvenga MJ, Chaney SF, Love PL, Catlow J, Swanson SP, Marek GJ. The 5-hydroxytryptamine$_{2A}$ receptor antagonist R-(+)-α-(2,3-Dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl-4-piperidinemethanol (M100907) attenuates impulsivity after both drug-induced disruption (dizocilpine) and enhancement (antidepressant drugs) of differential-reinforcement-of-low-rate 72-s behavior in the rat. J Pharm Exp Thera. 2008; 327:891–897.

Asgari K, Body S, Zhang Z, Fone KCF, Bradshaw CM, Szabadi E. Effects of 5-HT1A and 5-HT2A receptors stimulation on temporal differentiation performance in the fixed-interval peak procedure. Behav Processes. 2006; 71:250–257. [PubMed: 16098683]

Ayduk O, Mendoza-Denton R, Mischel W, Downey G, Peake PK, Rodriguez M. Regulating the interpersonal self: strategic self-regulation for coping with rejection sensitivity. J Pers Soc Psychol. 2000; 79:776–792. [PubMed: 11079241]

Baker DA, Tran-Nguyen LTL, Fuchs RA, Neisewander JL. Influence of individual differences and chronic fluoxetine treatment on cocaine-seeking behavior in rats. Psychopharmacology. 2001; 155:18–26. [PubMed: 11374332]

Balci F, Ludvig EA, Gibson JM, Allen BD, Frank KM, Kapustinski BJ, Fedolak TE, Brunner D. Pharmacological manipulations of interval timing using the peak procedure in make C3H mice. Psychopharmacology. 2008; 201:67–80. [PubMed: 18648777]

Balci, F.; Meck, WH.; Moore, H.; Brunner, D. Timing deficits in aging and neuropathology. In: Bizon, JL.; Woods, A., editors. Animal Models of Human Cognitive Aging. Humana Press; Totowa, NJ: 2009. p. 161-201.

Balsam PD, Drew MR, Gallistel CR. Time and associative learning. Comp Cogn Behav Rev. 2010; 5:1–22. [PubMed: 21359131]

Barr AM, Lehmann-Masten V, Paulus M, Gainetdinov RR, Caron MG, Geyer MA. The selective serotonin-2A receptor antagonist M100907 reverses behavioral deficits in dopamine transporter knockout mice. Neuropsychopharmacology. 2004; 29:221–228. [PubMed: 14603268]

Bickel WK, Marsch LA. Toward a behavioral economic understanding of drug dependence: delay discounting processes. Addiction. 2001; 96:73–86. [PubMed: 11177521]

Body S, Asgari K, Rickard JF, Zhang Z, Fone KCF, Bradshaw CM, Szabadi E. Effects of quipazine and m-chlorophenylbiguanide (m-CPBG) on temporal differentiation: evidence for the involvement of 5-HT2A but not 5-HT3 receptors in interval timing behaviour. Psychopharmacology. 2005; 181:289–298. [PubMed: 15864559]

Body S, Cheung THC, Bezzina G, Asgari K, Fone KCF, Glennon JC, Bradshaw CM, Szabadi E. Effects of d-amphetamine and DOI (2,5-dimethoxy-4-iodoamphetamine) on timing behavior: interaction between D_1 and 5-HT_{2A} receptors. Psychopharmacology. 2006; 189:331–343. [PubMed: 17051415]

Body S, Cheung THC, Valencia-Torres L, Olarte-Sánchez CM, Fone KCF, Bradshaw CM, Szabadi E. Pharmacological studies of performance on the free-operant psychophysical procedure. Behav Process. 2013; 95:71–89.

Body S, Kheramin S, Ho MY, Miranda Herrera F, Bradshaw CM, Szabadi E. Effects of fenfluramine on free-operant timing behaviour: evidence for involvement of 5-HT2A receptors. Psychopharmacology. 2004; 176:154–165. [PubMed: 15103450]

Brannon EM, Libertus ME, Meck WH, Woldorff MG. Electrophysiological measures of time processing in infant and adult brains: Weber's law holds. J Cogn Neurosci. 2008; 20:193–203. [PubMed: 18275328]

Broos N, Schmaal L, Wiskerke J, Kostelijk L, Lam T, Stoop N, et al. The relationship between impulsive choice and impulsive action: a cross-species translational study. PLoS ONE. 2012; 7 (5):e36781. [PubMed: 22574225]

Brunner D, Kacelnik A, Gibbon J. Memory for inter-reinforcement interval variability and patch departure decisions in the starling, *Sturnus vulgaris*. Animal Behav. 1996; 51:1025–1045.

Brunner D, Hen R. Insights into the neurobiology of impulsive behavior from serotonin receptor knockout mice. Ann N Y Acad Sci. 1997; 836:81–105. [PubMed: 9616795]

Buhusi CV, Aziz D, Winslow D, Carter RE, Swearingen JE, Buhusi MC. Interval timing accuracy and scalar timing in C57BL/6 mice. Behav Neurosci. 2009; 123:1102–1113. [PubMed: 19824777]

Buhusi CV, Meck WH. Differential effects of methamphetamine and haloperidol on the control of an internal clock. Behav Neurosci. 2002; 116:291–297. [PubMed: 11996314]

Buhusi CV, Meck WH. What makes us tick? Functional and neural mechanisms of interval timing. Nat Rev Neurosci. 2005; 6:755–765. [PubMed: 16163383]

Buhusi CV, Meck WH. Effect of clozapine on interval timing and working memory for time in the peak-interval procedure with gaps. Behav Process. 2007; 74:159–167.

Buhusi CV, Meck WH. Relative time sharing: new findings and an extension of the resource allocation model of temporal processing. Philos Trans R Soc. 2009; 364:1875–1885.

Buhusi, CV.; Meck, WH. Timing behavior. In: Stolerman, IP., editor. Encyclopedia of Psychopharmacology. Springer-Verlag; Heidelberg, Germany: 2010. p. 1319-1323.

Buhusi M, Scripa I, Williams CL, Buhusi CV. Impaired interval timing and spatial-temporal integration in mice deficient in CHL1, a gene associated with schizophrenia. Timing Time Percept. 2013; 1:21–38.

Cardinal RN, Robbins TW, Everitt BJ. The effects of d-amphetamine, chlordiazepoxide, alpha-flupenthixol and behavioral manipulations on choice of signaled and unsignaled delayed reinforcement in rats. Psychopharmacology (Berl). 2000; 152:362–375. [PubMed: 11140328]

Carlson SM, Moses LJ. Individual differences in inhibitory control and children's theory of mind. Child Dev. 2001; 4:1032–1053. [PubMed: 11480933]

Cheng RK, Ali YM, Meck WH. Ketamine "unlocks" the reduced clock-speed effect of cocaine following extended training: evidence for dopamine–glutamate interactions in timing and time perception. Neurobiol Learn Mem. 2007a; 88:149–159. [PubMed: 17513138]

Cheng RK, Etchegaray M, Meck WH. Impairments in timing, temporal memory, and reversal learning linked to neurotoxic regimens of methamphetamine intoxication. Brain Res. 2007b; 1186:255–266. [PubMed: 17996849]

Cheng RK, Hakak OL, Meck WH. Habit formation and the loss of control of an internal clock: inverse relationship between the level of baseline training and the clock-speed enhancing effects of methamphetamine. Psychopharmacology. 2007c; 193:351–362. [PubMed: 17464501]

Cheng RK, Liao RM. Dopamine receptor antagonists reverse amphetamine-induced behavioral alteration on a differential reinforcement of low-rate (DRL) operant task in the rat. Chin J Physiol. 2007; 50:77–88. [PubMed: 17608145]

Cheng RK, MacDonald CJ, Meck WH. Differential effects of cocaine and ketamine on time estimation: implications for neurobiological models of interval timing. Pharmacol Biochem Behav. 2006a; 85:114–122. [PubMed: 16920182]

Cheng RK, Meck WH. Prenatal choline supplementation increases sensitivity to time by reducing non-scalar sources of variance in adult temporal processing. Brain Res. 2007; 1186:242–254. [PubMed: 17996223]

Cheng RK, Meck WH, Williams CL. α7 nicotinic acetylcholine receptors and temporal memory: synergistic effects of combining prenatal choline and nicotine on reinforcement-induced resetting of an interval clock. Learn Mem. 2006b; 13:127–134. [PubMed: 16547161]

Cherek DR, Moeller FG, Dougherty DM, Rhoades H. Studies of violent and nonviolent male parolees: II. Laboratory and psychometric measurements of impulsivity. Biol Psychiatry. 1997; 41:523–529. [PubMed: 9046984]

Church RM, Meck WH, Gibbon J. Application of scalar timing theory to individual trials. J Exp Psychol Anim Behav Process. 1994; 20:135–155. [PubMed: 8189184]

Ciccocioppo R. The role of serotonin in craving: from basic research to human studies. Alcohol Alcohol. 1999; 34:244–253. [PubMed: 10344784]

Cordes S, Williamson LL, Alves K, Bhave SR, Rodriguez RM, Wetsel WC, Meck WH. The role of the norepinephrine transporter in interval timing. Abstr Soc Neurosci. 2008; 877.21

Coull JT, Cheng RK, Meck WH. Neuroanatomical and neurochemical substrates of timing. Neuropsychopharmacology. 2011; 36:3–25. [PubMed: 20668434]

Coull JT, Hwang HJ, Leyton M, Dagher A. Dopaminergic modulation of motor timing in healthy volunteers differs as a function of baseline DA precursor availability. Timing Time Percept. 2013; 1:77–98.

Crockett MJ, Clark L, Lieberman MD, Tabibnia G, Robbins TW. Impulsive choice and altruistic punishment are correlated and increase in tandem with serotonin depletion. Emotion. 2010; 10:855–862. [PubMed: 21171757]

Cui X. Hyperbolic discounting emerges from the scalar property of interval timing. Front Integr Neurosci. 2011; 5:24. [PubMed: 21713111]

Dalley JW, Everitt BJ, Robbins TW. Impulsivity, compulsivity, and top-down cognitive control. Neuron. 2011; 69:680–694. [PubMed: 21338879]

Daw ND, Kakade S, Dayan P. Opponent interaction between serotonin and dopamine. Neural Networks. 2002; 15:603–616. [PubMed: 12371515]

de Wit H, Crean J, Richards JB. Effects of d-amphetamine and ethanol on a measure of behavioral inhibition in humans. Behav Neurosci. 2000; 114:830–837. [PubMed: 10959541]

de Wit H, Enggasser JL, Richards JB. Acute administration of d-amphetamine decreases impulsivity in healthy volunteers. Neuropsychopharmacology. 2002; 27:813–825. [PubMed: 12431855]

Evenden JL. The pharmacology of impulsive behaviour in rats VII: the effects of serotonergic agonists and antagonists on responding under a discrimination task using unreliable visual stimuli. Psychopharmacology. 1999a; 146:422–431. [PubMed: 10550492]

Evenden JL. Varieties of impulsivity. Psychopharmacology. 1999b; 146:348–361. [PubMed: 10550486]

Evenden J, Ko T. The psychopharmacology of impulsive behavior in rats VIII: effects of amphetamine, methylphenidate, and other drugs on responding maintained by a fixed consecutive number avoidance schedule. Psychopharmacology. 2005; 180:294–305. [PubMed: 15717210]

Evenden JL, Ryan CN. The pharmacology of impulsive behaviour in rats: the effects of drugs on response choice with varying delays of reinforcement. Psychopharmacology. 1996; 128:161–170. [PubMed: 8956377]

Fantino E, Dunn R, Meck W. Percentage reinforcement and choice. J Exp Anal Behav. 1979; 32:335–340. [PubMed: 16812154]

Feldman RS, Smith WC. Chlordiazepoxide-fluoxetine interactions on food intake in free-feeding rats. Pharmacol Biochem Behav. 1978; 8:749–752. [PubMed: 308664]

Feola TW, Richards JB, de Wit H. Effects of d-amphetamine and alcohol on a measure of behavioral inhibition in rats. Behav Neurosci. 2000; 114:838–848. [PubMed: 10959542]

Gallistel CR, Gibbon J. Computational versus associative models of simple conditioning. Curr Direct Psychol Sci. 2001; 10:146–150.

Galtress T, Garcia A, Kirkpatrick K. Individual differences in impulsive choice and timing in rats. J Exp Anal Behav. 2012a; 98:65–87. [PubMed: 22851792]

Galtress T, Kirkpatrick K. The role of the nucleus accumbens core in impulsive choice, timing, and reward processing. Behav Neurosci. 2010; 124:26–43. [PubMed: 20141278]

Galtress T, Marshall AT, Kirkpatrick K. Motivation and timing: clues for modeling the reward system. Behav Process. 2012b; 90:142–153.

Garcia A, Kirkpatrick K. Impulsive choice behavior in four strains of rats: evaluation of possible models of attention-deficit/hyperactivity disorder. Behav Brain Res. 2013; 238:10–22. [PubMed: 23085479]

Gibbon J. Scalar expectancy theory and Webers law in animal timing. Psychol Rev. 1977; 84:279–325.

Gibbon J, Church RM. Representation of time. Cognition. 1990; 37:23–54. [PubMed: 2269007]

Gibbon J, Church RM. Comparison of variance and covariance patterns in parallel and serial theories of timing. J Exp Anal Behav. 1992; 57:393–406. [PubMed: 1602270]

Gibbon J, Church RM, Meck WH. Scalar timing in memory. Ann N Y Acad Sci. 1984; 423:52–77. [PubMed: 6588812]

Gu BM, Cheng RK, Yin B, Meck WH. Quinpirole-induced sensitization to noisy/sparse periodic input: temporal synchronization as a component of obsessive-compulsive disorder. Neuroscience. 2011; 179:143–150. [PubMed: 21284954]

Harrison AA, Everitt BJ, Robbins TW. Central 5-HT depletion enhances impulsive responding without affecting the accuracy of attentional performance: interactions with dopaminergic mechanisms. Psychopharmacology. 1997; 133:329–342. [PubMed: 9372531]

Hata T. Glutamate – a forgotten target for interval timing. Front Integr Neurosci. 2011; 5:27. [PubMed: 21734871]

Hayton SJ, Maracle AC, Olmstead MC. Opposite effects of amphetamine on impulsive action with fixed and variable delays to respond. Neuropsychopharmacology. 2012; 37:651–659. [PubMed: 21976042]

Hinton, SC.; Meck, WH. How time flies: functional and neural mechanisms of interval timing. In: Bradshaw, CM.; Szabadi, E., editors. Time and Behaviour: Psychological and Neurobiological Analyses. Elsevier; New York: 1997. p. 409-457.

Hinton SC, Meck WH. Frontal-striatal circuitry activated by human peak-interval timing in the supra-seconds range. Cogn Brain Res. 2004; 21:171–182.

Ho MY, al-Zahrani SS, Velazquez Martinez DN, Lopez Cabrera M, Bradshaw CM, Szabadi E. Effects of desipramine and fluvoxamine on timing behavior investigated with the fixed-interval peak procedure and the interval bisection task. Psychopharmacology. 1996; 125:274–284. [PubMed: 8815964]

Homberg JR, Arends B, Wardeh G, Raaso HS, Schoffelmeer ANM, De Vries TJ. Individual differences in the effects of serotonergic anxiolytic drugs on the motivation to self-administer cocaine. Neuroscience. 2004; 128:121–130. [PubMed: 15450359]

Jahanshahi M, Jones CRG, Zijlmans J, Katzenschlager R, Lee L, Quinn N, Frith CD, Lees AJ. Dopaminergic modulation of striato-frontal connectivity during motor timing in Parkinson's disease. Brain. 2010; 133:727–745. [PubMed: 20305278]

Jones CRG, Jahanshahi M. Dopamine modulates striato-frontal functioning during temporal processing. Front Integr Neurosci. 2011; 5:70. [PubMed: 22046150]

Jones, CRG.; Jahanshahi, M. Contributions of the basal ganglia to temporal processing: evidence from Parkinson's disease. Timing Time Percept. 2013. http://dx.doi.org/10.1163/22134468-00002009 (in press)

Jozefowiez J, Machado A. On the content of learning in interval timing: representation or associations? Behav Process. 2013; 95:8–17.

Jozefowiez, J.; Machado, A.; Staddon, JER. Cognitive versus associative decision rules in timing. In: Arstila, V.; Lloyd, D., editors. Subjective Time. MIT Press; Cambridge, MA: 2013.

Jupp B, Caprioli D, Dalley JW. Highly impulsive rats: modeling an endophenotype to determine the neurobiological, genetic and environmental mechanisms of addiction. Dis Model Mech. 2013; 6:302–311. [PubMed: 23355644]

Kacelnik A, Brunner D. Timing and foraging: Gibbon's scalar expectancy theory and optimal patch exploitation. Learn Motiv. 2002; 33:177–195.

Kayser AS, Allen DC, Navarro-Cebrian A, Mitchell JM, Fields HL. Dopamine, corticostriatal connectivity, and intertemporal choice. J Neurosci. 2012; 32:9402–9409. [PubMed: 22764248]

Kelm, MK.; Boettiger, CA. Effects of acute dopamine precursor depletion on immediate reward selection bias and working memory depend on catechol-O-methyltransferase genotype. J Cogn Neurosci. 2013. http://dx.doi.org/10.1162/jocn_a_00464 (in press)

Killeen, PR. Finding time. Behav Process. 2013. http://dx.doi.org/10.1016/j.beproc.2013.08.003 (in press)

Killeen PR, Fetterman JG. A behavioral theory of timing. Psychol Rev. 1988; 95:274–295. [PubMed: 3375401]

Kim S, Hwang J, Lee D. Prefrontal coding of temporally discounted values during intertemporal choice. Neuron. 2008; 59:161–172. [PubMed: 18614037]

Kirkpatrick, K. Interactions of timing and prediction error learning. Behav Process. 2013. http://dx.doi.org/10.1016/j.beproc.2013.08.005 (in press)

Kurti AN, Matell MS. Nucleus accumbens dopamine modulates response rate but not response timing in an interval timing task. Behav Neurosci. 2011; 125:215–225. [PubMed: 21463023]

Lake JI, Meck WH. Differential effects of amphetamine and haloperidol on temporal reproduction: dopaminergic regulation of attention and clock speed. Neuropsychologia. 2013; 51:284–292. [PubMed: 22982605]

Louie K, Glimcher PW. Separating value from choice: delay discounting activity in the lateral intraparietal area. J Neurosci. 2010; 30:5498–5507. [PubMed: 20410103]

Lustig C, Meck WH. Chronic treatment with haloperidol induces working memory deficits in feedback effects of interval timing. Brain Cogn. 2005; 58:9–16. [PubMed: 15878723]

MacDonald CJ, Cheng RK, Meck WH. Acquisition of “Start” and “Stop” response thresholds in peak-interval timing is differentially sensitive to protein synthesis inhibition in the dorsal and ventral striatum. Front Integr Neurosci. 2012; 6:10. [PubMed: 22435054]

MacDonald CJ, Cheng RK, Williams CL, Meck WH. Combined organizational and activational effects of short and long photoperiods on spatial and temporal memory in rats. Behav Process. 2007; 74:226–233.

MacDonald CJ, Meck WH. Systems-level integration of interval timing and reaction time. Neurosci Biobehav Rev. 2004; 28:747–769. [PubMed: 15555682]

MacDonald CJ, Meck WH. Differential effects of clozapine and haloperidol on interval timing in the supraseconds range. Psychopharmacology. 2005; 182:232–244. [PubMed: 16001114]

MacDonald CJ, Meck WH. Interaction of raclopride and preparatory-interval effects on simple reaction-time performance. Behav Brain Res. 2006; 175:62–74. [PubMed: 16962181]

Machado A. Learning the temporal dynamics of behavior. Psychol Rev. 1997; 72:195–206.

Malapani C, Dubois B, Rancurel G, Gibbon J. Cerebellar dysfunctions of temporal processing in the seconds range in humans. NeuroReport. 1998a; 9:3907–3912. [PubMed: 9875727]

Malapani C, Rakitin B, Levy R, Meck WH, Deweer B, Dubois B, Gibbon J. Coupled temporal memories in Parkinson’s disease: a dopamine-related dysfunction. J Cogn Neurosci. 1998b; 10:316–331. [PubMed: 9869707]

Malapani C, Deweer B, Gibbon J. Separating storage from retrieval dysfunction of temporal memory in Parkinson’s disease. J Cogn Neurosci. 2002; 14:311–322. [PubMed: 11970794]

Matell MS, Bateson M, Meck WH. Single-trials analyses demonstrate that increases in clock speed contribute to the methamphetamine-induced horizontal shifts in peak-interval timing functions. Psychopharmacology. 2006; 188:201–212. [PubMed: 16937099]

Matell MS, King GR, Meck WH. Differential modulation of clock speed by the administration of intermittent versus continuous cocaine. Behav Neurosci. 2004; 118:150–156. [PubMed: 14979791]

Matell MS, Meck WH. Reinforcement-induced within-trial resetting of an internal clock. Behav Process. 1999; 45:159–171.

Matell MS, Meck WH. Neuropsychological mechanisms of interval timing behavior. Bioessays. 2000; 22:94–103. [PubMed: 10649295]

Matell MS, Meck WH. Corticostriatal circuits and interval timing: coincidence-detection of oscillatory processes. Cogn Brain Res. 2004; 21:139–170.

Matell MS, Meck WH, Nicolelis MAL. Interval timing and the encoding of signal duration by ensembles of cortical and striatal neurons. Behav Neurosci. 2003; 117:760–773. [PubMed: 12931961]

Matell MS, Shea-Brown E, Gooch C, Wilson AG, Rinzel J. A heterogeneous population code for elapsed time in rat medial agranular cortex. Behav Neurosci. 2011; 125:54–73. [PubMed: 21319888]

Meck WH. Selective adjustment of the speed of internal clock and memory processes. J Exp Psychol Anim Behav Process. 1983; 9:171–201. [PubMed: 6842136]

Meck WH. Affinity for the dopamine D2 receptor predicts neuroleptic potency in decreasing the speed of an internal clock. Pharmacol Biochem Behav. 1986; 25:1185–1189. [PubMed: 2880350]

Meck WH. Neuropharmacology of timing and time perception. Cogn Brain Res. 1996; 3:227–242.

Meck WH. Choline uptake in the frontal cortex is proportional to the absolute error of a temporal memory translation constant in mature and aged rats. Learn Motiv. 2002; 33:88–104.

Meck, WH. Functional and Neural Mechanisms of Interval Timing. CRC Press LLC; Boca Raton, FL: 2003.

Meck WH. Temporal memory in mature and aged rats is sensitive to choline acetyltransferase inhibition. Brain Res. 2006a; 1108:168–175. [PubMed: 16854393]

Meck WH. Frontal cortex lesions eliminate the clock speed effect of dopaminergic drugs on interval timing. Brain Res. 2006b; 1108:157–167. [PubMed: 16844101]

Meck WH. Neuroanatomical localization of an internal clock: a functional link between mesolimbic, nigrostriatal, and mesocortical dopaminergic systems. Brain Res. 2006c; 1109:93–107. [PubMed: 16890210]

Meck WH. Acute ethanol potentiates the clock-speed enhancing effects of nicotine on timing and temporal memory. Alcohol Clin Exp Res. 2007; 31:2106–2113. [PubMed: 18034700]

Meck WH, Cheng RK, MacDonald CJ, Gainetdinov RR, Caron MG, Cevik MO. Gene-dose dependent effects of methamphetamine on interval timing in dopamine-transporter knockout mice. Neuropharmacology. 2012a; 62:1221–1229. [PubMed: 21296093]

Meck WH, Doyère V, Gruart A. Interval timing and time-based decision making. Front Integr Neurosci. 2012b; 6:13. [PubMed: 22479240]

Meck WH, Malapani C. Neuroimaging of interval timing. Cogn Brain Res. 2004; 21:133–137.

Meck WH, Penney TB, Pouthas V. Corticostriatal representation of time in animals and humans. Cur Opin Neurobiol. 2008; 18:145–152.

Meck WH, Williams CL. Characterization of the facilitative effects of perinatal choline supplementation on timing and temporal memory. NeuroReport. 1997; 8:2831–2835. [PubMed: 9376513]

Meck WH, Yin B. Fluoxetine normalizes interval-timing deficits in dopamine transporter knockout mice: contributions of the norepinephrine transporter and serotonin-2A receptors. Abstr Soc Neurosci. 2011; 610.04

Merchant, H.; Harrington, DL.; Meck, WH. Neural basis of the perception and estimation of time; Ann Rev Neurosci. 2013. p. 36http://dx.doi.org/10.1146/annurev-neuro-062012-170349

Miller, RR.; Witnauer, JE. Encyclopedia of the Sciences of Learning. Springer; Berlin: 2012. Comparator hypothesis of associative learning; p. 661-665.

Mischel W, Metzner R. Preference for delayed reward as a function of age, intelligence, and length of delay interval. J Abnorm Soc Psychol. 1962; 64:425–431. [PubMed: 14474526]

Mischel W, Shoda Y, Rodriguez MI. Delay of gratification in children. Science. 1989; 244:933–938. [PubMed: 2658056]

Miyazaki K, Miyazaki KW, Doya K. Activation of dorsal raphe serotonin neurons underlies waiting for delayed rewards. J Neurosci. 2011; 31:469–479. [PubMed: 21228157]

Mobini S, Body S, Ho MY, Bradshaw CM, Szabadi E, Deakin JF, Anderson IM. Effects of lesions of the orbitofrontal cortex on sensitivity to delayed and probabilistic reinforcement. Psychopharmacology (Berl). 2002; 160:290–298. [PubMed: 11889498]

Mobini S, Chiang TJ, Al-Ruwaitea AS, Ho MY, Bradshaw CM, Szabadi E. Effect of central 5-hydroxytryptamine depletion on inter-temporal choice: a quantitative analysis. Psychopharmacology. 2000; 149:313–318. [PubMed: 10823413]

Myerson J, Green L. Discounting of delayed rewards: models of individual choice. J Exp Anal Behav. 1995; 64:263–276. [PubMed: 16812772]

Oprisan SA, Buhusi CV. Why noise is useful in functional and neural mechanisms of interval timing? BMC Neurosci. 2013; 14:84. [PubMed: 23924391]

Paule MG, Meck WH, McMillan DE, McClure GYH, Bateson M, Popke EJ, Chelonis JJ, Hinton SC. The use of timing behaviors in animals and humans to detect drug and/or toxicant effects. Neurotox Teratol. 1999; 21:491–502.

Penney TB, Holder MD, Meck WH. Clonidine-induced antagonism of norepinephrine modulates the attentional processes involved in peak-interval timing. Exp Clin Psychopharmacol. 1996; 4:82–92.

Peters J, Büchel C. The neural mechanisms of inter-temporal decision-making: understanding variability. Trends Cogn Sci. 2011; 15:227–239. [PubMed: 21497544]

Petry NM. Delay discounting of money and alcohol in actively using alcoholics, currently abstinent alcoholics, and controls. Psychopharmacology. 2001; 154:243–250. [PubMed: 11351931]

Rachlin H, Green L. Commitment, choice and self-control. J Exp Anal Behav. 1972; 17:15–22. [PubMed: 16811561]

Rakitin BC, Gibbon J, Penney TB, Malapani C, Hinton SC, Meck WH. Scalar expectancy theory and peak-interval timing in humans. J Exp Psychol Anim Behav Process. 1998; 24:15–33. [PubMed: 9438963]

Ray D, Bossaerts P. Positive temporal dependence of the biological clock implies hyperbolic discounting. Front Neurosci. 2011; 5:2. [PubMed: 21441979]

Reynolds B, de Wit H, Richards J. Delay of gratification and delay discounting in rats. Behav Process. 2002; 59:157–168.

Reynolds B, Richards JB, Horn K, Karraker K. Delay discounting and probability discounting as related to cigarette smoking status in adults. Behav Process. 2004; 65:35–42.

Richards JB, Sabol KE, de Wit H. Effects of methamphetamine on a model of impulsive behavior in rats. Psychopharmacology. 1999; 146:432–439. [PubMed: 10550493]

Rivalan M, Gregoire S, Dellu-Hagedorn F. Reduction of impulsivity with amphetamine in an appetitive fixed consecutive number schedule with cue for optimal performance in rats. Psychopharmacology. 2007; 192:171–182. [PubMed: 17265075]

Samanez-Larkin GR, Mata R, Radu PT, Ballard IC, Carstensen LL, McClure SM. Age differences in striatal delay sensitivity during intertemporal choice in healthy adults. Front Neurosci. 2011; 5:126. [PubMed: 22110424]

Sanabria F, Acosta JI, Killeen PR, Neisewander JL, Bizo LA. Modeling the effects of fluoxetine on food-reinforced behavior. Behav Pharmacol. 2008; 19:61–70. [PubMed: 18195595]

Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. Science. 1997; 275:1593–1599. [PubMed: 9054347]

Schweighofer N, Bertin M, Shishida K, Okamoto Y, Tanaka SC, Yamawaki S, Doya K. Low-serotonin levels increase delayed reward discounting in humans. J Neurosci. 2008; 28:4528–4532. [PubMed: 18434531]

Seeyave DM, Coleman S, Appugliese D, Corwyn RF, Bradley RH, Davidson NS, Kaciroti N, Lumeng JC. Ability to delay gratification at age 4 years and risk of overweight at age 11 years. Arch Pediatr Adolesc Med. 2009; 163:303–308. [PubMed: 19349558]

Sellitto M, Ciaramelli E, di Pellegrino G. The neurobiology of intertemporal choice: insight from imaging and lesion studies. Rev Neurosci. 2011; 22:565–574. [PubMed: 21967518]

Shoda Y, Mischel W, Peake PK. Predicting adolescent cognitive and self-regulatory competences from preschool delay of gratification: identifying diagnostic conditions. Dev Psychol. 1990; 26:978–986.

Stephens DW, McLinn CM, Stevens JR. Discounting and reciprocity in an Iterated prisoner's dilemma. Science. 2002; 298:2216–2218. [PubMed: 12481142]

Sysoeva OV, Tonevitsky AG, Wackermann J. Genetic determinants of time perception mediated by the serotonergic system. PLoS ONE. 2010; 5 (9):e12650. [PubMed: 20862259]

Treisman M. Noise and Weber's law: the discrimination of brightness and other dimensions. Psychol Rev. 1964; 71:314–330. [PubMed: 14183614]

Wade TR, de Wit H, Richards JB. Effects of dopaminergic drugs on delayed reward as a measure of impulsive behavior in rats. Psychopharmacology. 2000; 150:90–101. [PubMed: 10867981]

Wiener M, Lohoff FW, Coslett HB. Double dissociation of dopamine genes and timing in humans. J Cogn Neurosci. 2011; 23:2811–2821. [PubMed: 21261454]

Wiener M, Magaro CM, Matell MS. Accurate timing but increased impulsivity following excitotoxic lesions of the subthalamic nucleus. Neurosci Lett. 2008; 440:176–180. [PubMed: 18562098]

Williamson LL, Cheng RK, Etchegaray M, Meck WH. "Speed" warps time: methamphetamine's interactive roles in drug abuse, habit formation, and the biological clocks of circadian and interval timing. Curr Drug Abuse Rev. 2008; 1:203–212. [PubMed: 19630719]

Willuhn I, Wanat MJ, Clark JJ, Phillips PE. Dopamine signaling in the nucleus accumbens of animals self-administering drugs of abuse. Cur Topic Behav Neurosci. 2010; 3:29–71.

Winstanley CA, Dalley JW, Theobald DE, Robbins TW. Global 5-HT depletion attenuates the ability of amphetamine to decrease impulsive choice on a delay-discounting task in rats. Psychopharmacology (Berl). 2003; 170:320–331. [PubMed: 12955303]

Winstanley CA, Dalley JW, Theobald DE, Robbins TW. Fractionating impulsivity: contrasting effects of central 5-HT depletion on different measures of impulsive behavior. Neuropsychopharmacology. 2004; 29:1331–1343. [PubMed: 15054475]

Winstanley CA, Theobald DE, Dalley JW, Cardinal RN, Robbins TW. Double dissociation between serotonergic and dopaminergic modulation of medial prefrontal and orbitofrontal cortex during a test of impulsive choice. Cereb Cortex. 2006; 16:106–114. [PubMed: 15829733]

Wise RA. Dopamine, learning and motivation. Nat Rev Neurosci. 2004; 5:483–494. [PubMed: 15152198]

Wogar MA, Bradshaw CM, Szabadi E. Effects of lesions of the ascending 5-hydroxytryptaminergic pathways on choice between delayed reinforcers. Psychopharmacology. 1993; 111:239–243. [PubMed: 7870958]

Wooters TE, Bardo MT. Methylphenidate and fluphenazine, but not amphetamine, differentially affect impulsive choice in spontaneously hypertensive, Wistar-Kyoto and Sprague-Dawley rats. Brain Res. 2011; 1396:45–53. [PubMed: 21570676]

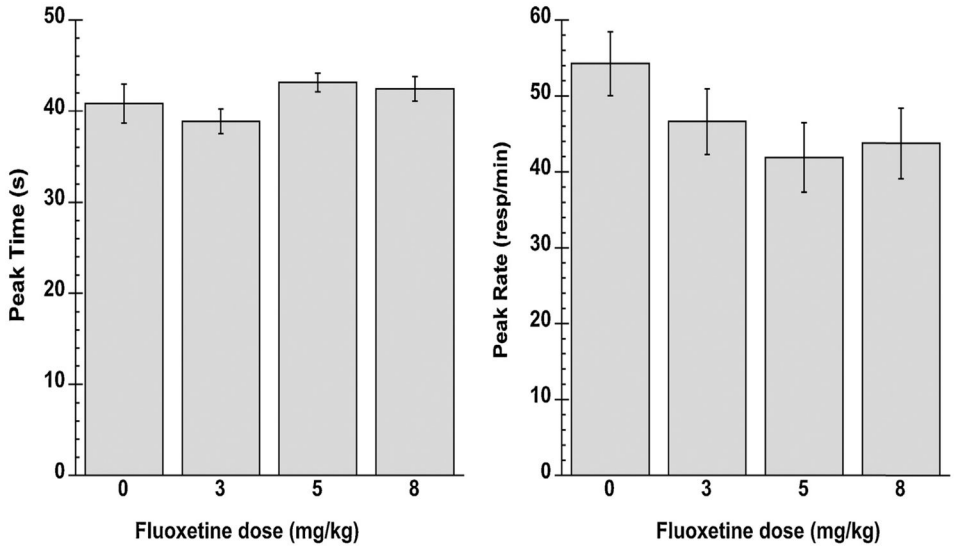

Fig. 1.

Mean ± SEM peak times (left panel) and peak rates (right panel) as a function of fluoxetine (FLX) dose for rats trained on a 40-s PI procedure.

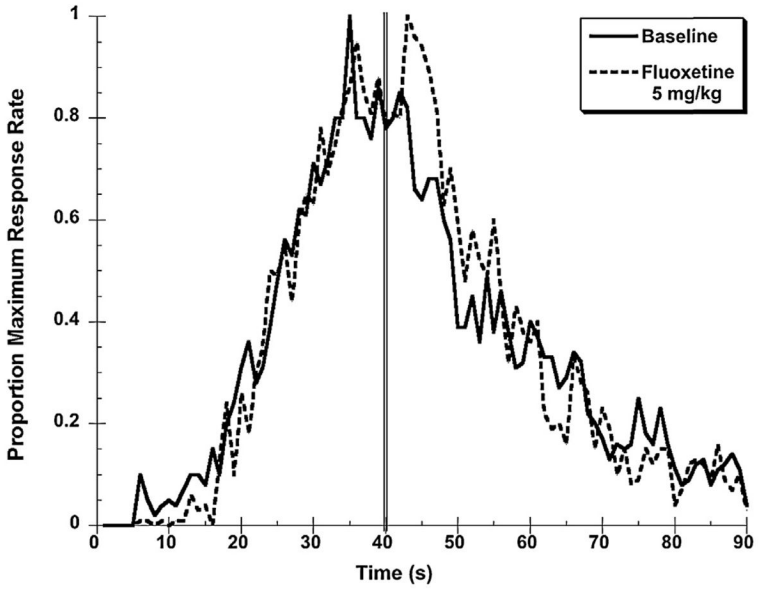

Fig. 2.

Mean proportion of maximum response rate (resp/min) as a function of signal duration (s) under vehicle baseline (solid line) and 5.0 mg/kg fluoxetine (FLX, broken line) treatment conditions. The accuracy and precision of timing the 40-s target duration did not differ as a function of FLX administration.

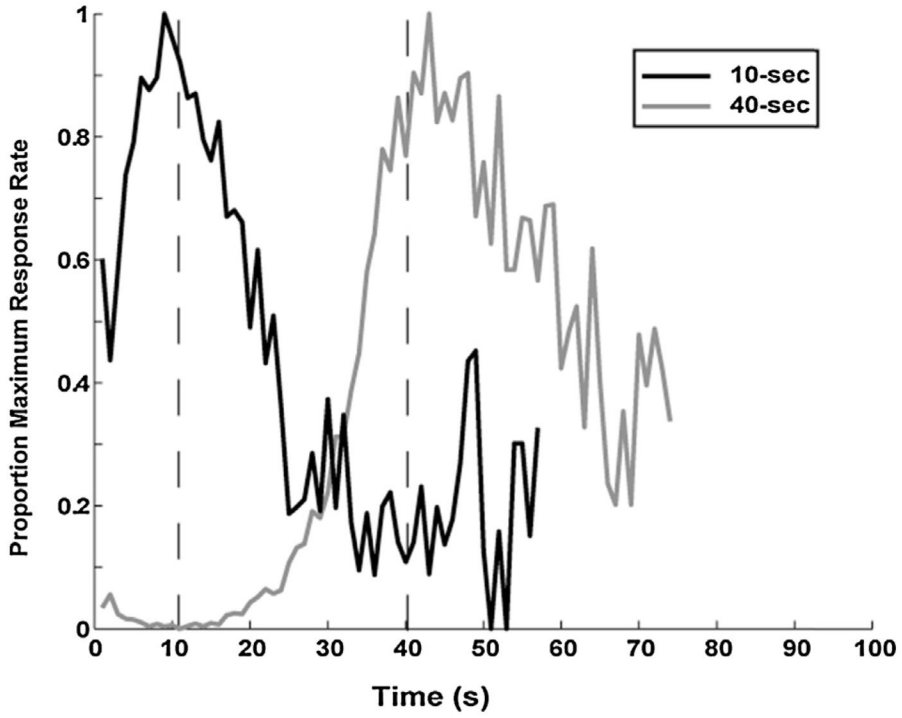

Fig. 3.

Mean proportion of maximum response rate (resp/min) as a function of signal duration (s) in the combined interval timing/inter-temporal choice task. The presence of the defection option did not prevent rats from learning the 10-s (black line) and 40-s (gray line) target durations.

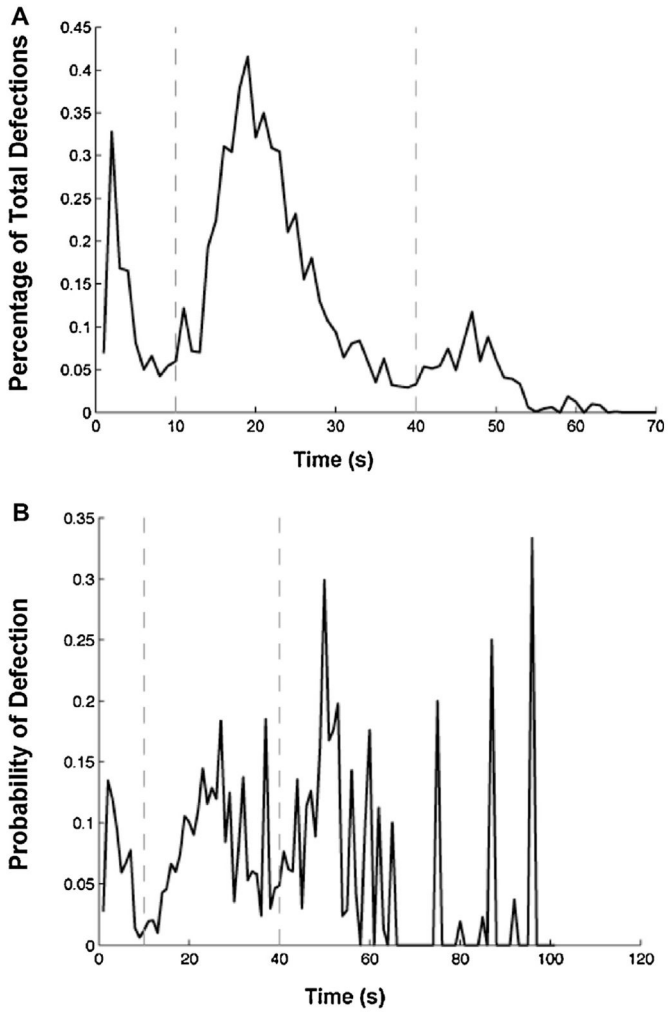

Fig. 4.

Mean percentage of maximum defection rate (across all trials, as defection occurs at a maximum of once per trial) as a function of signal duration (s) for all rats combined. The data indicate a tri-modal distribution with the first defection point occurring prior to the 10-s target duration, the second occurring between the two target durations at approximately the geometric mean (e.g., 20 s), and the last occurring after the 40-s target duration (panel A). Probability of defecting if this time point is reached (i.e., if the trial has not already ended due to prior defection or 40-s FI reinforcement (panel B).

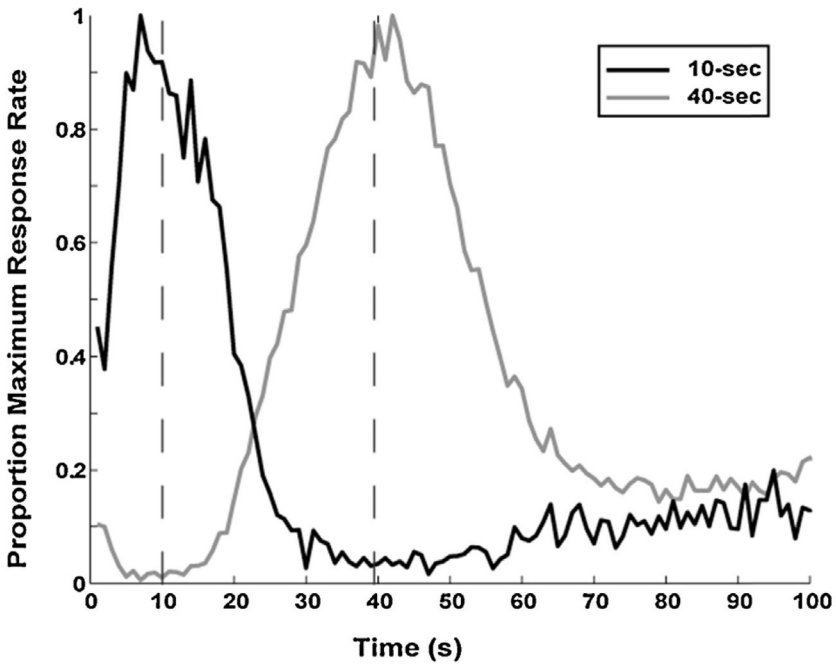

Fig. 5.

Mean proportion of maximum response rate (resp/min) as a function of signal duration (s) in the defection-absent (traditional peak procedure) task. The presence of the defection option in earlier sessions did not prevent rats from learning the 10-s (black line) and 40-s (gray line) target durations.

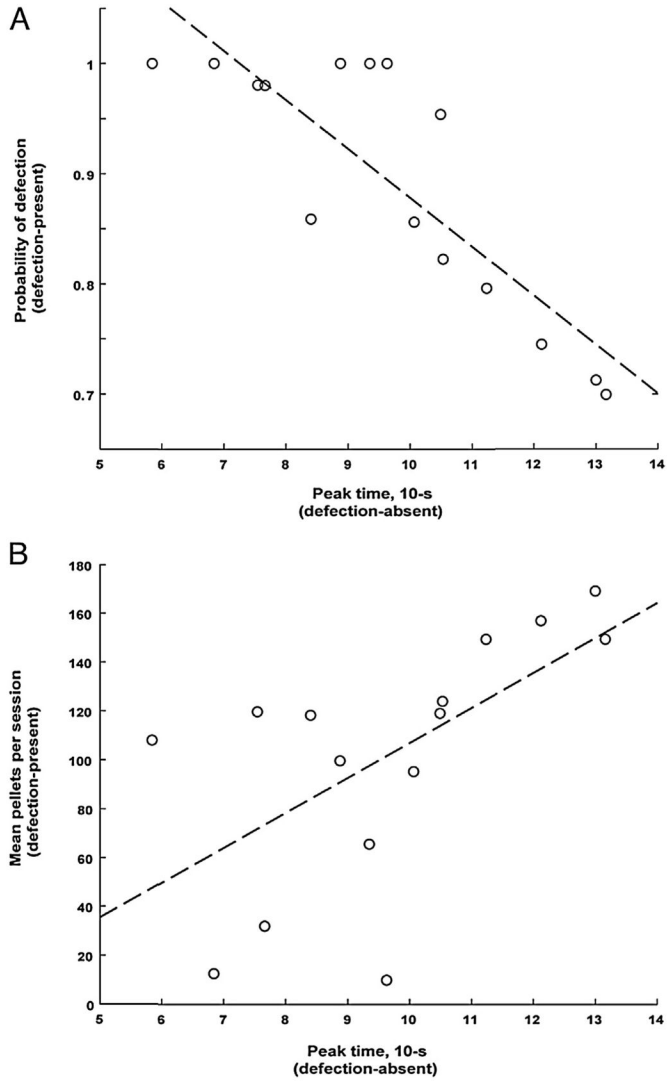

Fig. 6.

Peak times in the defection-absent condition are related to both percentage defection (panel A) and total pellets obtained (panel B) in the defection-present condition.

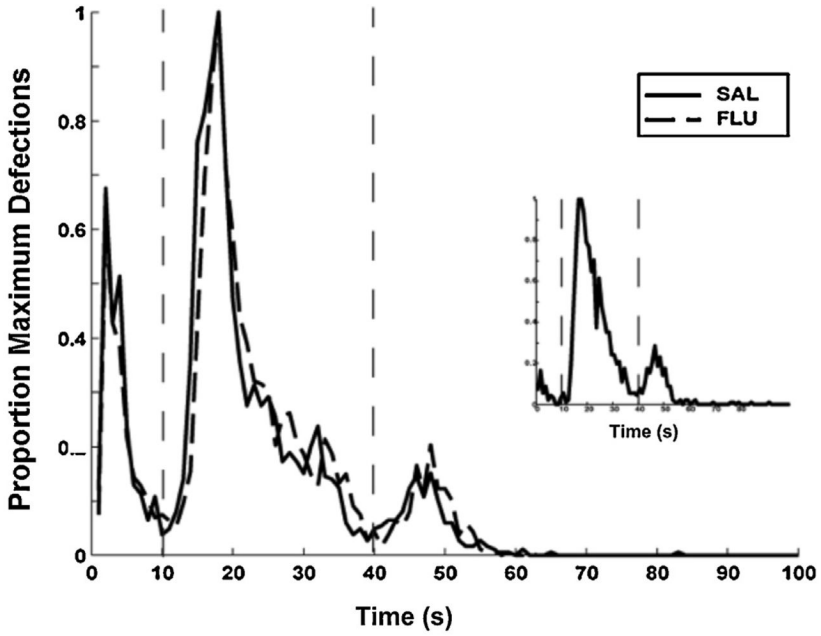

Fig. 7.

Mean proportion of maximum defections as a function of saline (SAL) baseline (solid line) and 5.0 mg/kg fluoxetine (FLX—dashed line) treatments across rats. The graphical inset displays the baseline level of defections in these same rats in Experiment 1, prior to drug manipulations in Experiment 2.

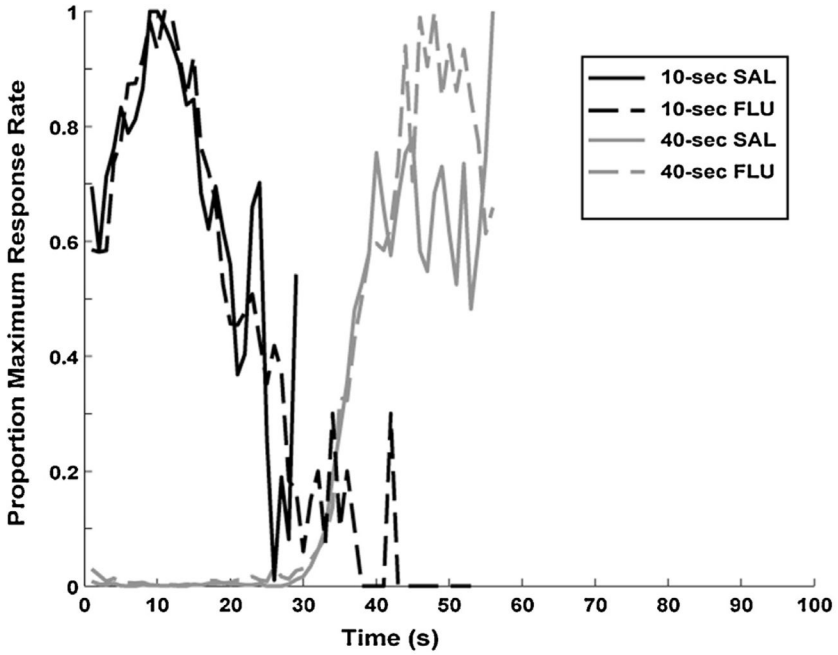

Fig. 8.

Mean proportion of maximum response rate (resp/min) as a function of signal duration (s) under vehicle baseline (SAL) and 5.0 mg/kg fluoxetine (FLX) treatment conditions for all rats combined. The accuracy of the timing of the 10-s and 40-s target did not differ as a function of FLX administration, but the precision of the 40-s target increased.

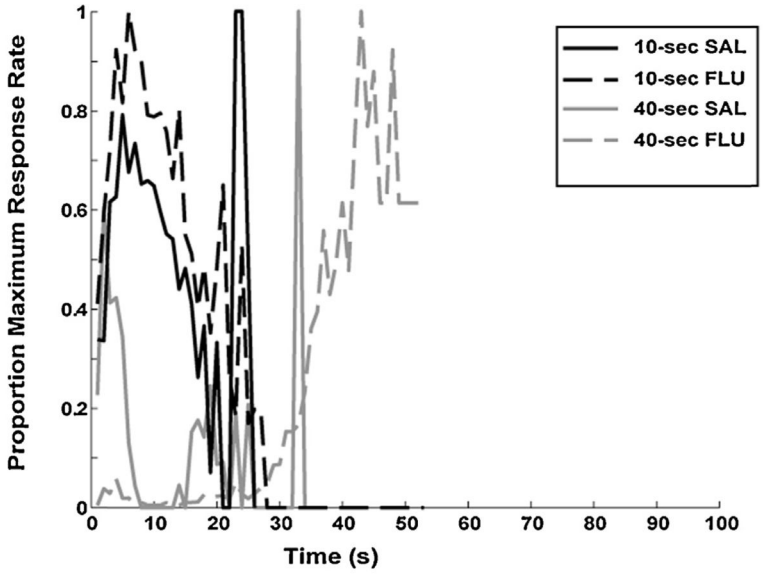

Fig. 9.

Mean proportion of maximum response rate (resp/min) as a function of signal duration (s) under vehicle (SAL) baseline =and 5.0 mg/kg fluoxetine (FLX) treatment conditions for an individual rat (S6). In this case, FLX administration delays defection times long enough to allow the 40-s peak function to appear. This particular rat did show a change in where defections were allocated, with FLX generating fewer in the <10 s range and more in the 40+ s range, $\chi^2(2) = 16.83$, $p < 0.001$.

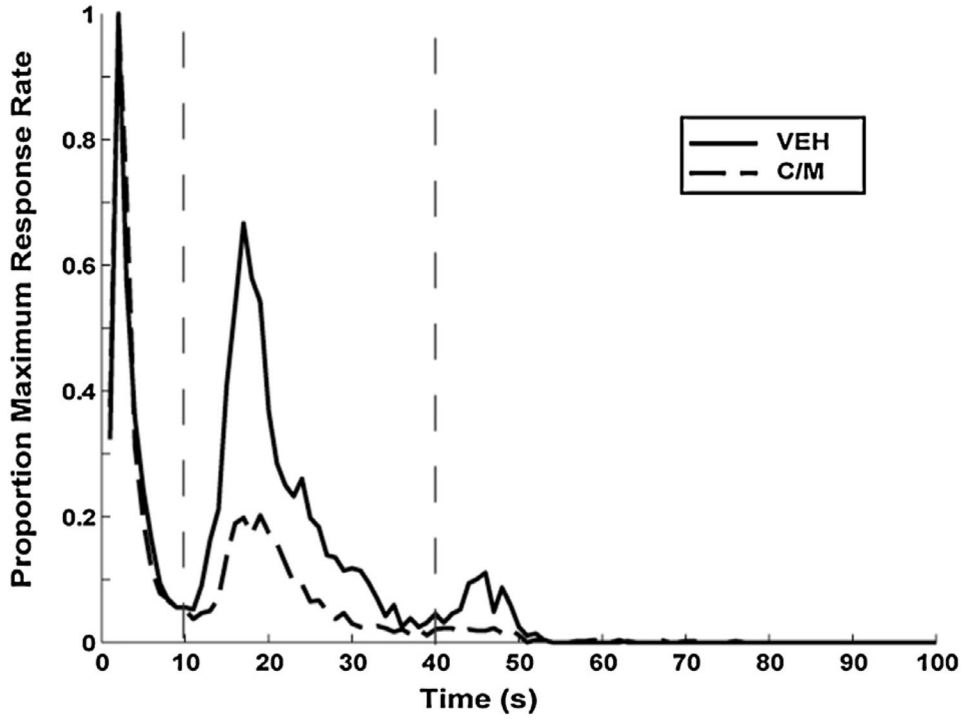

Fig. 10.

Defection times as a function of vehicle (VEH—solid line) baseline and 6 cocaine + methamphetamine (C/M—dashed line) treatments across rats.

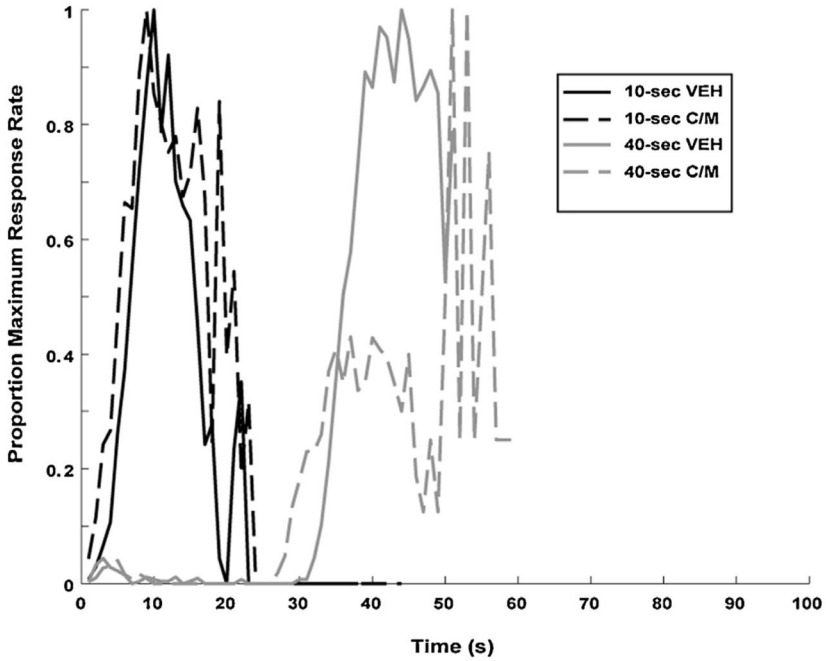

Fig. 11.

Mean proportion of maximum response rate (resp/min) plotted as a function of vehicle baseline (VEH, solid lines) and 15.0 mg/kg cocaine sessions pooled with 1.0 mg/kg methamphetamine sessions (C/M, broken lines) treatments as both the 10-s and 40-s target durations.

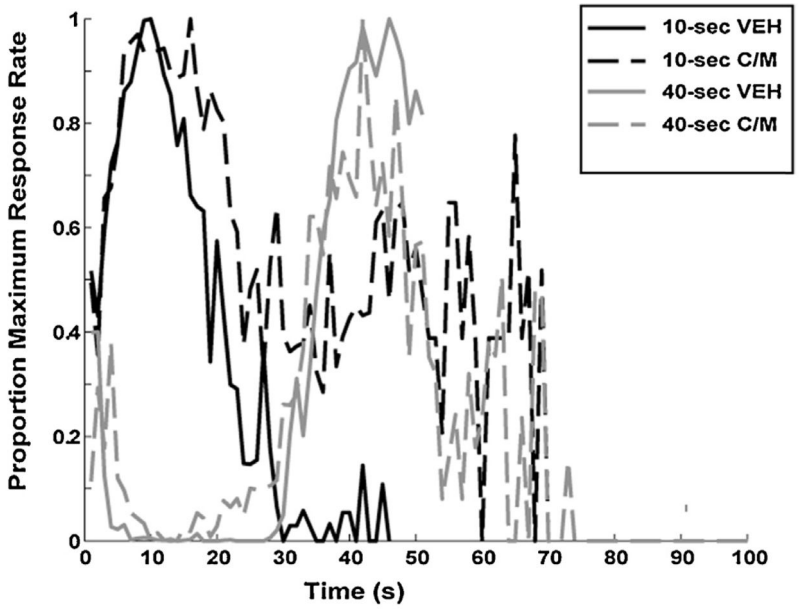

Fig. 12.

Mean proportion of maximum response rate (resp/min) as a function of signal duration (s) under vehicle baseline (VEH—solid lines) and cocaine + methamphetamine (COC + MAP —dashed lines) treatment conditions for all rats combined. Peak width increased with administration of these indirect dopamine agonists.

Table 1

Mean defection times for individual rats at three different duration ranges within a trial as well as the overall probability of defection.

Rat	Mean defection time (0–10 s)	Mean defection time (10–40 s)	Mean defection time (40+ s)	Mean defection time (all)	Mean defection proportion
1	None	18.28	46.40	26.42	.75
2	3.27	18.43	None	18.33	1.0
3	2.88	24.16	49.05	23.93	.98
4	5.04	24.97	52.28	31.47	.70
5	3.69	21.85	48.40	29.05	.71
6	2.54	15.87	None	2.62	1.0
7	1.49	18.19	53.97	17.04	.86
8	2.00	22.83	42.41	6.35	.98
9	3.73	21.01	47.44	27.37	.82
10	9.73	23.46	53.98	27.54	.86
11	2.42	16.82	None	4.82	1.0
12	2.08	21.26	None	19.87	1.0
13	4.21	19.53	46.14	27.73	.80
14	2.32	25.47	47.13	24.90	.95
15	3.78	17.11	None	14.76	1.0

Note: Data are combined across three sessions of a defection-available bi-peak procedure.

Table 2

Proportion of total defections occurring in the 0–10 s, 10–40 s, and 40+ s within-trial duration ranges under cocaine (COC), methamphetamine (MAP), fluoxetine (FLX), and saline (SAL) conditions.

Proportion of defections	0–10 s	10–40 s	40+ s
SAL (before FLX)	.18	.71	.11
FLX	.17	.71	.12
SAL (before COC)	.17	.73	.10
COC	.44	.48	.08
SAL (before MAP)	.40	.53	.07
MAP	.63	.36	.01