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Behavioral Mechanisms of Pramipexole-Induced Impulsivity: Discrimination Processes Underlying Decision-Making

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BEHAVIORAL MECHANISMS OF PRAMIPEXOLE-INDUCED IMPULSIVITY: DISCRIMINATION PROCESSES UNDERLYING DECISION-MAKING

by

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ABSTRACT

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Discrimination Processes Underlying Decision-Making

by

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Utah State University, 2012

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Faced with an intertemporal choice, an organism that chooses a "smaller-sooner" reinforcer over a "larger-later" reinforcer is said to behave impulsively. Individual differences in intertemporal choice are effectively modeled by generalized matching law and delay discounting equations that incorporate parameters corresponding to behavioral processes such as sensitivity to reinforcer amount or delay. By simulating changes in these processes and identifying conditions under which impulsive choice is likely to result, researchers are in a position to anticipate and examine potential behavioral mechanisms underlying clinical instances of impulsivity. Pramipexole, a dopamine agonist medication, is associated with reports of impulsive behavior in populations prescribed the drug, as well as in experimental subjects administered the compound prior to intertemporal choice sessions, although the latter findings are mixed. The present set of experiments was designed (a) to systematically replicate conditions under which

pramipexole increased impulsive choice, but also nonspecifically disrupted behavior, and (b) to elucidate behavioral mechanisms of pramipexole-induced impulsivity in rats. In Chapter 2, a behavioral task used previously by researchers reporting a nonspecific effect of pramipexole was modified to include procedural controls common in the intertemporal choice literature (centering response, no-delay sessions). In accord with previous findings, acute pramipexole nonspecifically disrupted choice behavior, while chronic pramipexole partially remediated elements of the disruption (i.e., decrease in initial-block choice). In Chapter 3, three experiments targeted behavioral processes critical for intertemporal choice. Experiment 1 evaluated the acute and chronic effects of pramipexole on rats' sensitivity to relative reinforcer delays in a concurrent-chains procedure. Contrary to the predicted effect, the drug decreased this measure, indicating the possibility of impaired stimulus control. Experiments 2 and 3 assessed the drug effect on discrimination of response-reinforcer contingencies and of reinforcer amounts, respectively, and revealed deficits in accuracy of similar magnitude across both preparations. Collectively, the results of these experiments suggest that previous findings of pramipexole-induced impulsivity and nonspecific disruption of behavior can be explained as impairments in discrimination processes required for intertemporal choice. Although the generality of the present findings may be limited to experimental settings with nonhumans, they demonstrate the utility of quantitatively modeling impulsivity.

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PUBLIC ABSTRACT

Behavioral Mechanisms of Pramipexole-Induced Impulsivity:

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Impulsivity represents a substantial and devastating cost to our economic, cultural, and physical prosperity. Using quantitative models of choice behavior, researchers are able to identify environmental conditions likely to promote impulsive decision-making. Such an approach is especially valuable in experimental efforts to better understand how drugs negatively affect choice in humans and nonhumans alike. For instance, pramipexole, a dopamine agonist medication prescribed for Parkinson's disease, has been associated with reports of increased rates of impulsive behavior. By which behavioral mechanisms pramipexole achieves these effects is unknown and requires further investigation.

The research reported herein sought to clarify pramipexole's effects on impulsive decision-making in rats according to two objectives. First, the goal of the experiment presented in Chapter 2 was to systematically replicate a previous study that reported an effect of pramipexole that was inconsistent with the extant literature. Second, the goal of the three experiments presented in Chapter 3 was to isolate behavioral processes that could contribute to impulsive choice and to describe quantitatively the mechanism(s) by which pramipexole negatively affects decision-making.

Results suggested that pramipexole significantly disrupted rats' discrimination of the source of food reinforcement, as well as discrimination of the amount of food received. These impairments are theoretically capable of increasing the probability of impulsive choice and may underlie pramipexole's effects as reported in the nonhuman drug literature. With respect to clinical instances of impulsive behavior, the present findings have limited generality. The approach documented herein, however, demonstrates the utility of quantitatively modeling aspects of impulsive decision-making in order to better understand complex drug effects.

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Science is a cooperative venture. As such, I am fortunate enough to have been influenced by the ideas and personalities of the following individuals:

My graduate advisor, Dr. Gregory Madden, who introduced me to the far-reaching implications of a mature understanding of impulsive decision-making. His examples of wisdom and humility are perhaps the most important lessons I take with me;

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My family, Steve, Susan, and Michael Johnson, who never questioned my decision to move across the country to pursue a field they knew little about. Every one of my professional accomplishments is a testament to their unconditional love and support;

My fiancé and best friend, Monica Francisco, who has shown me what it means to have a dream and to work tirelessly toward its realization. I am infinitely thankful that our paths have converged and that my short time here will be spent with her by my side. My love, always.

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CHAPTER 1

INTRODUCTION

Defining Impulsivity

Impulsivity represents a substantial and devastating cost to our economic, cultural, and physical prosperity. Recent developments suggest that financial decisions made by trusted institutions and businesses are easily swayed by the allure of immediate gratification, often at the expense of reasoned, long-term planning. Clean, alternative sources of energy remain underfunded and largely unexplored while the devastating consequences of current technologies remain relegated to a distant future. Substance abuse and unsafe sexual behaviors are prevalent despite life-threatening health risks and the positive benefits associated with abstinence. That examples such as these are so readily conjured speaks to the pervasiveness of impulsive decision-making in our everyday lives.

Central to the problem of impulsivity, and all of the examples illustrated above, is choice between consequences that are immediately forthcoming and those that are conferred only after some delay has elapsed. In a relatively simple choice situation in which two positive reinforcers differ in the delay to their receipt but are otherwise identical, it is perhaps not surprising that all animals, including humans, prefer the more immediate of the two. Given the perils of an unpredictable environment, natural selection has presumably favored organisms that were unwilling to wait when an equal opportunity was presently available. Something similar can be said for quantitative differences in amount. Because evolutionary pressures favor preference for larger reinforcers over

smaller reinforcers, choice in the absence of delay is demonstrably straight-forward and in the direction of larger reinforcers. Note, however, that neither of these simple choices–immediacy over delay or larger over smaller–constitutes an impulsive decision.

Impulsivity, as well as self-control, can only be demonstrated in a choice situation that combines differences in delay and amount, also known as an *intertemporal choice* (Ainslie, 1975; Rachlin & Green, 1972). In a typical intertemporal choice, a smaller reinforcer amount available relatively immediately is contrasted against a larger reinforcer amount available after a longer delay. Figure 1-1 illustrates such an intertemporal choice, with the vertical height of the bars corresponding to their objective values (1 and 3 units) and the horizontal distance from the choice point, T1, to each bar corresponding to the delay to the reinforcer (1 s and 10 s, respectively). Because the value of a reinforcer has been demonstrated empirically to decay hyperbolically as a function of delay to its delivery (e.g., Mazur, 1987), choice at time T1 is between the *discounted* values of the reinforcers (see Madden & Johnson, 2010 for a primer). In principle, the organism should choose the reinforcer associated with the higher discounted value. Given repeated choices, however, distributed rather than exclusive choice is not uncommon, especially as the features of the choice alternatives increase in similarity to one another (Mazur, 2010).

Under these conditions, individuals who prefer the "smaller-sooner" (SS) reinforcer because its value exceeds that of the other alternative at time T1 are said to behave impulsively, while those who prefer the "larger-later" (LL) reinforcer for the opposite reason are described as exhibiting "self-control." It is worth noting that

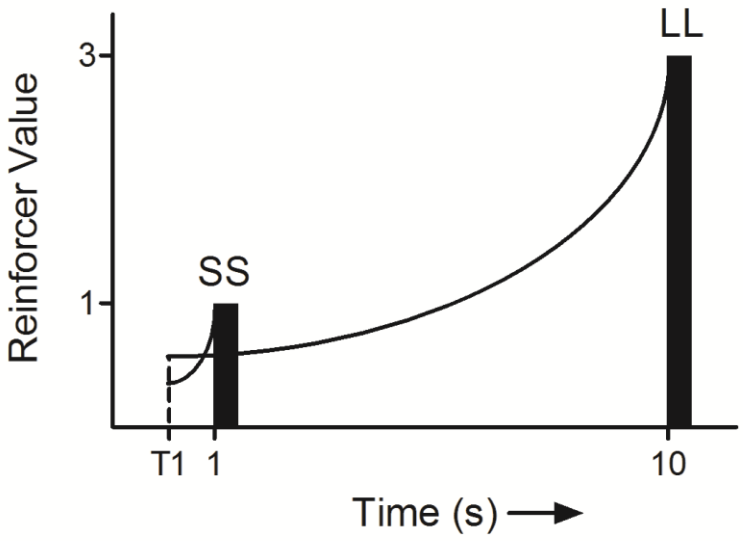

Figure 1-1. A hypothetical intertemporal choice. At time T1, the organism faces a choice between a small reinforcer (1 unit) delivered relatively immediately (1 s) and a larger reinforcer (3 units) available after a longer delay (10 s). Because both reinforcers are delayed, their values are discounted at T1.

impulsive *choice* represents just one of many "impulsivities." Failures to inhibit a prepotent response (i.e., impulsive *action*; e.g., Diergaarde et al., 2008) or to attend to relevant stimuli (e.g., Robbins, 2002) satisfy equally well colloquial definitions of impulsivity and are potentially related to impulsive choice (Pattij, Schetters, Janssen, Wiskerke, & Schoffelmeer, 2009; Robinson et al., 2009; but see de Wit, 2009), which is the focus of the research presented herein.

Based on the fundamental conflict arising from differences in delay and amount, researchers have advanced the study of impulsivity in a nonhuman laboratory context. In these preparations, nonhuman subjects, typically rats or pigeons, respond on levers or keys to make choices between reinforcers differing along these two dimensions. As in humans, the degree of preference for an SS reinforcer has been shown to differ both

across and within species (e.g., Green, Fry, & Myerson, 1994; Koffarnus & Woods, 2011; Tobin & Logue, 1994). At present, the sources of these individual differences are not well understood. Regardless of their origin, individual differences in impulsivity pose an interesting challenge to models of choice behavior. The next section will show that contemporary efforts to quantitatively characterize choice in general and impulsive choice specifically have, in large part, met this challenge and in doing so provide researchers with testable predictions regarding the influence of certain environmental factors, such as drug administration, on impulsive decision-making.

Quantitative Models of Choice and Impulsivity

All behavior may be conceptualized as choice (Herrnstein, 1970). Allocating time and effort to one activity necessarily detracts from time and effort devoted to alternative activities. How should one choose between multiple courses of action? Normative models of decision-making based on economic principles suggest that, given time constraints, organisms should attempt to maximize their returns (Herrnstein, 1990). One translation of this prediction in economic terms is that an organism should tailor its investment to an option based on its rate of return. Translated yet again into the terminology of behavior analysis, the proportion of responses allocated to a choice alternative should be determined by the proportion of reinforcement obtained from that alternative:

$$\frac{R_1}{R_1+R_2} = \frac{r_1}{r_1+r_2}. \quad (1)$$

In other words, Equation 1, better known as the *matching law*, states that the proportion of responding for an option (R_1) is equal to (i.e., matches) the proportion of

reinforcement obtained from that alternative (r_1; Herrnstein, 1961). Equation 1 can be rewritten to express the same relation as a ratio:

$$\frac{R_1}{R_2} = \frac{r_1}{r_2}. \quad (2)$$

As in Equation 1, Equation 2 predicts a linear relation between *relative* rates of reinforcement and *relative* responding. The particular schedule of reinforcement in use does not reduce the utility of Equation 2. For instance, concurrent ratio schedules of reinforcement (e.g., fixed-ratio) require an organism to emit an experimenter-specified number of responses prior to earning reinforcement. Under these circumstances, the organism should, as predicted by normative models, choose the richer alternative exclusively (i.e., complete the least work possible for the same amount of reinforcement). Because all reinforcement is obtained from a single source, and all responding occurred on the alternative that provided it, matching is obtained.

Equation 2 also describes performance under concurrent interval schedules (e.g., variable-interval [VI]). On a VI schedule, reinforcement is earned only after an unpredictable amount of time has elapsed and the organism has responded on the apparatus. Because responding exclusively on a single operanda results in lower reinforcement rates (i.e., reinforcers available periodically on the other operanda are not obtained), responding on concurrent VI schedules adaptively occurs at high rates on both operanda. Assuming only reinforcement frequency differs between the concurrent VI schedules, the organism should match relative response allocation to relative reinforcement rates. Thus, in the cases of concurrent ratio and interval schedules of

reinforcement, response allocation consistent with perfect matching allows the organism to maximize obtained reinforcement and to satisfy normative economic models.

One weakness of the formulations above is that they represent what organisms *should* do. Although perfect matching is predicted, it is not always obtained. In fact, *undermatching*, in which response allocation favors the leaner of two alternatives more than is predicted, is a more typical result of matching studies (Baum, 1974). Based upon the psychophysical assertions of Stevens's power law (Stevens, 1957), Baum proposed the *generalized matching law* to quantify individual differences in matching:

$$\log\left(\frac{R_1}{R_2}\right) = r \log\left(\frac{r_1}{r_2}\right) + \log b. \quad (3)$$

Response allocation in Equation 3 remains a linear function of relative reinforcement rates, but with a slope of *r* and a y-intercept of log *b*. Unlike in Equations 1 and 2, the slope of the matching function in Equation 3, conceptualized as sensitivity to relative reinforcement rates, can depart from unity and thus accurately describe behavioral performances such as undermatching. Another advantage of Equation 3 is its ability to describe bias toward one response alternative (log *b*) resulting from factors other than the independent variable. By allowing these two parameters to vary, Equation 3 outperforms earlier versions of the matching law by more accurately modeling choice behavior.

The examples provided in the beginning of the previous section suggest that choice is not controlled exclusively by rates of reinforcement. Additional variables such as delay to reinforcement and reinforcement amount are critical determinants of choice behavior, especially in intertemporal choice situations. Soon after the development of Equation 1, Chung and Herrnstein (1967) equalized reinforcement rates and

demonstrated a negative relation between choice and delay to reinforcement. That is, as reinforcement associated with one option became increasingly delayed, choice increasingly favored the other alternative. Equation 3 can be expanded beyond reinforcement rates to include other parameters of interest, such as delay or amount:

$$\log\left(\frac{R_1}{R_2}\right) = d\log\left(\frac{D_2}{D_1}\right) + a\log\left(\frac{A_1}{A_2}\right) + \log b. \quad (4)$$

The concatenated matching law (Rachlin & Baum, 1969) extends the concept of sensitivity to all features of the choice situation. On one hand, if an organism is perfectly sensitive to all features of the choice situation (d and a = 1) and does not exhibit any biases ($\log b = 0$), choice will reflect the sum of the reinforcer delay and amount ratios. On the other hand, if the organism is *imperfectly* sensitive to *any* aspect of the choice situation, this insensitivity will be reflected in the relevant sensitivity parameter.

By including parameters designed to describe the sensitivity of behavior to relative reinforcement delays and amounts, researchers extended matching accounts of behavior to intertemporal choice situations (Ito & Nakamura, 1998; Ito & Oyama, 1996; Logue, Peña-Correal, Rodriguez, & Kabela, 1986; Logue, Rodriguez, Peña-Correal, & Mauro, 1984; White & Pipe, 1987). Logue et al. (1984), for instance, used Equation 4 to compare relative sensitivities to delay and amount in pigeons that had received self-control training and those that had not (Mazur & Logue, 1978). Logue and colleagues suggested that Equation 4 could be summarized as follows:

$$\log\left(\frac{R_1}{R_2}\right) = \log\left(\frac{V_1}{V_2}\right), \quad (5)$$

wherein relative response allocation (i.e., choice) is equivalent to the relative *values* of the two outcomes (i.e., the combined effects of reinforcement delays and amounts). At

the same time, however, the integration of these two frameworks was limited to concurrent-chains procedures and almost exclusively to concurrent VI schedules.

In a seminal paper, Mazur (1987) reiterated findings from the literature that choice in concurrent-chains procedures was influenced not only by features of terminal-link schedules (e.g., reinforcement amount), but also the durations of initial-link schedules (e.g., Fantino, 1969). To minimize this "initial-link" effect, Mazur proposed using *discrete-choice* procedures in which a single response on either alternative initiated the reinforcement sequence. An important consequence of reducing the initial-link schedule to a single response is that response allocation within a trial is necessarily exclusive. Given the relation described in Equation 5, exclusive choice should result from the difference in relative reinforcer value (Ho, Mobini, Chiang, Bradshaw, & Szabadi, 1999; Logue, 1988).

In addition to these procedural considerations, the primary contribution of Mazur (1987) was the formal description of the decay of reinforcer value resulting from the introduction of a delay to reinforcement. To assess this *delay discounting* phenomenon, Mazur used pigeons' choices between 2 s and 6 s access to grain (Experiment 1). The delay to the smaller reinforcer amount (SS) was fixed by the experimenter across conditions, but was always of shorter duration than the delay to the larger reinforcer amount (LL), which varied as a function of the pigeon's prior choices. For example, if the pigeon chose the SS reinforcer on two consecutive trials, the delay to the LL reinforcer was slightly decreased. If the LL reinforcer was chosen twice, then its delay was slightly increased. If the SS and LL reinforcers were chosen once each on consecutive trials, a

pattern indicating *indifference* between the choice alternatives, then the LL delay remained unchanged. Once stable over several trials, these *indifference points* (LL delays) were plotted by Mazur as a function of the SS delay. Of four models hypothesized to describe the relation between reinforcer value and delay of reinforcement, the empirical data were most consistent with a hyperbolic model:

$$v = \frac{\mathrm{A}}{1+k\mathrm{D}}. \qquad (6)$$

In Equation 6, the subjective value of a reinforcer, *V*, of objective magnitude *A* declines as an inverse function of delay to reinforcement delivery *D*, a process illustrated in Figure 1-1 and simulated in Figure 1-2.

The rate at which value decays (i.e., the steepness of the curve in Figure 1-2) is described by *k*, a free parameter that varies across individuals as well as across states experienced by organisms (Odum & Bauman, 2010). Higher *k* estimates (i.e., steeper delay discounting) are often associated with drug dependency (Baker, Johnson, & Bickel, 2003; Bickel, Odum, & Madden, 1999; Coffey, Gudleski, Saladin, & Brady, 2003; Heyman & Gibb, 2006; Johnson, Bickel, & Baker, 2007; Kirby & Petry, 2004; Kirby, Petry, & Bickel, 1999; Madden, Petry, Badger, & Bickel, 1997; Mitchell, 1999; Ohmura, Takahashi, & Kitamura, 2005; Petry, 2001; Reynolds, Richards, Horn, & Karraker, 2004) and treatment failure in abusing populations (Stanger et al., 2011; Washio et al., 2011; Yoon et al., 2007).

Hyperbolic delay discounting has been replicated across species using a variety of discrete-choice procedures (e.g., Johnson, 2012; Reynolds & Schiffbauer, 2004; Richards, Mitchell, de Wit, & Seiden, 1997). One assumption of Equation 6, likely

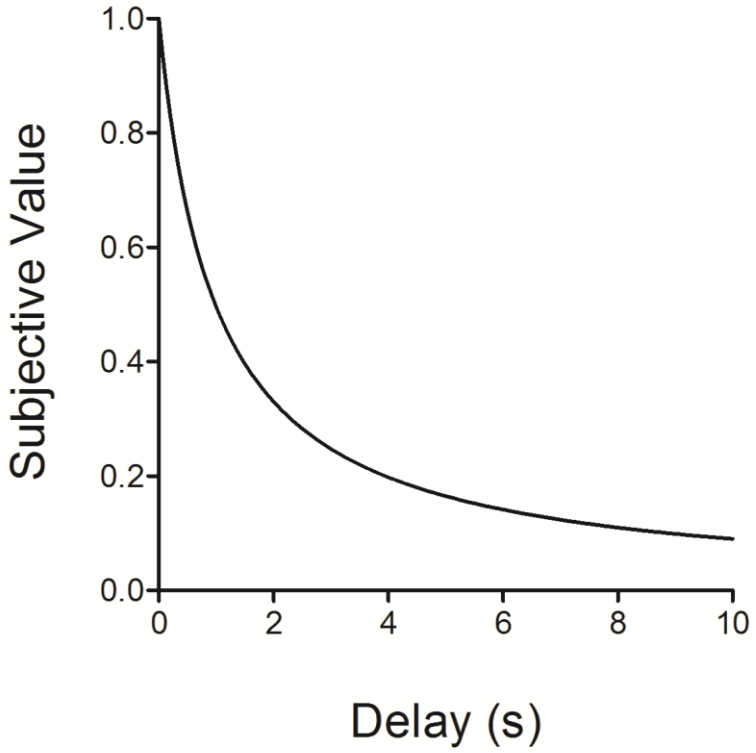

Figure 1-2. A hypothetical delay discounting curve. When delivered immediately, the reinforcer retains its full objective value. Increasing the delay to reinforcer delivery rapidly decreases the subjective value (*V* in Equation 6) of the reinforcer at a rate *k* in accordance with the hyperbolic model proposed by Mazur (1987).

satisfied on most occasions, is that the choice behavior is perfectly sensitive to relative reinforcer amounts and delays in effect. Under certain conditions (e.g., drug administration), however, the assumption of perfect sensitivity may be violated and lead to poor model convergence. To accommodate departures from perfect sensitivity, researchers have proposed versions of Equation 6 that in many ways mirror the historical development of the generalized matching law (Equation 3) from the strict matching law (Equation 2). Specifically, these *hyperboloid* models, so-called for their approximation of hyperbolic discounting, include parameters for sensitivity to relative reinforcer amounts

(*a*) and sensitivity to relative delay to reinforcement (*d*; Green & Myerson, 2004; Locey & Dallery, 2009; Loewenstein & Prelec, 1992; Myerson & Green, 1995; Rachlin, 2006):

$$v = \frac{\mathrm{A}^{a}}{(1+k\mathrm{D})^{d}}. \quad (7)$$

Model comparisons between hyperboloid (Equation 7) and hyperbolic (Equation 6) discounting equations favor the former family and suggest that the assumption of perfect sensitivity is not always a prudent one (McKerchar, Green, & Myerson, 2010; McKerchar et al., 2009). Perhaps more importantly, the inclusion of sensitivity parameters in discounting models like Equation 7 unifies the logic once separating parallel efforts to model intertemporal choice using concurrent-chains (matching law) and discrete-choice (delay discounting) procedures. Reformulating Equation 4 to incorporate the empirical evidence for delay discounting into analyses of response allocation data obtained in concurrent-chains preparations (e.g., Pitts & Febbo, 2004):

$$\log\left(\frac{V_1}{V_2}\right) = d\,\log\left(\frac{1+kD_2}{1+kD_1}\right) + a\,\log\left(\frac{A_1}{A_2}\right) \quad (8)$$

According to the unified framework of Equations 7 and 8, intertemporal choice reflects not only the effects of delay discounting processes, but also related sensitivities to relative reinforcer amount and psychophysically scaled delay variables. The section that follows will attempt to demonstrate quantitatively how changes in these behavioral processes influence the relative values of SS and LL choice alternatives and, in effect, the outcome of intertemporal choice. Because little is known about the interaction between delay discounting rate (*k*) and the sensitivity parameters under consideration, discounting rate is assumed constant at 1 in the following simulations. In effect, changes in behavioral

processes such as sensitivities to relative reinforcer delays or relative reinforcer amounts, induced by drug administration for example, will be shown to qualify as candidate behavioral mechanisms of intertemporal choice.

Behavioral Mechanisms of Intertemporal Choice

As discussed in preceding sections, organisms display consistent preferences for immediate over delayed sources of reinforcement. Likewise, organisms prefer large amounts of reinforcement over small amounts of reinforcement. Extrapolated to an intertemporal choice scenario, these "default" preferences interact and compete to determine decision-making. Using the ability of Equation 8 to capture individual differences (e.g., differences in delay discounting or sensitivity to relative reinforcer amounts or relative reinforcer delays), researchers can speculate about the conditions under which organisms will choose impulsively (all else being equal). Each of the following model simulations involves a behavioral process fundamental to impulsivity as evaluated in intertemporal choice.

One reason why an individual might choose impulsively is if it displays *enhanced* sensitivity to relative reinforcer delays (i.e., $d > 1$). As an example, let us modify slightly the intertemporal choice depicted in Figure 1-1. In our new choice situation, an organism at time T1 must choose between R_1, a SS reinforcer of 1 unit delivered after 2 s, and R_2, a LL reinforcer of 3 units delivered after 6 s, and presumably does so on the basis of whichever alternative has the greater subjective value at T1. Assuming a delay

discounting rate of 1, and perfect sensitivity to both relative reinforcer amounts and relative reinforcer delays (d and a = 1), Equation 8 predicts:

$$\log\left(\frac{V_1}{V_2}\right) = 1\log\left(\frac{1+1*6}{1+1*2}\right) + 1\log\left(\frac{1}{3}\right)$$

$$\log\left(\frac{V_1}{V_2}\right) = 0.37 - 0.48$$

$$\log\left(\frac{V_1}{V_2}\right) = -0.11$$

In this instance, the value of the LL reinforcer exceeds that of the SS reinforcer. This fact is verified by solving for V_1 and V_2 according to Equation 7, which results in discounted values of 0.33 and 0.43, respectively–the logarithmic ratio of which is equal to -0.11. Because the organism should choose the reinforcer with the greater relative value, V_2, which reflects the LL reinforcer, is selected.

Assuming the same intertemporal choice scenario, which choice alternative would be chosen should the same organism display *enhanced* sensitivity to relative reinforcer delays (e.g., d = 1.5)? Equation 8 now predicts:

$$\log\left(\frac{V_1}{V_2}\right) = 1.5\log\left(\frac{1+1*6}{1+1*2}\right) + 1\log\left(\frac{1}{3}\right)$$

$$\log\left(\frac{V_1}{V_2}\right) = 0.55 - 0.48$$

$$\log\left(\frac{V_1}{V_2}\right) = 0.07$$

Under conditions in which enhanced sensitivity to relative reinforcer delays is observed, the organism will reverse its previously demonstrated preference for R_2 (the LL reinforcer) and favor the more valuable reinforcer associated with R_1 (the SS reinforcer).

This reversal can again be confirmed in the context of Equation 7, which arrives at values of 0.19 and 0.16 for R_1 and R_2, respectively; the log ratio of these values is also 0.07.

To demonstrate further the influence of this sensitivity parameter on intertemporal choice, simulations based on Equations 7 and 8 were conducted across a range of delay sensitivity values. Specifically, an approach similar to that of Mazur (1987) was adopted to estimate LL delays at which a hypothetical organism with k and $a = 1$ was indifferent between R_1 and R_2. That is, given an "experimenter-programmed" delay to 1 reinforcer unit (SS), at what delay to 3 units (LL) would $V_1 = V_2$? The results of the simulations are shown in Figure 1-3. When sensitivity to relative reinforcer delays was low (e.g., $d = 0.5$), the LL delay at indifference tended to be of longer duration in comparison to LL delays given the same SS delay but with higher sensitivity values. In other words, as sensitivity to relative reinforcer delays increases, the LL delay at indifference for any SS delay grows shorter. Poor tolerance of LL delays is a hallmark of increased impulsivity in an intertemporal choice context and is consistent with the predictions of the model.

The functions shown in Figure 1-3 also accord with the predictions of hyperbolic delay discounting made by Mazur (1987). In his Figure 3.3, Mazur illustrated functions consistent with four competing models of the relation between reinforcer delay and value. Hyperbolic discounting (Equation 6), which his empirical data confirmed, required (a) that the slope of the function relating LL delay at indifference and SS delay be greater than 1, and (b) a non-zero y-intercept. Although Mazur did not originally consider Equation 7, the model also predicts a linear relation between reinforcer delays with slope > 1 and y-intercept $\neq 0$ and when d and $a = 1$ reduces to Equation 6. As such, the

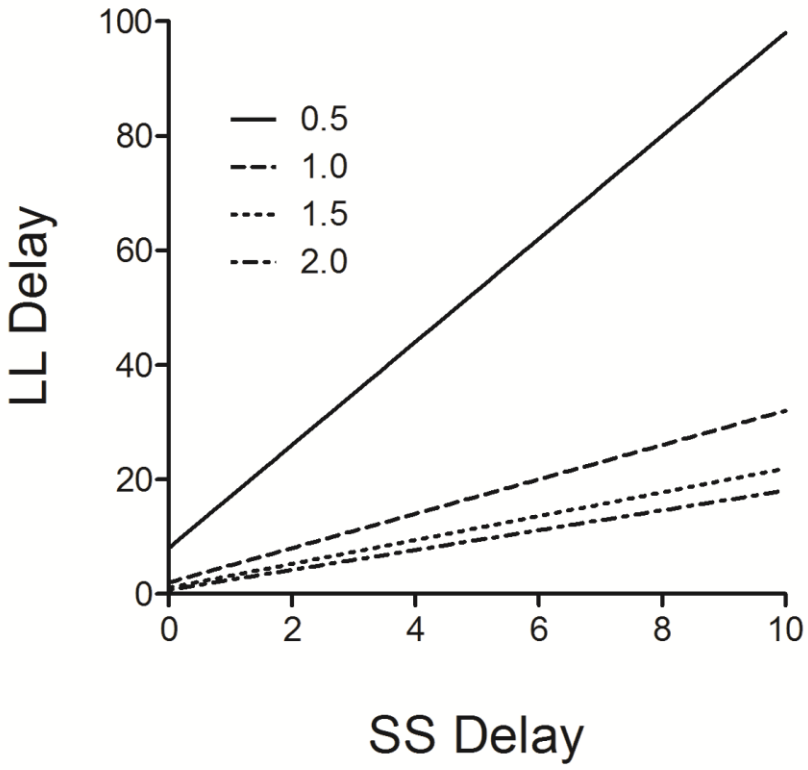

Figure 1-3. Simulated effects of changes in sensitivity to relative reinforcer delay on LL indifference delays. This delay-delay plot, similar to those reported in Mazur (1987), shows that as sensitivity to relative reinforcer delays (*d*) in Equation 8 increases, the organism is indifferent between progressively shorter LL delays (y-axis), a behavioral pattern consistent with increased impulsivity.

simulations conducted above serve to advance our understanding of the role of sensitivity to relative reinforcer delay in intertemporal choice situations.

Similar logic predicts increased impulsive choice if an individual displays *diminished* sensitivity to relative reinforcer amount (i.e., $a < 1$). Once again, the modified intertemporal choice depicted in Figure 1-1 serves as our example. For an organism with perfect sensitivity to relative reinforcer delay and amount (d and $a = 1$), choice at time T1 between R_1, a SS of 1 unit delivered after 2 s, and R_2, a LL of 3 units delivered after 6 s,

should reflect the objective values held by these parameters. As before, Equation 8 predicts:

$$\log\left(\frac{V_1}{V_2}\right) = 1\log\left(\frac{1+1*6}{1+1*2}\right) + 1\log\left(\frac{1}{3}\right)$$

$$\log\left(\frac{V_1}{V_2}\right) = 0.37 - 0.48$$

$$\log\left(\frac{V_1}{V_2}\right) = -0.11.$$

The hypothetical organism in this example is predicted to choose R_2, the LL reinforcer of subjective value 0.43, over R_1, the SS reinforcer of subjective value 0.33.

According to Equation 8, diminished sensitivity to relative reinforcer amount should increase the frequency of SS choice. If a = 0.5, then Equation 8 predicts:

$$\log\left(\frac{V_1}{V_2}\right) = 1\log\left(\frac{1+1*6}{1+1*2}\right) + 0.5\log\left(\frac{1}{3}\right)$$

$$\log\left(\frac{V_1}{V_2}\right) = 0.37 - 0.24$$

$$\log\left(\frac{V_1}{V_2}\right) = 0.13.$$

Now the discounted values of the reinforcers are 0.33 and 0.25 for the SS and LL reinforcers, respectively, the logarithmic ratio of which is 0.13. Reducing sensitivity to relative reinforcer amount, like enhancing sensitivity to relative reinforcer delay, also produces a reversal in preference.

The simulations previously used to predict the relation between sensitivity to relative reinforcer delay and LL delays at indifference were conducted across a range of amount-sensitivity values. Figure 1-4 depicts the results. As sensitivity to reinforcer amount decreases, LL delays become progressively shorter, indicating that sensitivity to

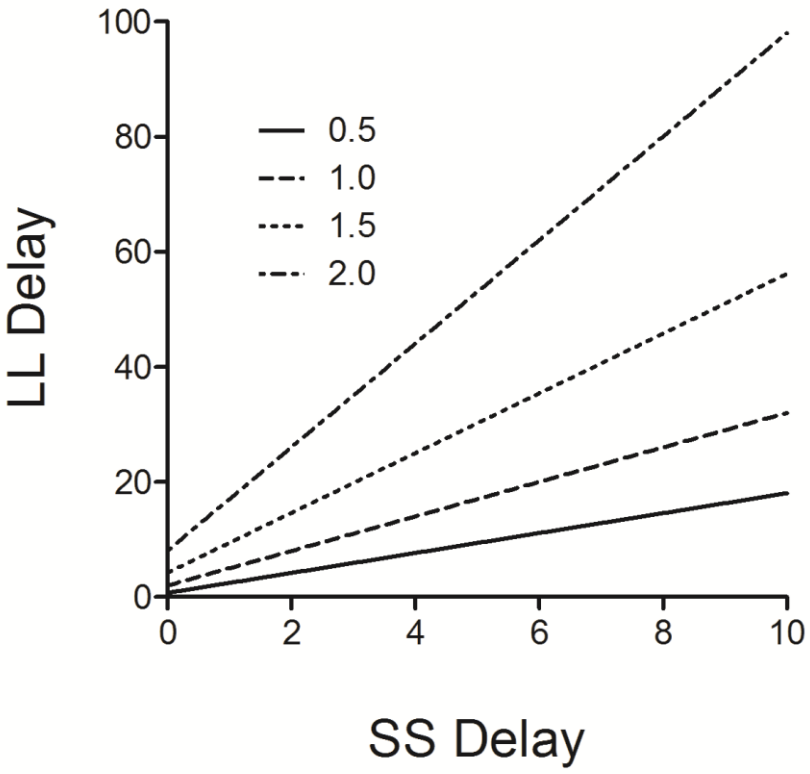

Figure 1-4. Simulated effects of changes in sensitivity to relative reinforcer amount on LL indifference delays. This delay-delay plot shows that as sensitivity to relative reinforcer amount (*a*) in Equation 8 increases, the organism is indifferent between progressively shorter LL delays (y-axis), a behavioral pattern consistent with increased impulsivity.

relative reinforcer amount increases the likelihood of SS choice.

The functions shown in Figure 1-4 are, like those of Figure 1-3, consistent with the predictions of hyperbolic discounting (Equations 6 and 7); in all cases, the slopes of the functions exceeded 1 and the y-intercepts were greater than zero. Comparing the two figures reveals the inverse relation between sensitivity to relative reinforcer delay and amount predicted by Equation 8. For example, by halving amount sensitivity (i.e., a = 0.5), one obtains the same set of LL delays at indifference as would be produced by

doubling delay sensitivity (i.e., $d = 2.0$). By and large, the simulations conducted with sensitivity to relative reinforcer amount concur with those involving sensitivity to relative reinforcer delay: By manipulating these parameters in an ordinal manner, the relative value of a SS reinforcer can be shown to exceed that of LL reinforcer, whereas this was not the case under conditions of perfect sensitivity. Specifically, Equations 7 and 8 predict that enhanced sensitivity to relative reinforcer delay and diminished sensitivity to relative reinforcer amount are likely to increase the frequency of SS choice.

Although organisms may vary naturally in the degree to which choice is sensitive to differences in reinforcer delays and amounts, experimental manipulations such as presession drug administration have been shown to induce changes in sensitivity likely to promote impulsive choice (Locey & Dallery, 2011; Maguire, Rodewald, Hughes, & Pitts, 2009; Pitts & Febbo, 2004). As such, the quantitative framework outlined above serves as a practical foundation for the elucidation of behavioral mechanisms of drug action (Branch, 1984). Elucidation of behavioral mechanisms of drug action involves the comparison of baseline (nondrug) performances to those resulting from drug administration, typically with an emphasis on a specific behavioral process thought to be responsible for the behavioral change (e.g., sensitivity to relative delay or amount). Identifying a drug's capacity to alter baseline levels of impulsivity is of apparent import not just for compounds with potential abuse liability, but also for clinically prescribed compounds. The next section introduces one such compound of interest, the dopamine (DA) agonist pramipexole (PPX), thought to affect the frequency of impulsive behavior in clinical and experimental settings with human and nonhuman subjects. Implications for

applying quantitative models of choice (Equations 7 and 8) in an effort to isolate and identify the source of PPX's effects on impulsivity will be explored.

Pramipexole and Impulsivity

PPX is a DA agonist prescribed primarily as part of DA-replacement therapy for Parkinson's disease (PD), but has documented efficacy in restless legs syndrome (RLS; Winkelman et al., 2006), fibromyalgia (Holman & Myers, 2005), and depression (Inoue et al., 2010; Zarate et al., 2004). PPX has particular affinity for D2-family receptors, specifically the D_2 and D_3 subtypes (Bennet & Piercey, 1999; Kvernmo, Härtter, & Bürger, 2006), which are predominantly expressed along the mesocorticolimbic pathway. Projections of dopaminergic neurons in these brain regions and their abundance of D_2 and D_3 receptors subtypes have recently garnered attention for their influential role in learning (Waelti, Dickinson, & Schultz, 2001) and decision-making processes (Heidbreder et al., 2007; St. Onge & Floresco, 2009). Impairment of these processes following administration of PPX and other DA agonists has increased interest in the contributions of DA receptor pharmacology to complex behavioral performances such as impulsive choice (Abler, Hahlbrock, Unrath, Grön, & Kassubek, 2009; Boulougouris, Castañé, & Robbins, 2009; Pizzagalli et al., 2008; see Smith, Becker, & Kapur, 2005, for a theoretical proposal).

The possible relation between PPX and impulsivity was initially identified through clinical reports of emergent pathological gambling (e.g., Dodd et al., 2005; Driver-Dunckley, Samanta, & Stacy, 2003), hypersexuality (e.g., Giladi, Weitzman,

Schreiber, Shabtai, & Peretz, 2007; Klos, Bower, Josephs, Matsumoto, & Ahlskog, 2005), binge eating (Hassan et al., 2011), and compulsive shopping (Cornelius, Tippmann-Peikert, Slocumb, Frerichs, & Silber, 2010) in patients taking the drug for PD or RLS (Voon et al., 2011). A comprehensive cross-sectional survey of more than 3000 PD patients revealed that individuals taking DA medications like PPX were 2-3.5 times more likely than those not taking DA medications to present with impulse control disordered behavior (ICD; Weintraub et al., 2010). With respect to gambling specifically, a survey of the Food and Drug Administration's Adverse Event Database found that 58% of drug-related incidents of pathological gambling involved PPX (Szarfman, Doraiswamy, Tonning, & Levine, 2006). Clinical findings are, however, strictly correlational as they do not control for threats to internal validity (e.g., maturation, selection), and therefore do not satisfy the stringent requirements of experimental evidence. These shortcomings notwithstanding, ICDs tend to subside shortly after decreasing or discontinuing DA medications (Avila, Cardona, Martín-Baranera, Bello, & Sastre, 2011; Mamikonyan et al., 2008), which further suggests the involvement of D_2/D_3 stimulation in the development of impulsive behavior.

Experimental results from studies using human participants with and without PD have provided mixed support for the hypothesis that PPX induces impulsivity. In patients with PD, Voon et al. (2010) found stronger preference for SS over LL reinforcement in patients who had previously reported a DA-related ICD versus those who had not, but only when medication regimens were in effect (i.e., no significant difference between groups in off-state). This finding of increased SS preference in PD patients reporting

ICDs but not in those without ICDs has since been replicated by Housden, O'Sullivan, Joyce, Lees, and Roiser (2010) and suggests that PPX may enhance pre-existing neuroanatomical susceptibilities in certain individuals to behave impulsively or take risks (e.g., Rao et al., 2010; Voon et al., 2011). One factor that does not appear to determine the effect of PPX and other DA medications is whether individuals are diagnosed with PD; neither Voon et al. nor Housden et al. reported significant differences in impulsivity between PD patients without ICDs and matched controls when the former group was "on" (both studies) or "off" the DA medication (Voon et al., 2011; but see Milenkova et al., 2011 for a PD-control difference, regardless of medication status). Nonetheless, much remains for clarification regarding the linkage between PD and impulsivity.

Two studies have investigated the effects of PPX on impulsivity (Hamidovic, Kang, & de Wit, 2008) and risk taking (Riba, Krämer, Heldmann, Richter, & Münte, 2008) in healthy human volunteers. Hamidovic et al. (2008) found no effect of either low (0.25 mg) or moderate (0.5 mg) doses of PPX on intertemporal choice compared to within-subject placebo. However, a nonsignificant trend toward increased impulsivity suggested that the effect could have achieved significance had their sample size (n = 8) been larger. Riba et al. (2008) detected a significant increase in the likelihood that participants would take a gambling-related risk (i.e., wager a large amount) following an unexpectedly large win after taking PPX (0.5 mg) compared to their own performances under placebo. A third study investigated the effects of the naturally-occurring DA precursor $_{L}$-DOPA on intertemporal choice in healthy adults and detected significant increases in degree of SS preference relative to placebo conditions (Pine, Shiner,

Seymour, & Dolan, 2010). Although the investigation of neurologically intact populations removes from consideration the potential influence of PD on PPX-, or more generally DA-, induced impulsivity, human drug research is still potentially contaminated by confounding variables (e.g., genetic predisposition, learning history).

To address these concerns, researchers have initiated the use of nonhuman models to address questions regarding PPX and impulsivity. Compared to human participants, nonhuman models afford researchers a greater degree of experimental control over variables such as life history, diet, and sleep cycle (Sidman, 1960). To the extent that nonhuman physiology involved in decision-making is homologous to that of humans, findings of nonhuman studies are generally applicable to human choice situations. Nonhuman models, therefore, permit the investigation of drug-behavior interactions in the absence of complex and often confounding aspects of human behavior.

Because PPX has been associated with emergent pathological gambling in clinical populations, researchers have attempted to develop valid nonhuman models of this behavior. Johnson, Madden, Brewer, Pinkston, and Fowler (2011) and Johnson, Madden, and Stein (2012) arranged for rats choices to earn identical food reinforcers upon completion of predictable or unpredictable amounts of work, the latter of which captured functional aspects of gambling ventures available to humans. In separate nondrug baseline conditions, rats either preferred the predictable amount of work (low-gambling) or the unpredictable amount of work (high-gambling). In both studies, PPX increased rats' choice for the gambling-like schedule of reinforcement above saline levels in the low-gambling baseline condition; in neither case did PPX affect significantly choice in

the high-gambling baseline condition. Employing intracranial self-stimulation (ICSS) as a reinforcer rather than food, Rokosik and Napier (2012) evaluated the effects of chronically administered PPX on rats' discounting of probabilistic outcomes. Interaction between the drug and PD-like symptoms was investigated in one group of rats following intrastriatal 6-OHDA-induced lesions, a commonly used animal model of PD (Schober, 2004; Simola, Morelli, & Carta, 2007); another group of rats received sham lesions (i.e., all but 6-OHDA injection). Under saline conditions, all rats' choice for a large, but probabilistic period of ICSS declined characteristically as a function of the reinforcer probability. During the chronic assessment, PPX increased choice for this same reinforcer regardless of whether rats were PD-like or sham, suggesting that the drug decreased rats' sensitivity to the negative effects of risk.

Related nonhuman work has examined PPX effects on intertemporal choice in rats. Madden, Johnson, Brewer, Pinkston, and Fowler (2010) examined the effects of PPX on rats' intertemporal choices using a fixed-delay procedure. In a fixed-delay procedure, subjects make repeated choices between SS and LL reinforcers whose features do not change within session (e.g., fixed LL delay). Using a within-subject experimental design, rats experienced two conditions, one in which their baseline preference favored the SS reinforcer (1 food pellet after 0.01 s) and one in which it favored the LL reinforcer (3 food pellets after X s). Preference was generated by titration of the LL delay (X s) between conditions until preference stabilized at a given delay within a baseline. Madden et al. (2010) then administered PPX (0.1, 0.18, and 0.3 mg/kg) prior to sessions. The results are shown in Figure 1-5. When baseline preference favored the LL reinforcer

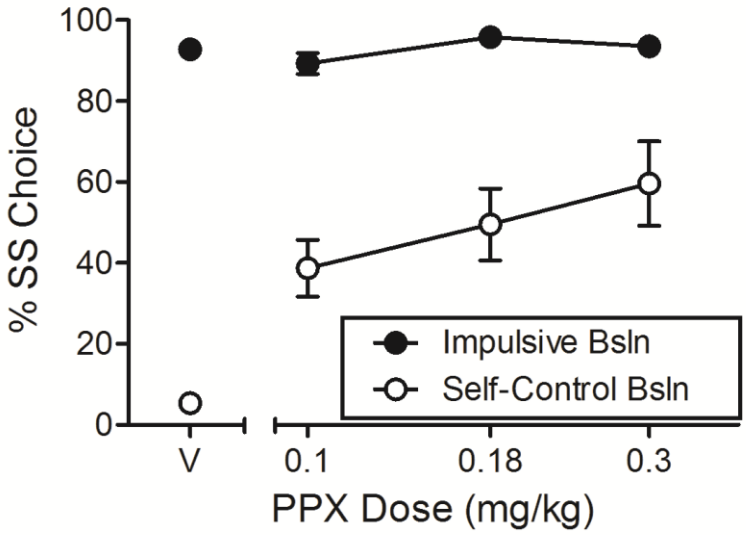

Figure 1-5. Effects of PPX on intertemporal choice in rats (Madden et al., 2010). PPX increased rats' preference for a SS reinforcer in a condition of baseline LL preference (open circles; self-control baseline). SS preference was unaffected by PPX in a control condition of baseline SS preference (closed circles; impulsive baseline). Data represent group means (±SEM).

(self-control baseline), PPX significantly and dose-dependently increased preference for the SS reinforcer above saline levels. PPX did not significantly affect preference relative to saline when the same rats preferred the SS reinforcer. While the former result of increased SS preference is intriguing with respect to the hypothesized relation between PPX and impulsivity, the latter finding also suggests that PPX does not simply impair decision-making regardless of underlying preference. If so-called *nonspecific effects* (e.g., poor discrimination) were influential, preference in both baselines would have

trended toward indifference (i.e., 50% choice). Because the drug effect was only observed in one of the two baselines, the authors concluded that PPX's effects on impulsivity in a nonhuman model were generally consistent with clinically-documented development of impulsive behavior.

A subsequent study by Koffarnus, Newman, Grundt, Rice, and Woods (2011) investigated the effects of a number of DA compounds on intertemporal choice. Rather than the fixed-delay procedure of Madden et al. (2010), Koffarnus et al. (2011) employed an increasing-delay procedure. In an increasing-delay procedure, the LL delay typically increases across multiple blocks of trials within individual sessions, enabling researchers to evaluate drug effects across a range of delays (Evenden & Ryan, 1996). Additionally, Koffarnus et al. (2011) delivered 1 or 3 sucrose pellets as their reinforcers, the larger being available after 0, 10, 20, 40, or 60 s. Data from this experiment are shown in Figure 1-6. Preference for the LL reinforcer under baseline (nondrug) and saline conditions was highest early in sessions (0 s) and declined characteristically as the LL delay increased. PPX (0.032 and 0.1 mg/kg) did not significantly affect intertemporal choice, although trend-level shifts toward increased SS were visually apparent at intermediate LL delays. The highest PPX dose (0.32 mg/kg) significantly increased SS choice across all choice blocks, but did so even in the initial trial block (1 vs. 3 pellets, both immediate). The latter finding could reflect a decrease in sensitivity to relative reinforcer amount, a nonspecific impairment of discrimination, or both. In sum, the findings of Koffarnus et al. (2011) suggest that at lower doses PPX has little to no effect on impulsive choice, while at higher doses PPX affects sensitivity to relative reinforcer amount or impairs

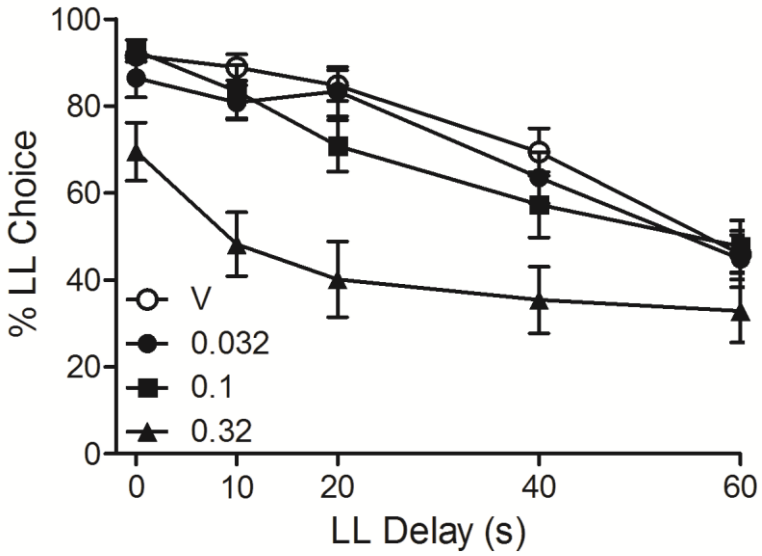

Figure 1-6. Effects of PPX on intertemporal choice in rats (Koffarnus et al., 2011). Low PPX doses (0.032 & 0.1) did not affect rats' preferences across a range of LL delays. A high PPX dose (0.32) shifted preference toward indifference. Data are group means (±SEM). Adapted from "Effects of Selective Dopaminergic Compounds on a Delay-discounting Task," by M. N. Koffarnus, A. H. Newman, P. Grundt, K. C. Rice, and J. H. Woods, 2011, *Behavioural Pharmacology, 22,* p. 306. Copyright 2011 by Wolters Kluwer Health.

discrimination of the choice alternatives, both of which may result in increased SS preference.

In summary, the DA agonist medication PPX and its effects on impulsive behavior are unclear and in need of further elucidation. On one hand, PPX appears to increase the probability of impulsive behaviors such as pathological gambling and hypersexuality in clinical populations. On the other hand, when administered under rigorous experimental protocols, PPX increases impulsivity (Madden et al., 2010; Riba et al., 2008), has no effect (Hamidovic et al., 2008), or affects preference in a manner consistent with nonspecific impairment of discrimination (Koffarnus et al., 2011).

Reconciliation of these discrepant results depends upon the identification of behavioral mechanisms influential in determining the form of the drug effect. Ultimately, a consistent, unified theory regarding the interaction between PPX and impulsive decision-making is desired.

The final section will outline a research agenda that is sympathetic to these goals. Informed by preceding discussions regarding the theoretical, procedural, and empirical bases of impulsivity, the present series of experiments will attempt to elucidate the behavioral mechanisms underlying PPX-induced impulsivity. Conceptually, the research presented herein will emphasize the role of behavioral processes thought to be critical to choice situations likely to produce impulsivity.

The Research Agenda

At present, experimental evidence regarding the effects of PPX on impulsivity is mixed and in need of clarification. With respect to studies investigating the drug in nonhumans, only two studies have been conducted using different experimental procedures (Koffarnus et al., 2011; Madden et al., 2010). In short, Madden et al. (2010) found that PPX increased SS choice when nondrug preference for the SS reinforcer was low. In a separate condition in which nondrug SS choice was high, SS choice in the same rats was unaffected by the drug. This pattern of results suggested that PPX selectively increased impulsivity without nonspecifically disrupting baseline preferences. Koffarnus et al. (2011) found that PPX did not affect SS choice (low doses), decreased sensitivity to relative reinforcer amount, or nonspecifically disrupted discrimination (high dose). This

pattern of results is in disagreement with the results of Madden et al. (2010), which forwarded an account of PPX-induced impulsivity independent of nonspecific drug effects.

Given the conflicting nature of these reports, the research presented herein was conducted in an effort to further evaluate the experimental conditions under which PPX-induced impulsivity is likely to be observed. Although frequently employed by researchers interested in the effects of pharmacological variables on decision-making, the methods used by Koffarnus et al. (2011) omitted some procedures often used in studies using the increasing-delay procedure (no-delay sessions, centering response prior to choice), the absence of which may have influenced the form of the obtained preference functions. The goal of Chapter 2 was therefore to establish the validity of the findings reported by Koffarnus et al. (2011) by systematically replicating the increasing-delay procedure in a manner more commonly arranged in the extant drug literature.

A recurring theme throughout the subsequent experiments as presented in Chapter 3 was the quantification of behavioral processes under nondrug and saline conditions and following subsequent PPX administration. A change in the behavioral process–that is, the manner in which environmental input is processed into behavioral output–constitutes a potential behavioral mechanism underlying PPX-induced impulsivity. Experiment 1 targeted specifically the capacity of PPX to modulate sensitivity to relative reinforcer delay, one of two primary behavioral processes believed to underlie impulsive decision-making (see above simulations). Experiments 2 and 3 evaluated the effects of PPX on elementary discrimination processes, specifically the discrimination of responses

producing reinforcement (left/right levers) and the discrimination of reinforcer amounts (small/large), respectively. In theory, each of these behavioral processes is critical to decision-making and, as such, may contribute to clinical and experimental manifestations of increased impulsivity.

Although the PPX effects reported previously were produced via acute administration, the present research explored the drug effect under chronic administration in addition to acute administration where appropriate. The rationale for this additional manipulation was twofold. First, clinical populations administer PPX chronically and frequently enough to maintain beneficial levels (Antonini & Calandrella, 2011), a variable that has not yet been explored in nonhuman PPX studies of intertemporal choice. Second, acute PPX administration significantly alters the behavior of DA neurons, whereas chronic PPX administration restores neuronal activity to near-baseline levels (Chernoloz, El Mansari, & Blier, 2009; Maj, Rogóz, Margas, Kata, & Dziedzicka-Wasylewska, 2000), an effect that may influence the presence or absence of any nonspecific drug effects.

CHAPTER 2

EFFECTS OF PRAMIPEXOLE ON INTERTEMPORAL CHOICE[1]

Abstract

Pramipexole (PPX), a D_2/D_3 dopamine agonist medication prescribed as pharmacotherapy for a range of clinical disorders, has been associated with an increase in the frequency of impulsive behaviors. Two experiments using nonhuman subjects have evaluated the drug's acute effect on intertemporal choice, wherein rats chose between a small amount of reinforcement delivered immediately and a larger amount delivered following a delay. Madden et al. (2010) reported PPX-induced increases in rats' choice of the small, immediate reinforcer (i.e., impulsive choice); Koffarnus et al. (2011) reported that PPX may have nonspecifically disrupted rats' decision-making. The procedures employed in the latter experiment omitted features traditionally included by other researchers using the increasing-delay procedure (no-delay sessions, centering response), the absence of which may have influenced Koffarnus and others' (2011) findings. The present experiment systematically replicated the procedures of Koffarnus et al. (2011), including these procedural features, in male Wistar rats. At higher doses (0.1-0.3 mg/kg), acute PPX disrupted rats' choice between 1 and 3 food pellets delivered immediately in a manner consistent with Koffarnus et al. (2011) and indicative of nonspecific impairment of choice. At lower doses (0.01 and 0.03 mg/kg), acute PPX did not disrupt rats' initial-block choice and choice at nonzero delays nonsignificantly trended toward increased

[1] Coauthored with Gregory J. Madden, Adam T. Brewer, Jonathan W. Pinkston, and Stephen C. Fowler.

impulsive choice relative to saline. This pattern of results reproduces the primary findings of Koffarnus et al. (2011). Chronic PPX (0.1 and 0.3 mg/kg), which was not investigated in either of the earlier reports, partially reduced disruptions observed in the acute assessment. Interactions between PPX and the procedures used by Madden et al. (2010) and Koffarnus et al. (2011) likely underlie mixed findings in the literature. Identifying behavioral mechanisms of PPX-induced impulsivity common to both procedures may serve to unify these divergent outcomes.

Introduction

Clinical reports have implicated the D_2/D_3 dopamine (DA) agonist pramipexole (PPX) in the development of impulse control disordered behaviors (ICDs). Among ICDs reported are pathological gambling (e.g., Dodd et al., 2005; Driver-Dunckley et al., 2003), hypersexuality (e.g., Giladi et al., 2007; Klos et al., 2005), and compulsive eating or shopping (Cornelius et al., 2010; Hassan et al., 2011). Individuals prescribed the drug as pharmacotherapy for Parkinson's disease, restless legs syndrome, fibromyalgia, and treatment-resistant depression sometimes report the appearance of ICDs shortly after initiation of the regimen and resolution of the behavior coinciding with titration or discontinuation of PPX and other dopamine agonists (e.g., Avila et al., 2011).

Researchers have evaluated experimentally the effects of PPX on impulsive decision-making in humans with and without PD. Voon et al. (2010) and Housden et al. (2010) assessed delay discounting of PD patients with and without ICDs and reported significantly steeper discounting among the PD-ICD group but only when DA

medications were in use. Delay discounting of PD patients not reporting ICDs did not differ significantly from that of matched non-PD controls in either study regardless of DA status ("on" vs. "off"), suggesting that PD is not a necessary condition for observing ICDs. Two studies have examined aspects of impulsivity in healthy volunteers administered PPX. Hamidovic et al. (2008) observed only trend-level shifts in within-subject rates of delay discounting on and off PPX. Likewise, Riba et al. (2008) detected a significant effect of PPX in only one behavioral measure of their gambling task, the probability that participants would place a large bet following an unexpectedly large win.

Nonhuman models of impulsive decision-making have also been used to evaluate the putative impulsivity-inducing effects of PPX. Madden et al. (2010) administered PPX acutely prior to sessions in which male rats made intertemporal choices for either small, immediate food reinforcers or larger, delayed food reinforcers. Against a nondrug baseline of preference for the "larger-later" (LL) reinforcer, PPX increased rats' choice of the "smaller-sooner" (SS) reinforcer, the impulsive choice. The same PPX doses did not affect choice in a control condition in which baseline preference favored the SS reinforcer. Koffarnus et al. (2011) administered a range of dopaminergic compounds, including PPX, to male rats in a similar intertemporal choice procedure. Across the same range of PPX doses investigated by Madden et al. (2010), rats' choice for a SS reinforcer either did not achieve statistical significance from saline vehicle (low doses) or was nonspecifically disrupted, indicating a possible impairment in stimulus control (high dose). At face value, the findings of Madden et al. (2010) and Koffarnus et al. (2011) are contradictory. However, the possibility that procedural differences are responsible for this

disagreement should be considered. Additionally, each set of results represents only a single experiment with PPX and is therefore to be interpreted with caution until replications have confirmed their external validity.

Of particular interest to the present study is the fact that Madden et al. (2010) used a fixed-delay procedure, investigating only a single LL delay for each subject in each of their two baseline conditions. Baseline conditions constrained nondrug preference to either low (≤ 20%) or high (≥ 80%) SS choice by titrating individual-subject LL delay values between conditions. Alternatively, Koffarnus et al. (2011) used an increasing-delay procedure to examine intertemporal choice across a range of LL delays within each session. Concerns have been raised regarding the possibility of carry-over effects with increasing-delay procedures (Fox, Hand, & Reilly, 2008; Madden, Smith, Brewer, Pinkston, & Johnson, 2008). By definition, a carry-over effect implies that the effects of preceding trial blocks (i.e., shorter delays to LL reinforcers) influence choice in subsequent trial blocks, thereby inflating the measure of SS-LL preference in favor of the LL reinforcer. Suggestive of a carry-over effect, Koffarnus and others' (2011) rats were approximately indifferent (i.e., 50% choice) between an immediate SS reinforcer and a larger reinforcer delivered following a 60-s delay whereas Diller, Saunders, and Anderson (2008), for example, showed that the same strain rarely chose a LL reinforcer when delayed by 16 s. To avoid or reduce the influence of carry-over effects in prior research using increasing-delay procedures, researchers have incorporated occasional "no-delay" sessions. In a no-delay session, the LL delay does not increment across trial blocks, in which case the subject should prefer the LL throughout the entire session.

Koffarnus et al. (2011) did not incorporate no-delay sessions into their experimental protocol and therefore may have increased the likelihood that preference was inflated.

Another procedural feature traditionally incorporated into nonhuman decision-making protocols is the centering response. Prior to nonhumans choosing between concurrently available alternatives, "forced-choice" trials are typically programmed to expose the subject to the consequences of choosing either alternative in isolation. Following these trials, subjects are then required to choose between both alternatives in "free-choice" trials. In both trial types, the response alternatives are made available to the subject contingent upon a centering response. This procedural detail is included in an effort to discourage subjects from developing idiosyncratic biases in favor of one alternative. Choice trials in the procedure used by Koffarnus et al. (2011) were not preceded by a centering response, the absence of which may have encouraged biased choice, especially in sessions in which PPX was administered. The plausibility of PPX-induced bias is bolstered by reports of perseverative responding following administration of the drug (Boulougouris et al., 2009; Haluk & Floresco, 2009).

The present experiment systematically replicated the procedures of Koffarnus et al. (2011) by including these procedural control features. Intermittent no-delay sessions were scheduled to minimize the influence of carry-over effects, which could influence the PPX effect. A centering response also preceded all forced- and free-choice trials to reduce the likelihood of bias. In addition to replicating the acute procedures, the present experiment also evaluated the chronic effects of intermediate (0.1 mg/kg) and high (0.3 mg/kg) PPX doses. This latter manipulation was conducted to address the concern that

clinical patients who develop ICDs administer PPX according to a chronic rather than an acute regimen, a difference that may distinguish human cases from nonhuman demonstrations.

Methods

Subjects

Twelve experimentally naïve male Wistar rats served as subjects in the present experiment. Rats arrived in the colony weighing approximately 325-350 grams (~ 9 weeks) and were housed individually in polycarbonate cages in a room maintained on a 12/12 programmed light/dark cycle. With the exception of experimental sessions, which were conducted seven days per week, water was continuously available. At least two hours after each session, supplementary chow was provided in order to maintain weights of 375 grams. Animal use was in accordance with the Institutional Animal Care and Use Committee (IACUC) of the University of Kansas.

Apparatus

Sessions were conducted in standard operant conditioning chambers housed within sound-attenuating cubicles (Med Associates Inc., St. Albans, VT). Centered on the front wall of the chamber was a nonretractable lever with an accompanying stimulus lamp. Equidistant from each side of the center lever were left and right retractable side levers with stimulus lamps located above each lever. Located directly below the center lever was a food receptacle into which a pellet dispenser delivered 45 mg nutritional rodent pellets (Bio-Serv, Frenchtown, NJ). A houselight provided general illumination

except during the inter-trial interval (ITI). Chambers were also equipped with a white noise speaker and ventilation fan. All experimental events were coordinated and recorded via a PC in an adjacent room.

Behavioral Procedure

Lever pressing was initially trained using an autoshaping procedure. Once reliable responding was established, experimental sessions operated in similar respects to Evenden and Ryan (1996) and Koffarnus et al. (2011; i.e., increasing-delay procedure). Sessions were composed of 40 trials separated into four blocks of 10 trials each. Within each trial block, the first four trials were forced-choice trials followed by six free-choice trials. During forced-choice trials, only one lever was made available to ensure that subject experience the SS (1 food pellet) and LL (3 food pellets) reinforcers (two of each randomly). During free-choice trials, levers associated with SS and LL reinforcers were both made available, permitting choice between the two options. Prior to either forced- or free-choices, a signaled center-lever response was used to ensure the subject was equidistant from both side levers. Side levers were inserted following an effective center-lever response (see Table 2-1 for LL lever assignment). If the SS was selected, both levers were retracted, stimulus lights were extinguished, and 1 food pellet was delivered to the food receptacle after 0.01 seconds (the minimum temporal resolution of the software). If the LL was selected, the same sequence was enacted, except that the stimulus light above the LL lever remained illuminated for the duration of the LL delay in effect. Once the LL delay had elapsed, three food pellets were delivered to the food receptacle. Failure to press the center or either side lever within 30 s of insertion ended

the trial and incremented an omission counter. Following each reinforcer delivery sequence, the houselight was extinguished. A variable ITI ensured that trials began every 100 seconds.

At the beginning of each session (i.e., first trial block), the SS and LL reinforcers were both available immediately (0.01 s). In each subsequent trial block, the LL delay increased by 10 s to produce LL delays of 10, 20 and 30 s. Separating each trial block was a 180-s blackout used to signal a change in LL delay. On a randomly selected day of the week, a regular session was replaced by a no-delay session. In a no-delay session, the LL reinforcer remained immediately available beyond the first trial block.

Drug Procedure

In order to begin the acute dosing assessment, rats' percent LL choice had to meet quantitative stability criteria. First, at least 20 nondrug baseline sessions had to be conducted. Second, mean percent LL choice from the most recent 6 sessions could not differ by more than 10% from mean percent LL choice from the preceding 6 sessions in any trial block. Lastly, no omitted trials could occur during this same 12-session window.

Once stability was achieved, saline or PPX (0.01, 0.03, 0.1, 0.18, and 0.3 mg/kg) was administered subcutaneously 10 minutes prior to every fifth session in a descending dose order beginning with saline. Two rats (G1R1 and P1R1) received only two administrations of 0.01 mg/kg as the decision to add this dose was made after their first dosing series had been completed. No-delay sessions occurred on the second day after each acute dose. The sequence of doses was assessed three times.

Four days following completion of the acute dosing assessment subjects experienced chronic (i.e., daily) dosing with either saline or PPX (0.1 and 0.3 mg/kg) for at least 14 consecutive sessions. All subjects completed chronic dosing with 0.1 mg/kg first. A 12-day washout period separated the 0.1 mg/kg dosing period from a period of "chronic" saline administration. Following the saline assessment, rats were re-introduced to nondrug baseline conditions. Once quantitative stability was achieved, the chronic 0.3 mg/kg dosing period was initiated.

Data Analysis

The primary dependent measure of interest was the percentage of choices for the LL reinforcer in each trial block. Percent LL choice data from no-delay sessions conducted during the acute assessment were evaluated in a one-way repeated-measures analysis of variance (ANOVA; IBM SPSS Statistics 20) with Trial Block as the single within-subject factor. For the acute dosing assessment, a two-way repeated-measures ANOVA was used to evaluate the Dose (saline, 0.01, 0.03, 0.1, 0.18, and 0.3 mg/kg) X Delay (0, 10, 20, and 30 s) effect.

For the chronic dosing assessment, the mean percent LL choice for each trial block across the last 4 sessions was used in a two-way repeated-measures ANOVA (Dose X Delay). In the event that data failed to meet assumptions of sphericity, results were interpreted using Greenhouse-Geisser adjusted degrees of freedom. Significant interactions were decomposed with alpha-corrected one-way ANOVAs. All post-hoc pairwise comparisons used Bonferroni-corrected alpha criteria. Effect sizes were calculated as generalized eta squared (Bakeman, 2005).

Three rats (G1R3, G1R4, and P1R2) exhibited either hyper- or hyposensitivity to LL delays under nondrug baseline conditions. For these rats, PPX administration would have only been capable of shifting LL choice in one direction; on this basis these rats were excluded from the above analyses. Early in the course of the chronic PPX assessment, two rats (B1G1 and B1G2) fell ill and were euthanized; their data were excluded from chronic analyses.

Results

Table 2-1 shows the number of sessions required for individual rats to meet stability criteria. On average, the acute dosing assessment began after approximately 45 sessions (M = 45.67, SD = 8.74). Fewer sessions were required, on average, to initiate the 0.3 mg/kg chronic assessment (M = 23.86, SD = 2.42).

Percent LL choice from no-delay sessions (data not shown) differed significantly across trial blocks, $F(3, 24) = 6.25$, $p < .01$, $\eta_G^2 = .44$. Specifically, LL choice declined monotonically, significant linear contrast, $F(1, 8) = 22.27$, $p < .01$, $\eta_G^2 = .74$. Only LL choice in the final trial block (M = 93.34, SD = 4.28) was significantly lower than LL choice in the first trial block (M = 98.95, SD = 1.21), $p < .02$.

Acute PPX dose interacted significantly with the LL delay in effect, $F(15, 120) = 6.61$, $p < .001$, $\eta_G^2 = .18$ (Figure 2-1). Follow-up one-way ANOVAs with corrected alphas ($p = 0.5/4 = .013$) conducted at each LL delay revealed significant main effects of PPX dose in only the first trial block (0 s), $F(2.21, 17.70) = 7.22$, $p < .01$, $\eta_G^2 = .47$. In the first trial block when both reinforcers were available immediately, acute PPX,

Table 2-1

Lever Assignment of the LL Reinforcer and Sessions to Stability for Individual Rats in Acute and Chronic PPX Assessments

		Sessions to stability	
Rat	LL Lever	Acute	Chronic
B1G1	Right	41	-
B1G2	Left	50	-
B1G3	Right	43	23
B1G4	Left	41	23
G1R1	Right	40	19[a]
G1R2	Left	40	26
P1R1	Right	43	27
P1R3	Right	44	25
P1R4	Left	69	24

[a]Did not complete minimum sessions for stability assessment due to experimenter error.

especially at higher doses (top panel of Figure 2-1), produced visual decreases in LL choice from saline. Lower acute PPX doses (bottom panel of Figure 2-1) did not disrupt LL choice in this way. However, at no dose in the first trial block was choice affected to a degree as to differentiate it significantly from saline choice (all pairwise *p*'s > .15).

Omissions occurred infrequently in the acute assessment and were affected by PPX dose, $F(1.08, 8.61) = 5.74$, $p < .05$, $\eta_G^2 = .42$. These data are shown in Table 2-2, which displays individual-subject mean percent LL choice at each LL delay, as well as the mean number of omissions per session in this assessment.

Figure 2-2 shows that chronic PPX also interacted significantly with LL delays, $F(6, 36) = 5.83$, $p < .001$, $\eta_G^2 = .17$. This interaction was further investigated at each LL delay using one-way ANOVAs ($p = .013$). In only the fourth (30 s) trial block, $F(2, 12) = 16.74$, $p < .001$, $\eta_G^2 = .74$, chronic 0.3 mg/kg significantly increased LL choice above

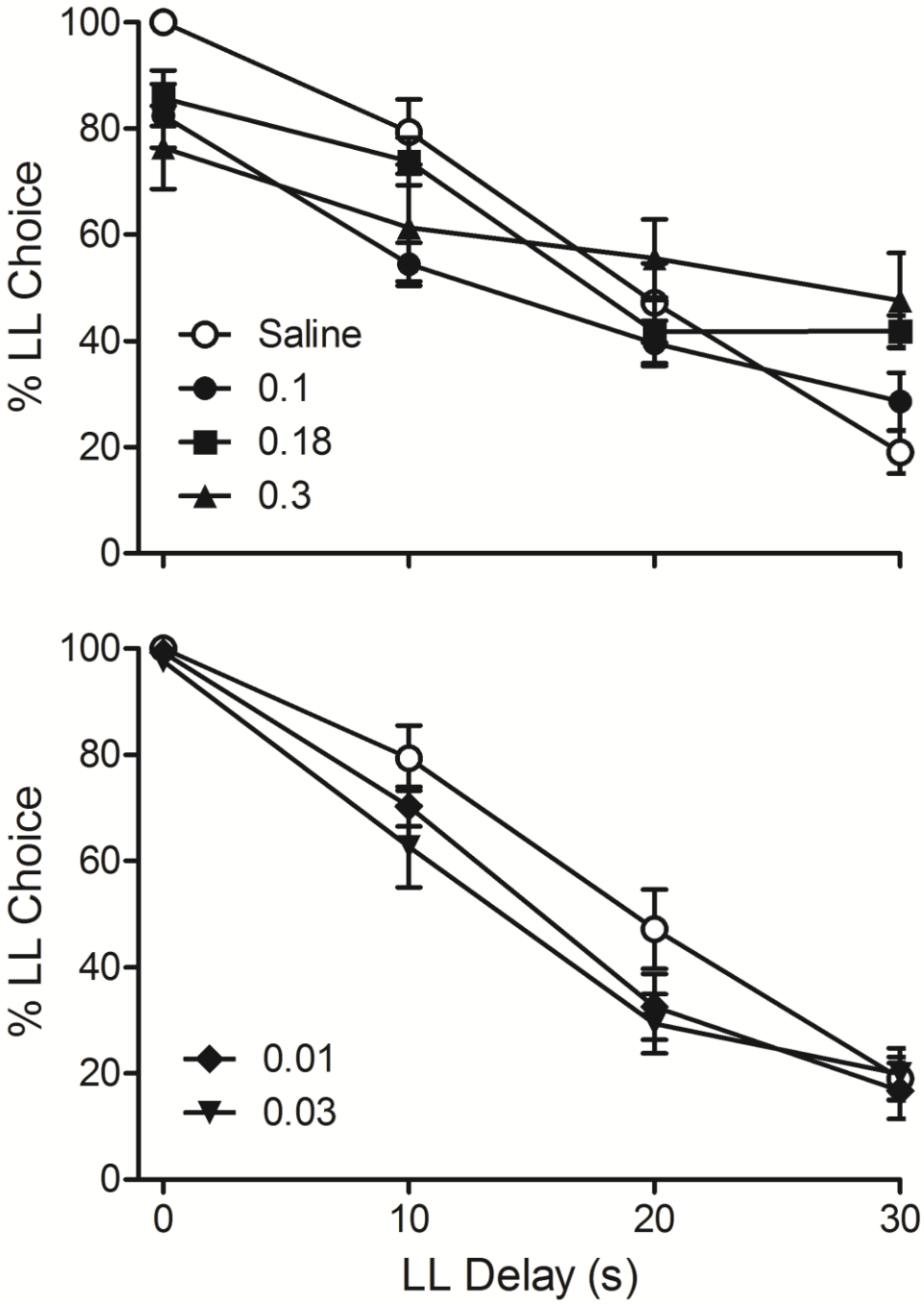

Figure 2-1. Effects of acute PPX on LL choice as a function of LL delay. The top panel depicts doses that disrupted initial-block choice; shown in the bottom panel are doses that did not have this effect. Data are group means (±SEM).

Table 2-2

Percent LL Choice at Each LL Delay and Omissions in the Acute PPX Assessment

Rat	PPX (mg/kg)	LL delay (s) 0	10	20	30	Omissions per session
B1G1	Saline	94.44 (4.54)	33.33 (7.86)	5.56 (4.54)	5.56 (4.54)	0.00 (0.00)
	0.01	100.00 (0.00)	22.22 (4.53)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
	0.03	94.44 (4.54)	22.22 (9.07)	5.56 (4.54)	11.11 (4.54)	0.00 (0.00)
	0.1	100.00 (0.00)	38.89 (4.54)	16.67 (7.86)	16.67 (7.86)	0.00 (0.00)
	0.18	83.33 (7.86)	55.55 (12.00)	27.78 (16.36)	22.22 (9.07)	0.00 (0.00)
	0.3	88.89 (9.07)	72.22 (12.00)	15.56 (19.77)	50.00 (7.86)	0.00 (0.00)
B1G2	Saline	100.00 (0.00)	83.33 (7.86)	77.78 (18.15)	44.44 (19.77)	0.00 (0.00)
	0.01	100.00 (0.00)	100.00 (0.00)	77.78 (4.53)	66.67 (0.00)	0.00 (0.00)
	0.03	100.00 (0.00)	94.44 (4.54)	38.89 (4.54)	38.89 (9.07)	0.00 (0.00)
	0.1	88.89 (4.54)	55.56 (9.07)	44.44 (9.07)	44.44 (19.77)	0.00 (0.00)
	0.18	77.78 (9.07)	50.00 (20.79)	66.66 (13.61)	55.56 (16.35)	0.33 (0.27)
	0.3	66.67 (7.86)	67.78 (19.90)	50.00 (20.79)	27.78 (4.53)	1.00 (0.82)
B1G3	Saline	100.00 (0.00)	94.44 (4.54)	33.33 (7.86)	11.11 (4.54)	0.00 (0.00)
	0.01	100.00 (0.00)	61.11 (4.54)	22.22 (12.00)	0.00 (0.00)	0.00 (0.00)
	0.03	94.44 (4.54)	55.56 (4.54)	22.22 (12.00)	16.67 (13.61)	0.00 (0.00)
	0.1	100.00 (0.00)	38.89 (12.00)	55.55 (12.00)	33.33 (7.86)	0.00 (0.00)
	0.18	100.00 (0.00)	66.67 (7.86)	33.34 (13.61)	44.44 (19.77)	0.00 (0.00)
	0.3	94.44 (4.54)	88.89 (4.54)	83.33 (7.86)	77.78 (9.07)	4.33 (3.54)
B1G4	Saline	100.00 (0.00)	94.44 (4.54)	77.78 (12.00)	33.33 (15.71)	0.00 (0.00)
	0.01	100.00 (0.00)	61.11 (12.00)	33.33 (15.71)	5.56 (4.54)	0.00 (0.00)
	0.03	100.00 (0.00)	61.11 (18.14)	22.22 (4.53)	5.56 (4.54)	0.00 (0.00)
	0.1	66.67 (15.71)	61.11 (9.07)	38.89 (9.07)	16.67 (0.00)	0.00 (0.00)
	0.18	55.55 (12.00)	66.66 (13.61)	22.22 (4.53)	27.78 (4.53)	0.00 (0.00)
	0.3	33.34 (13.61)	11.11 (9.07)	50.00 (7.86)	33.33 (7.86)	0.00 (0.00)
G1R1	Saline	100.00 (0.00)	55.56 (9.07)	50.00 (13.61)	16.67 (7.86)	0.00 (0.00)
	0.01[a]	100.00 (0.00)	66.67 (11.78)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
	0.03	88.89 (9.07)	22.22 (12.00)	5.56 (4.54)	11.11 (4.54)	0.00 (0.00)
	0.1	61.11 (12.00)	47.78 (12.80)	22.22 (4.53)	22.22 (12.00)	0.33 (0.27)
	0.18	83.33 (0.00)	55.56 (16.35)	22.22 (12.00)	33.33 (7.86)	1.33 (1.09)
	0.3	77.78 (4.53)	44.44 (9.07)	52.22 (6.35)	33.33 (13.61)	0.67 (0.27)
G1R2	Saline	100.00 (0.00)	72.22 (12.00)	44.44 (16.35)	16.67 (7.86)	0.00 (0.00)
	0.01	94.44 (4.54)	61.11 (4.54)	38.89 (12.00)	33.33 (7.86)	0.00 (0.00)
	0.03	100.00 (0.00)	88.89 (4.54)	50.00 (15.71)	16.67 (7.86)	0.00 (0.00)

(table continues)

Rat	PPX (mg/kg)	LL delay (s) 0	10	20	30	Omissions per session
	0.1	66.67 (27.22)	44.45 (18.15)	33.33 (15.71)	44.44 (24.00)	0.00 (0.00)
	0.18	83.33 (7.86)	72.22 (12.00)	38.89 (4.54)	44.44 (4.54)	0.00 (0.00)
	0.3	83.33 (7.86)	44.44 (24.00)	16.67 (7.86)	11.11 (9.07)	2.00 (1.63)
P1R1	Saline	100.00 (0.00)	61.11 (4.54)	11.11 (4.54)	0.00 (0.00)	0.00 (0.00)
	0.01[a]	100.00 (0.00)	75.00 (5.89)	33.34 (23.57)	16.67 (11.78)	0.00 (0.00)
	0.03	100.00 (0.00)	55.55 (12.00)	27.78 (9.07)	33.33 (7.86)	0.00 (0.00)
	0.1	94.44 (4.54)	61.11 (18.14)	33.33 (0.00)	5.56 (4.54)	0.33 (0.27)
	0.18	88.89 (4.54)	83.33 (7.86)	55.56 (19.77)	44.44 (24.00)	0.33 (0.27)
	0.3	91.67 (6.80)	81.11 (9.47)	61.11 (25.26)	50.00 (14.14)	4.67 (1.91)
P1R3	Saline	100.00 (0.00)	77.78 (9.07)	63.33 (15.15)	27.78 (4.53)	0.33 (0.27)
	0.01	100.00 (0.00)	77.78 (4.53)	44.44 (24.00)	27.78 (16.36)	2.67 (2.18)
	0.03	100.00 (0.00)	77.78 (4.53)	27.78 (9.07)	44.44 (19.77)	0.00 (0.00)
	0.1	87.78 (5.05)	55.56 (4.54)	37.78 (17.24)	27.78 (4.53)	1.67 (0.98)
	0.18	88.89 (4.54)	77.78 (4.53)	64.45 (1.82)	53.89 (13.97)	1.33 (0.54)
	0.3	93.33 (5.44)	86.11 (6.00)	53.33 (8.32)	83.33 (7.86)	10.33 (2.37)
P1R4	Saline	100.00 (0.00)	100.00 (0.00)	50.00 (15.71)	27.78 (12.00)	0.00 (0.00)
	0.01	100.00 (0.00)	88.89 (4.54)	55.56 (4.54)	33.34 (13.61)	0.33 (0.27)
	0.03	100.00 (0.00)	77.78 (4.53)	50.00 (0.00)	11.11 (4.54)	0.33 (0.27)
	0.1	100.00 (0.00)	72.22 (12.00)	55.56 (4.54)	50.00 (13.61)	0.00 (0.00)
	0.18	100.00 (0.00)	94.44 (4.54)	55.56 (4.54)	44.44 (4.54)	0.33 (0.27)
	0.3	61.11 (18.14)	73.33 (21.77)	72.22 (12.00)	44.45 (18.15)	1.33 (1.09)

Note. Standard error of the mean of three administrations per dose is in parentheses.
[a] Only two administrations.

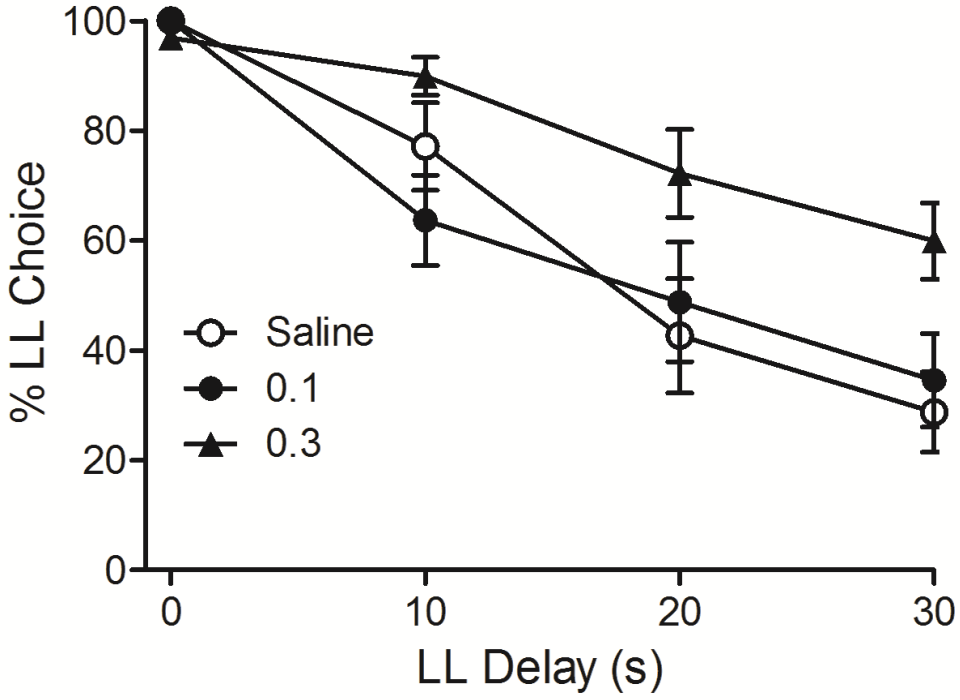

Figure 2-2. Effects of chronic PPX on LL choice as a function of LL delay. Data are group means (±SEM).

both saline and chronic 0.1 mg/kg levels.

Chronic PPX administration resulted in infrequent omissions and did not reduce their occurrence below the rate observed in the acute assessment ($p > .25$). Table 2-3 displays individual-subject mean percent LL choice at each LL delay and mean omissions per session over the final four sessions of the chronic assessment.

Table 2-3

Percent LL Choice at Each LL Delay and Omissions in the Chronic PPX Assessment

Rat	PPX (mg/kg)	LL delay (s) 0	10	20	30	Omissions per session
B1G3	Saline	100.00 (0.00)	62.50 (12.33)	16.67 (10.21)	4.17 (3.61)	0.00 (0.00)
	0.1	100.00 (0.00)	66.67 (5.89)	37.50 (6.91)	41.67 (9.32)	0.00 (0.00)
	0.3	100.00 (0.00)	75.00 (4.17)	58.33 (9.32)	62.50 (3.61)	0.75 (0.42)
B1G4	Saline	100.00 (0.00)	95.24 (4.17)	66.67 (8.33)	20.83 (6.91)	0.00 (0.00)
	0.1	100.00 (0.00)	62.50 (12.33)	25.00 (9.32)	16.67 (8.33)	0.00 (0.00)
	0.3	100.00 (0.00)	79.17 (10.83)	75.00 (7.22)	58.33 (9.32)	0.00 (0.00)
G1R1	Saline	100.00 (0.00)	36.11 (8.89)	2.78 (3.11)	5.56 (3.93)	0.00 (0.00)
	0.1	100.00 (0.00)	20.83 (10.83)	12.50 (3.61)	8.33 (7.22)	0.00 (0.00)
	0.3	91.67 (7.22)	91.67 (4.17)	54.17 (18.04)	35.42 (13.94)	1.00 (0.35)
G1R2	Saline	100.00 (0.00)	95.83 (3.61)	58.33 (7.22)	50.00 (5.89)	0.00 (0.00)
	0.1	100.00 (0.00)	87.50 (6.91)	87.50 (6.91)	62.50 (3.61)	0.00 (0.00)
	0.3	100.00 (0.00)	95.83 (3.61)	100.00 (0.00)	70.84 (3.61)	0.00 (0.00)
P1R1	Saline	100.00 (0.00)	75.00 (9.32)	20.84 (9.08)	25.00 (7.22)	0.00 (0.00)
	0.1	100.00 (0.00)	62.50 (3.61)	29.17 (6.91)	16.67 (0.00)	0.00 (0.00)
	0.3	100.00 (0.00)	87.50 (6.91)	37.50 (13.66)	54.17 (9.08)	0.00 (0.00)
P1R3	Saline	100.00 (0.00)	100.00 (0.00)	83.33 (10.21)	37.50 (6.91)	0.00 (0.00)
	0.1	100.00 (0.00)	54.17 (3.61)	58.33 (9.32)	25.00 (7.22)	0.00 (0.00)
	0.3	91.11 (3.66)	100.00 (0.00)	89.58 (5.41)	42.50 (8.77)	7.17 (2.20)
P1R4	Saline	100.00 (0.00)	75.00 (9.32)	50.00 (15.59)	58.33 (9.32)	0.00 (0.00)
	0.1	100.00 (0.00)	91.67 (7.22)	91.67 (4.17)	70.84 (9.08)	0.00 (0.00)
	0.3	95.83 (3.60)	100.00 (0.00)	90.83 (4.62)	95.83 (3.61)	5.75 (1.08)

Note. Standard error of the mean of the final four administrations per dose is in parentheses.

Discussion

The present experiment attempted to systematically replicate the within-session increasing-delay procedures used by Koffarnus et al. (2011) to investigate the effects of acute PPX on intertemporal choice. Intermittent no-delay sessions, in which the LL delay did not increment across trial blocks, and a centering response requirement were included to address potential concerns regarding the influence of carry-over effects and the development of response biases, respectively. Along with these procedural modifications, the present experiment also assessed PPX's effects on intertemporal choice when the drug was administered chronically before sessions. Results of relevance to the research conducted by Koffarnus et al. (2011), as well as to previous attempts to investigate the drug effect on nonhuman intertemporal choice (Madden et al., 2010) will be discussed and interpreted in turn.

A primary rationale for conducting the present experiment was the inclusion of certain procedural details omitted by Koffarnus et al. (2011), the absence of which may have affected the form of the drug effect. First, no-delay sessions were occasionally substituted for normal sessions (i.e., increasing-delay) in the present experiment to encourage rats to discriminate the presence/absence of a LL delay prior to choice opportunities. If rats' choice for the LL reinforcer declined during no-delay sessions, as was characteristic of normal sessions in which LL delays were present, then concerns regarding carry-over effects or habitually inflexible choice may be warranted. Although LL reinforcer choice declined slightly across trial blocks, there was little evidence to suggest that carry-over effects influenced the present findings. Second, prior to insertion

of the side levers corresponding to the choice alternatives, rats were required to emit a centering response. In principle, this procedural detail should discourage the development of lever biases or response perseveration resulting from PPX administration (e.g., Boulougouris et al., 2009; Haluk & Floresco, 2009). However, because there were no trials in which the centering response was not required, it is difficult to conclude that this manipulation was effective at deterring bias or reducing the likelihood of perseverative responding.

With respect to the findings of Koffarnus et al. (2011), the present experiment reproduced shifts in rats' intertemporal choice produced by administration of low (0.01-0.03 mg/kg) and high (0.1-0.3 mg/kg) acute PPX doses. At the highest dose investigated (0.32 mg/kg), Koffarnus et al. (2011) observed an across-block decrease in choice for the LL reinforcer, including the initial trial block in which both reinforcers were available immediately. Similar changes in the form of the preference function were observed at higher doses (0.1-0.3 mg/kg) in the present experiment. Koffarnus et al. (2011) did not report any effects of lower PPX doses (0.032 and 0.1 mg/kg). The present experiment also found no effect of lower PPX doses (0.01 and 0.03 mg/kg), although the group preference function shifted toward indifference (i.e., 50% choice) at the 0.1 mg/kg PPX dose, which did not occur in the Koffarnus et al. (2011) study. Despite these formal changes–some of which contributed to the interaction between PPX dose and LL delay–further investigation at each LL delay revealed that only LL choice in the first trial block (0 s) was significantly affected by the drug following alpha corrections. In interpreting the apparent lack of drug effect, the variability of LL choice at the individual subject

level should be considered. Standard errors of the mean, for example, increased dose-dependently, $F(1, 8) = 14.71$, $p < .01$, $\eta_G^2 = .29$, as well as delay-dependently, $F(1, 8) = 13.54$, $p < .01$, $\eta_G^2 = .32$ (significant linear contrasts). By increasing sample sizes, future researchers may proactively improve the likelihood of detecting significant acute PPX-induced changes in intertemporal choice.

Rats also received PPX chronically (0.1 and 0.3 mg/kg for 14 consecutive sessions each), a regimen more closely approximating the manner in which clinical populations administer the drug and other DA agonist medications. As in the acute assessment, chronic PPX dose interacted with the LL delay in effect. Compared to the form of the preference functions generated with acute administration of these same doses, the form of the chronic preference functions differed in that the decrease in LL reinforcer choice in the initial trial block observed with acute PPX was not observed. More generally, restoration of near-exclusive LL reinforcer choice in this trial block was accompanied by an across-block upward shift in LL reinforcer choice relative to the acute functions. This increase was most pronounced in the final trial block (30 s), at which LL choice was significantly affected by the 0.3 mg/kg dose. Thus, in addition to restoring initial block choice for the LL reinforcer, PPX *increased* rats' choice for the LL reinforcer at a single dose.

Despite reproducing the findings of Koffarnus et al. (2011), the present data are in contrast to the report of increased SS choice following acute PPX administration by Madden et al. (2010). In both Koffarnus et al. (2011) and the present work, higher PPX doses disrupted rats' choice for a larger food reinforcer (3 pellets) over smaller food

reinforcer (1 pellet) in the absence of delays to reinforcement (i.e., sensitivity to relative reinforcer amount). Koffarnus et al. (2011) also observed concomitant flattening of the preference function (i.e., reduced effect of LL delay) at the highest PPX dose investigated. The preference functions produced herein also exhibited a tendency toward a reduced effect of LL delay as PPX dose increased. Consistent with this trend, PPX tended to increase LL choice above saline levels in the final trial block (30 s). Collectively, the directions in which LL choice was shifted provide suggestive evidence that the drug at least partially impaired stimulus control over choice behavior. By contrast, the procedure used by Madden et al. (2010) was designed specifically to address the possibility that PPX had such an effect. Essentially, a control condition in which rats predominantly chose the SS reinforcer on more than 80% of trials provided the experimenters the opportunity to observe PPX-induced decreases in SS choice. Coupled with the PPX-induced increases in SS choice observed in the opposite baseline condition ($\leq$ 20% SS choice), decreased SS choice would indicate that, rather than simply increasing SS choice specifically, PPX may disrupt stimulus control over choice behavior and promote indifference between the two alternatives. Such a decrease in the control condition was not observed, suggesting that the PPX effect in the opposite baseline was likely not due to nonspecific drug effects such as poor stimulus control.

To reconcile these divergent findings, it is worth considering that although both procedures–fixed-delay and increasing-delay–are designed to provide researchers with steady-state baseline indices of intertemporal choice, the manner in which drugs interact with static and dynamic decision-making performances remains relatively unknown.

Comparatively, the fixed-delay procedure requires only that subjects discriminate a single intertemporal choice throughout each session while the increasing-delay procedure requires successive discriminations of LL delays as this variable is incremented within the session. Drug administration in such a dynamic environment may increase the likelihood that independent variables are rendered less consequential and that choice trends toward indifference between the two alternatives. This procedural analysis may explain in part the complex behavioral effects of PPX in the present experiment, namely the diminished effect of LL delay on choice with increasing acute and chronic doses. Additional research, however, is required to further elucidate the behavioral processes underlying PPX-induced impulsivity and whether the mechanisms responsible for changes in intertemporal choice are generally applicable to clinical ICDs.

A few shortcomings of the present experiment deserve comment. First, although replication of the procedures used by Koffarnus et al. (2011) was a primary objective, the findings of Madden et al. (2010) also represent an isolated report in need of replication. Previous experiments using the fixed-delay procedure suggest the preparation generates baseline performances that are sensitive to PPX manipulations of gambling-like behavior (Johnson et al., 2011; Johnson et al., 2012). Beyond these three experiments, however, there are no reported attempts to further validate the fixed-delay procedure, from which researchers interested in PPX and intertemporal choice would likely benefit. Second, PPX was not administered prior to no-delay sessions. Impairments in no-delay sessions could be useful in determining whether choice is globally disrupted regardless of the presence or absence of delays or if disruptions observed in the present experiment are

specific to choices involving delay to reinforcement. Finally, while not obviously problematic in the interpretation of the findings, subject attrition did occur, especially between the acute and chronic assessments. The within-subjects design was preferable in that intrasubject variability was minimized (Sidman, 1960). Although a comparable sample size to the one in the present experiment was used by Koffarnus et al. (2011; n = 12), researchers attempting to replicate the present experiment may choose a larger sample size in an effort to reduce this variability further and increase one's ability to detect significant differences between PPX doses.

In a systematic replication of Koffarnus et al. (2011), acute and chronic PPX administration altered rats' choice for a LL reinforcer as its delay increased across blocks of trials. In both assessments, the effect of LL delay on choice was reduced in drug sessions (i.e., preference functions became increasingly shallow relative to saline) and, in the chronic assessment, acute disruptions in choice for larger over smaller food reinforcement were remediated. Compared to the findings of Madden et al. (2010), the present results suggest that PPX may nonspecifically impair aspects of stimulus control rather than simply increasing SS choice. Specifying the drug's effects on behavioral processes involved in complex performances such as intertemporal choice may yet reveal a unifying framework for understanding the mechanisms responsible for PPX-induced impulsivity.

CHAPTER 3

BEHAVIORAL MECHANISMS OF PRAMIPEXOLE-INDUCED IMPULSIVITY

Abstract

The effects of pharmacological variables on complex operant behavior can be understood through the investigation of behavioral mechanisms of drug action. Pramipexole (PPX), a D_2/D_3 dopamine (DA) receptor agonist, is associated with increased rates of impulsive behavior in clinical populations prescribed the drug as well as in nonhumans (rats) administered PPX prior to making intertemporal choices. Experiments in the latter category have produced divergent findings and require further explication. Madden et al. (2010) reported increased choice for a "smaller-sooner" (SS) reward in rats with PPX administration, while Koffarnus et al. (2011) and the experiment presented in Chapter 2 suggested that similar doses of the drug may nonspecifically impair stimulus control of choice behavior. Across three experiments, the present study attempted to elucidate the contributions of behavioral processes recruited during intertemporal choice and potentially affected by PPX administration in a manner likely to produce the pattern of results observed in prior research. Experiment 1 evaluated rats' sensitivity to relative reinforcer delays in a concurrent-chains preparation following acute (0.03-0.3 mg/kg) and chronic (0.18 mg/kg) PPX administration. Acute PPX decreased sensitivity to relative reinforcer delay, an outcome inconsistent with the interpretation of previous findings. Experiment 2 examined an alternative explanation for the findings of

Experiment 1 and previous studies, namely that PPX impairs the accuracy with which rats discriminated response-reinforcer contingencies. Chronic PPX (0.18 mg/kg) reduced accuracy of this discrimination in a symbolic matching-to-sample task. Experiment 3 investigated the effects of the same chronic PPX dose on rats' discrimination of different reinforcer amounts (1 vs. 3 pellets). In similar respect to Experiment 2, PPX reduced the accuracy of amount discrimination. As noted in Chapter 2, impaired amount discrimination in an intertemporal choice can increase SS choice by reducing the influence of amount differences on choice. Whether PPX effects elucidated in contrived procedures are operative in intertemporal choice experiments or clinical instances of impulsive behavior is presently unknown and remains an area of emphasis for future research.

Introduction

Beginning with the inception of their field of study, behavioral pharmacologists have sought to describe and elucidate the effects of pharmacological variables on acquisition (i.e., learning) and maintenance of behavioral performances. Initial efforts were focused largely on the systematic evaluation of drug classes (e.g., stimulants) applied to aversively- and positively-motivated operant behaviors, typically lever pressing in rats or key pecking in pigeons under simple schedules of reinforcement (e.g., fixed-interval; Boren, 1961; Clark & Steele, 1966; Cook & Kelleher, 1962; Dews, 1958; Gollub & Brady, 1965; Kelleher, Fry, Deegan, & Cook, 1961; Weiss & Laties, 1964). Drug-induced changes in rate or topography of responding were of primary interest and

served to underscore the dependency of complex drug-behavior interactions upon environmental variables.

Subsequent approaches to behavioral pharmacology have since promoted the identification of *behavioral mechanisms of drug action* (Branch, 1984, 1991; Thompson & Schuster, 1968). Such an approach requires that, prior to the assessment of drug effects, the functional relations between behavior and environmental variables that support its occurrence under nondrug conditions are specified. This information in hand, researchers are then equipped to interpret the particular action of a drug in terms of a change in a behavioral process, that is, the manner in which behavior is influenced by a particular environmental variable. A change in a behavioral process therefore constitutes a potential behavioral mechanism of drug action.

Applied to complex behavioral performances such as impulsive decision-making, the utility of this analytic strategy is realized in the isolation of behavioral processes germane to the phenomenon of interest and the observation of drug-induced changes in these processes consistent with clinically relevant behavioral problems. For instance, pramipexole (PPX), a D_2/D_3 dopamine (DA) agonist prescribed in the treatment of Parkinson's disease, restless legs syndrome, fibromyalgia and treatment-resistant depression has been associated with the development of a range of impulse control disordered behaviors (ICDs). Documented ICDs include pathological gambling (e.g., Dodd et al., 2005, Driver-Dunckley et al., 2003), hypersexuality (e.g., Giladi et al., 2007; Klos et al., 2005), and compulsive eating (Hassan et al., 2011) or shopping (Cornelius et al., 2010). Although the exact etiology of ICDs remains unknown, their manifestation is

coincident with initiation of PPX or other DA agonist regimens; ICDs typically cease following decreases in agonist dosage or termination of the regimen (Avila et al., 2011; Mamikonyan et al., 2008). Assuming that PPX and other DA agonists affect functional relations between the expression of ICDs and variables in the clinical environment which either support or discourage this class of impulsive behavior, an experimental analysis of behavioral mechanisms underlying these drug effects is warranted.

The search for candidate behavioral mechanisms of PPX-induced impulsivity has also been instigated by findings that the drug affects intertemporal choice in nonhumans. Madden et al. (2010) observed that PPX (0.1-0.3 mg/kg) increased the frequency of rats' choice of a smaller, sooner (SS) reinforcer (1 food pellet) when administered in a condition in which nondrug choice favored a larger, later (LL) reinforcer (3 pellets delivered after a delay). In a separate condition of nondrug SS preference, PPX did not affect rats' choice for this alternative; the results of this control condition suggested that PPX-related increases in SS choice were not the product of nonspecific disruption of choice (e.g., impairment of stimulus control). Using an increasing-delay procedure (Evenden & Ryan, 1996), Koffarnus et al. (2011) also assessed the effects of PPX on intertemporal choice. Only one PPX dose (0.32 mg/kg), however, increased the frequency of SS choice above saline levels and did so in a manner suggestive of nonspecific disruption of choice when both reinforcers were available immediately (1 vs. 3 sucrose pellets). The experiment presented in Chapter 2 systematically replicated the procedures of Koffarnus et al. (2011) and reproduced this disruption induced by higher PPX doses (0.1-0.3 mg/kg).

These mixed findings raise two questions. First, which behavioral mechanisms contribute to instances of PPX-induced impulsivity as observed by Madden et al. (2010)? Second, are the same behavioral mechanisms equally likely to contribute to instances of PPX-induced disruption of choice as observed by Koffarnus et al. (2011) and systematically replicated in Chapter 2? The first mechanism by which PPX could increase impulsive choice is by enhancing sensitivity to relative reinforcer delay across concurrently available alternatives. As noted in Chapter 1, if PPX increases sensitivity to relative reinforcer delay, this would increase preference for SS reinforcers.

Two other behavioral processes might be affected by PPX and these were explored in Experiment 2 and 3 after it was learned that sensitivity to relative reinforcer delays was *decreased* by PPX. Experiment 2 assessed the effects of chronic PPX on rats' discrimination of response-reinforcer contingencies using a symbolic matching-to-sample (SMTS) procedure. Specifically, rats were required to report which of two responses–left or right lever press–produced a food pellet on a given trial. Reduced accuracy of this discrimination following PPX administration might provide an alternative explanation for the results of Experiment 1, namely that rats were less able to discriminate which response produced the reinforcer in the concurrent-chains procedure. In terms of response allocation, imperfect discrimination of response-reinforcer contingencies would be expected to produce more equally-distributed responding and shallower-sloped matching functions. The SMTS procedure was modified slightly for Experiment 3 to assess the drug's effects on rats' discrimination of small (1 pellet) and large (3 pellets) food amounts. These two discrimination processes were targeted for investigation as PPX-

induced disruptions in their integrity were hypothesized to increase the likelihood of SS choice in intertemporal choice situations.

Experiment 1

Introduction

One of the limitations of discrete-choice procedures used to investigate PPX's effects on intertemporal choice is the inability to dissociate the contributions of individual behavioral processes to complex decision-making performances. In large part, this is due to the choice structure, which concurrently arranges differences in amount and delay. Consequently, if PPX affects preference in a discrete-choice procedure, it is difficult–if not impossible–to specify the behavioral mechanism or mechanisms responsible for the drug effect.

Further inspection of the behavioral processes thought to underlie PPX's effects on intertemporal choice can, however, be carried out by coupling a concurrent-chains preparation with the analytical logic of Equation 8. Rather than presenting the organism with an intertemporal choice, one reinforcement parameter (e.g., differences in amount) can be equalized, leaving the remaining reinforcement parameter (e.g., differences in reinforcer delay) to determine response allocation. Sensitivity to the isolated parameter, a putative behavioral process, can then be characterized quantitatively as the slope of Equation 4. Against a saline baseline, changes in the behavioral process of interest (e.g., sensitivity to relative reinforcer delays or reinforcer amounts) following PPX administration constitute a potential behavioral mechanism of PPX-induced impulsivity.

In concert with the predictions of Equation 8, the increase in SS choice observed by Madden et al. (2010) could have been due to an increase in sensitivity to relative reinforcer delay (see Fig. 1-3) or a decrease in sensitivity to relative reinforcer amount (see Fig. 1-4). Using a concurrent-chains procedure and the analytical logic outlined above, changes in these behavioral processes can be described as changes in the slope of the matching function. In the case of increased delay sensitivity, the steeper-sloped matching function expected following PPX administration is easily interpreted. With respect to decreased amount sensitivity, however, one cannot confidently deduce that a shallower matching function produced by PPX is the result of said behavioral mechanism. An alternative explanation for a shallower slope could be that PPX impaired stimulus control, rendering the two alternatives generally less discriminable regardless of sensitivity to relative reinforcer amounts. This latter effect, albeit undesirable in the context of a concurrent-chains preparation, may provide evidence in support of the interpretations of Koffarnus et al. (2011) and Chapter 2, namely that PPX administration may disrupt aspects of stimulus control.

In an effort to distinguish between these interpretations, Experiment 1 evaluated the acute and chronic PPX effect on sensitivity to relative reinforcer delay in a concurrent-chains preparation. On one hand, if PPX increased sensitivity to relative reinforcer delay, as might have been the case in Madden et al. (2010), the slope of the matching function produced with PPX was predicted to be greater than the slope of the nondrug (i.e., saline) matching function. On the other hand, if PPX nonspecifically disrupted choice by impairing stimulus control, as might have been the case in Koffarnus

et al. (2011) and Chapter 2, the slope of the matching function was predicted to be lesser than the slope of the nondrug matching function. A trend toward equalized response allocation observed as a relatively shallow function might therefore signal that differences in the independent variable (i.e., terminal-link delays to reinforcement) were inconsequential due to poor discrimination of features of the choice alternatives.

Methods

Subjects. Twelve experimentally naïve male Wistar rats served as subjects. Rats arrived in the colony weighing approximately 325-350 grams (~ 9 weeks) and were housed individually in polycarbonate cages in a room maintained on a 12/12 programmed light/dark cycle. With the exception of experimental sessions, which were conducted 7 days per week, water was continuously available. At least 2 hours after each session, supplementary chow was provided in order to maintain weights of 375 grams.

All rats having completed the acute assessment served as subjects in the chronic assessment (n = 11, see below). With the exception of the drug administration regimen, all environmental conditions–experimental and extra-experimental–were identical across assessments. Animal use was in accordance with the Institutional Animal Care and Use Committee (IACUC) of the University of Kansas.

Apparatus. Experimental sessions were conducted in six identical operant conditioning chambers (24.1 cm x 30.5 cm x 21.0 cm; Med Associates Inc., St. Albans, VT). The intelligence panel of each chamber featured two low-profile, retractable side levers (ENV-112CM, Med Associates Inc.) spaced horizontally 11 cm apart. A 28-volt DC cue light was located 6 cm above each lever. Positioned 1 cm above the floor and

centered between the side levers was a pellet receptacle into which nutritional grain-based rodent pellets could be delivered (45 mg; Bio-Serv, Frenchtown, NJ). A speaker generated white noise to mask extraneous sound and a fan ventilated the sound-attenuating cubicle in which each chamber was located. Experimental sessions were executed by a PC running MED-PC® IV software in an adjacent room.

Behavioral procedure. Lever pressing was initially trained using an autoshaping procedure. Once reliable responding had been established, a concurrent-chains procedure was introduced for 40-trial sessions (see Pitts & Febbo, 2004). Each trial began with both levers inserted into the chamber and the stimulus light above each lever lit. During the initial link of the concurrent-chains schedules, dependent VI 30-s schedules (Stubbs & Pliskoff, 1969) were programmed according to two separate distributions (Fleshler & Hoffman, 1962). On each trial, the left or right lever randomly granted terminal-link access with two restrictions: (a) The same lever could not produce terminal-link access on more than 3 consecutive trials, and (b) left and right levers were selected an equal number of times per session (20 each). A 3-s changeover delay (COD) was programmed; responses emitted during the COD could not produce terminal-link access.

When a lever press granted terminal-link access, the levers were retracted, the stimulus light above the unselected lever was extinguished, and a delay to reinforcement was initiated. The duration of the terminal-link delay depended upon the lever selected and the experimental condition (see below). After the terminal-link delay, two food pellets were delivered to the receptacle regardless of which alternative produced

terminal-link access. Trials ended with an ITI in which all stimuli were off; the ITI duration was adjusted so that trials started every 100 s.

Response allocation was investigated in three conditions in which the terminal-link delays were manipulated. In the first condition, both terminal-link delays were 7.5 s (equal delay condition). In subsequent conditions, left/right terminal-link delays were 12 s/3 s and 3 s/12 s; the order in which rats experienced these unequal delay conditions was counterbalanced across subjects (Table 3-1).

Baseline (no-injection) sessions continued in each condition for at least 20 sessions and until (a) the mean initial-link response proportion (left/total) from the last three sessions deviated by $\leq .05$ from the mean of the previous three sessions, and (b) no monotonic trend was visually apparent over the last six sessions. After response allocation met these stability criteria, the acute dosing assessment began.

Drug procedure. PPX hydrochloride (*N*'-propyl-4,5,6,7-tetrahydrobenzothiazole-2,6-diamine dihydrochloride) was synthesized and provided by Drs. Shaomeng Wang and Jianyong Chen (University of Michigan, Ann Arbor, MI). PPX was dissolved in physiological saline (0.9% NaCl) and was administered subcutaneously at a volume of 1.0 ml/kg.

Ten minutes prior to every fifth session, saline or PPX (0.03, 0.1, 0.18, and 0.3 mg/kg) was administered subcutaneously in a descending dose order beginning with saline. The sequence of doses was assessed twice in each delay condition.

Following completion of the acute dosing assessment and a 4-day washout period, subjects experienced chronic (i.e., daily) dosing with either saline or PPX (0.18 mg/kg)

for at least 14 consecutive sessions in an order counterbalanced across subjects. Four-day washout periods separated each chronic regimen. The order of delay conditions experienced in the chronic assessment was opposite that of the order experienced in the acute assessment with stability reassessed for each condition.

Data analysis. For both acute and chronic dosing assessments, the logarithm of the response allocation ratio for each dose was plotted as a function of the logarithm of the terminal-link delay ratio in each experimental condition. For the acute assessment, linear regressions were performed on the geometric means from the two dosing series. Because reinforcer amounts were equivalent across alternatives, Equation 8 could be reduced to a version in which response allocation ($\log[R_1/R_2]$) is determined exclusively by the ratio of reinforcer delays:

$$\log\left(\frac{R_1}{R_2}\right) = d\log\left(\frac{1+kD_2}{1+kD_1}\right) + \log b. \quad (9)$$

Equation 9 was used to estimate sensitivity to relative reinforcer delay (d) and bias ($\log b$) for the acute assessment; these parameters were estimated for the chronic assessment using the final 6 sessions of the chronic assessment. To quantitatively isolate changes in d from PPX-induced changes in the rate of delay discounting (k), model fits assumed a constant k of 1 (see Pitts & Febbo, 2004). Parameters were analyzed using a one-way repeated-measures ANOVA with Dose (saline, 0.03, 0.1, 0.18, and 0.3 mg/kg) as the only within-subject factor.

Because reports of D_2/D_3 DA agonist-induced response perseveration are not uncommon (Boulougouris et al., 2009; Haluk & Floresco, 2009), the effects of PPX on

average bout length (i.e., number of responses preceding a changeover event) was evaluated using a two-way, repeated-measures ANOVA (Delay Condition, Dose).

Dopamine agonists (e.g., amphetamine) have also been shown to produce rate-dependent effects on responding (Dews, 1958; Lucki & DeLong, 1983). Rate dependency occurs when drugs decrease responding that occurs at a high rate and concomitantly increase responding that occurs at a low rate (see Branch, 1984). As it pertains to the present experiment, response rates from PPX sessions (expressed as a proportion of saline rates) were examined for rate-dependency using a three-way, repeated-measures ANOVA (Delay Condition, Dose, Lever).

In the acute assessment, one rat (P1) fell ill, was euthanized, and was excluded from all analyses. In the chronic assessment, response allocation failed to stabilize for two rats (G3 and P2) in the third and final delay condition. Data from these two subjects were excluded from statistical analyses comparing acute and chronic assessments.

Pairwise comparisons were evaluated using Bonferroni-corrected alphas. Effects sizes were calculated as generalized eta squared (see Bakeman, 2005). For cases where data violated assumptions of normality, Greenhouse-Geisser adjusted degrees of freedom were used to estimate criterion for significance. All effects and interactions were significant at the $p < .05$ level.

Results

Rats required an average of 27.55 (SD = 9.35) and 29.22 (SD = 7.91) sessions to achieve stability prior to acute and chronic PPX assessments, respectively (Table 3-1).

Table 3-1

Sequence of Delay Conditions and Sessions to Stability for Individual Rats in the Acute and Chronic PPX Assessments of Experiment 1

		Acute		Chronic	
Rat	Delay (s) (Left/Right)	Condition	Sessions to Stability	Condition	Sessions to Stability
G1	7.5/7.5	1	23	3	25
	12/3	2	24	2	23
	3/12	3	30	1	-
G2	7.5/7.5	1	22	3	56
	12/3	2	23	2	22
	3/12	3	30	1	-
G3	7.5/7.5	1	22	-	-
	12/3	2	20	-	-
	3/12	3	26	-	-
G4	7.5/7.5	1	20	3	39
	12/3	2	20	2	34
	3/12	3	40	1	-
R1B1	7.5/7.5	1	22	3	23
	12/3	2	24	2	27
	3/12	3	44	1	-
R1B2	7.5/7.5	1	20	3	33
	12/3	2	22	2	28
	3/12	3	34	1	-
R1B3	7.5/7.5	1	23	3	30
	12/3	3	47	1	-
	3/12	2	23	2	27
P2	7.5/7.5	1	20	-	-
	12/3	3	45	-	-
	3/12	2	21	-	-
B1R1	7.5/7.5	1	20	3	23
	12/3	3	47	1	-
	3/12	2	20	2	25
B1R2	7.5/7.5	1	20	3	33
	12/3	3	42	1	-
	3/12	2	24	2	27
B1R3	7.5/7.5	1	23	3	23
	12/3	3	46	1	-
	3/12	2	22	2	28

For rats completing both assessments, significantly more sessions were required to achieve stability prior to the chronic assessment, $F(1, 9) = 13.55$, $p < .01$, $\eta_G^2 = .31$.

Figure 3-1 depicts the effects of acute PPX on sensitivity to relative reinforcer delay (*d*; top graph) and bias (log *b*; bottom graph) for individual subjects and for the group average (see Table 3-2 for individual-subject parameter estimates). Sensitivity to relative reinforcer delay was significantly reduced by acute PPX, $F(1.64, 16.4) = 13.98$, $p < .001$, $\eta_G^2 = .58$, in a dose-dependent manner (significant linear contrast: $F[1, 10] = 18.616$, $p = .002$, $\eta_G^2 = .65$). Bonferroni-corrected pairwise comparisons revealed that the only PPX dose at which sensitivity to relative reinforcer delay was significantly lower than saline was 0.3 mg/kg ($p = .02$). Sensitivity at higher PPX doses (0.1, 0.18, and 0.3 mg/kg) was also significantly lower than sensitivity at the 0.03 mg/kg dose (all p's $< .03$). Bias was unaffected by acute PPX ($p > .20$). Table 3-3 also displays left- and right-lever response output (on which the above regressions were performed), left and right local response rates, and changeover responses emitted at each acute saline or PPX administration in each delay condition for each rat.

Sensitivity to relative reinforcer delay and bias under chronic PPX (0.18 mg/kg) administration (Figure 3-2) did not differ significantly from chronic saline sessions ($p = .07$ and .11, respectively). However, when compared to sensitivity at the same dose when administered acutely, sensitivity under chronic PPX administration was significantly higher, $t(8) = -4.11$, $p = .003$. Bias, on the other hand, was not significantly affected by PPX assessment ($p > .35$). Table 3-4 displays mean left- and right-lever response output, mean left and right local response rates, and mean changeover responses emitted

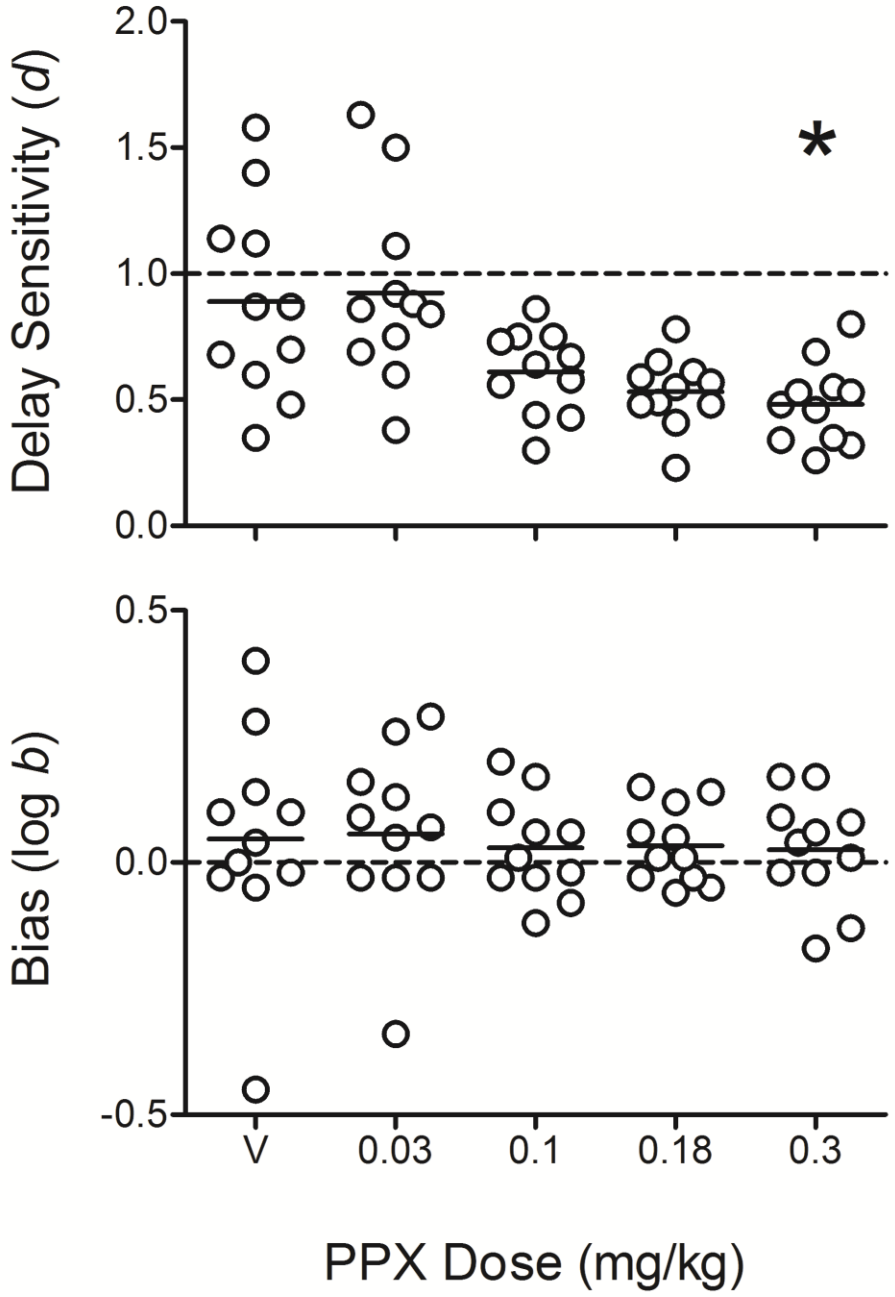

Figure 3-1. Parameters of best-fitting linear regressions of individual-subject initial-link response allocation from the acute PPX assessment of Experiment 1. Each point corresponds to an individual subject's sensitivity to relative reinforcer delays (*d*) or bias (log *b*) estimate with solid lines representing group averages. Asterisk denotes dose is significantly different from saline at the $p < .05$ level.

Table 3-2

Parameter Estimates from the Acute and Chronic PPX Assessments of Experiment 1

		Acute			Chronic		
Rat	PPX (mg/kg)	Slope (*d*)	Bias (log *b*)	VAC (R^2)	Slope (*d*)	Bias (log *b*)	VAC (R^2)
G1	Saline	0.72	0.40	1.00	0.59	0.54	0.91
	0.03	0.92	0.29	1.00			
	0.1	0.64	0.17	0.99			
	0.18	0.41	0.15	0.84	0.67	0.34	0.99
	0.3	0.48	0.17	0.93			
G2	Saline	1.40	0.04	1.00	1.82	-0.03	1.00
	0.03	1.63	0.13	0.96			
	0.1	0.86	-0.08	0.99			
	0.18	0.78	-0.03	1.00	0.98	0.08	0.99
	0.3	0.80	-0.17	0.98			
G3	Saline	0.68	-0.45	0.89	-	-	-
	0.03	0.88	-0.34	0.98			
	0.1	0.75	-0.12	0.95			
	0.18	0.65	-0.06	0.99	-	-	-
	0.3	0.69	0.01	0.96			
G4	Saline	1.12	-0.02	1.00	1.32	-0.10	0.88
	0.03	0.84	-0.03	0.99			
	0.1	0.56	-0.03	1.00			
	0.18	0.61	-0.05	0.95	0.77	-0.02	0.97
	0.3	0.53	-0.13	0.81			
R1B1	Saline	1.58	0.00	1.00	0.93	0.26	0.95
	0.03	1.50	-0.03	1.00			
	0.1	0.67	0.01	1.00			
	0.18	0.49	0.06	0.99	0.80	0.14	0.93
	0.3	0.46	0.04	0.99			
R1B2	Saline	0.60	0.28	0.93	0.49	0.52	0.98
	0.03	0.60	0.26	0.99			
	0.1	0.58	0.20	0.98			
	0.18	0.56	0.14	1.00	0.71	0.25	0.94
	0.3	0.35	0.06	1.00			

(table continues)

		Acute			Chronic		
Rat	PPX (mg/kg)	Slope (*d*)	Bias (log *b*)	VAC (R^2)	Slope (*d*)	Bias (log *b*)	VAC (R^2)
R1B3	Saline	0.87	-0.03	0.98	0.83	-0.06	0.90
	0.03	0.75	-0.03	0.94			
	0.1	0.44	-0.03	0.86			
	0.18	0.48	0.01	0.92	0.76	-0.03	1.00
	0.3	0.53	-0.02	0.88			
P2	Saline	0.35	-0.05	0.73	-	-	-
	0.03	0.38	0.09	0.99			
	0.1	0.30	-0.02	0.99			
	0.18	0.23	-0.03	0.78	-	-	-
	0.3	0.32	-0.02	0.82			
B1R1	Saline	0.87	0.14	0.68	0.72	0.06	0.99
	0.03	0.86	0.07	0.82			
	0.1	0.75	0.06	0.99			
	0.18	0.57	0.01	0.99	0.59	-0.03	1.00
	0.3	0.26	0.17	0.37			
B1R2	Saline	0.48	0.10	0.90	0.73	0.13	1.00
	0.03	0.69	0.05	0.97			
	0.1	0.43	0.10	0.98			
	0.18	0.59	0.12	1.00	0.52	0.03	0.98
	0.3	0.34	0.09	0.77			
B1R3	Saline	1.14	0.10	0.95	1.21	0.09	0.99
	0.03	1.11	0.16	0.97			
	0.1	0.73	0.06	0.99			
	0.18	0.48	0.05	0.98	0.68	-0.02	0.96
	0.3	0.55	0.08	0.85			

Note. Slope (sensitivity to relative reinforcer delays; *d*), bias (log *b*), and variance accounted for (VAC; R^2) estimates from best-fitting linear regressions of response allocation in the acute and chronic PPX assessments.

Table 3-3

Behavioral Measures from the Acute PPX Assessment of Experiment 1

			Left lever		Right lever		
Rat	Delay pair (Left/right)	PPX (mg/kg)	Responses	Local rate	Responses	Local rate	Changeover events
G1	7.5 s/7.5 s	Saline	850/981	1.32/2.09	309/426	1.29/2.11	46/54
		0.03	893/789	1.51/1.41	391/428	1.63/1.27	56/56
		0.1	516/682	0.84/1.35	324/407	1.04/1.35	57/60
		0.18	516/480	0.91/1.24	415/487	1.30/1.11	51/52
		0.3	327/468	0.37/0.78	327/309	0.67/0.79	46/71
	12 s/3 s	Saline	807/673	1.89/2.10	595/729	1.95/1.88	54/65
		0.03	608/480	1.87/1.46	791/879	1.89/1.80	51/72
		0.1	493/377	0.84/1.35	619/684	1.32/1.18	62/68
		0.18	440/316	0.85/0.93	378/394	0.80/0.69	49/46
		0.3	350/322	0.56/0.91	319/423	0.39/0.60	47/61
	3 s/12 s	Saline	1126/1239	2.38/2.15	277/154	1.25/1.00	59/33
		0.03	1169/1176	1.65/1.83	209/207	1.17/1.22	36/36
		0.1	602/675	0.40/1.06	186/250	0.58/0.62	59/66
		0.18	339/544	0.14/0.69	184/150	0.49/0.45	48/50
		0.3	414/762	0.57/0.56	214/188	0.72/0.54	38/50
G2	7.5 s/7.5 s	Saline	525/632	1.19/1.23	557/458	1.41/1.36	62/64
		0.03	422/339	0.88/0.83	433/465	1.03/1.02	59/52
		0.1	304/349	0.70/0.80	438/462	0.75/0.91	57/56
		0.18	382/317	0.78/0.71	297/465	0.85/0.75	38/65
		0.3	201/341	0.40/0.33	343/331	0.40/0.36	45/46
	12 s/3 s	Saline	258/212	1.01/1.06	1131/1180	1.30/1.41	63/71
		0.03	239/195	0.83/0.95	793/926	1.17/1.12	68/58
		0.1	230/188	0.70/0.80	568/729	0.93/0.92	57/55
		0.18	199/200	0.44/0.68	520/562	0.68/0.72	52/65
		0.3	170/116	0.35/0.53	575/562	0.42/0.22	44/33
	3 s/12 s	Saline	1191/1194	1.49/1.66	207/224	1.85/1.96	30/39
		0.03	1293/1273	1.62/1.50	105/117	1.26/1.12	23/25
		0.1	662/716	1.15/1.04	315/248	1.27/0.87	41/43
		0.18	456/689	0.75/1.00	242/231	0.72/0.99	41/52
		0.3	388/436	0.51/0.44	316/201	0.40/0.34	82/46
G3	7.5 s/7.5 s	Saline	228/193	0.36/0.56	420/443	0.63/0.51	27/32
		0.03	210/215	0.49/0.55	401/365	0.42/0.53	33/35
		0.1	326/310	0.50/0.60	330/330	0.44/0.56	47/37
		0.18	219/221	0.44/0.45	314/251	0.45/0.41	59/47
		0.3	222/230	0.35/0.49	203/364	0.30/0.44	50/36

(table continues)

Rat	Delay pair (Left/right)	PPX (mg/kg)	Left lever Responses	Left lever Local rate	Right lever Responses	Right lever Local rate	Changeover events
	12 s/3 s	Saline	174/111	0.98/1.33	776/1303	0.74/1.17	44/28
		0.03	152/178	1.04/1.03	1028/1200	0.85/0.86	41/38
		0.1	144/167	0.50/0.60	507/597	0.51/0.58	31/37
		0.18	196/163	0.51/0.47	299/583	0.38/0.48	37/46
		0.3	187/177	0.46/0.55	310/434	0.39/0.47	43/37
	3 s/12 s	Saline	421/650	1.46/1.38	830/728	1.21/1.10	27/42
		0.03	626/569	1.43/1.46	527/496	0.91/0.89	51/57
		0.1	512/629	1.19/1.11	353/324	0.60/0.51	51/40
		0.18	495/577	0.77/0.95	325/232	0.51/0.56	61/42
		0.3	471/862	0.51/0.91	216/295	0.48/0.69	42/36
G4	7.5 s/7.5 s	Saline	642/544	1.42/1.60	549/791	1.36/1.51	64/45
		0.03	504/410	1.26/1.17	509/601	1.08/1.13	53/57
		0.1	462/393	1.05/1.09	407/509	0.92/1.03	60/48
		0.18	434/416	1.01/0.81	342/455	0.88/0.78	50/44
		0.3	267/355	0.82/0.79	313/281	0.63/0.77	42/40
	12 s/3 s	Saline	315/250	1.32/1.16	1006/1130	1.56/1.64	56/50
		0.03	354/281	1.23/1.23	677/1085	1.22/1.66	54/49
		0.1	275/413	1.05/1.09	585/861	1.01/1.16	53/65
		0.18	303/265	1.02/0.87	689/746	1.14/1.07	53/61
		0.3	200/228	0.60/0.60	386/1063	0.63/0.81	48/37
	3 s/12 s	Saline	994/1178	1.85/2.23	381/230	1.17/1.49	58/34
		0.03	868/957	1.50/1.69	301/387	1.00/1.15	50/64
		0.1	641/572	1.32/1.17	267/440	1.01/0.90	41/56
		0.18	474/778	1.28/1.22	400/330	0.99/0.99	50/68
		0.3	353/508	0.43/0.69	249/547	0.57/0.75	41/41
R1B1	7.5 s/7.5 s	Saline	761/587	2.89/2.74	651/815	2.10/2.23	60/57
		0.03	659/650	2.64/2.07	743/762	1.91/2.15	51/58
		0.1	582/717	0.94/1.70	570/672	0.67/1.32	72/50
		0.18	662/485	1.03/1.06	533/523	0.63/0.96	178/162
		0.3	714/390	0.58/0.65	512/392	0.34/0.49	223/200
	12 s/3 s	Saline	242/158	1.59/1.11	1167/1236	2.13/1.64	37/49
		0.03	211/161	1.20/1.06	1130/1104	1.47/1.34	49/53
		0.1	391/316	0.94/1.70	922/641	1.30/1.17	61/58
		0.18	378/456	1.34/0.30	660/562	1.12/0.77	92/104
		0.3	428/402	0.71/1.01	753/614	0.49/0.87	127/114
	3 s/12 s	Saline	1113/1191	1.54/1.63	171/178	0.90/0.81	63/61
		0.03	927/880	1.35/1.62	154/170	0.68/0.64	46/43
		0.1	645/515	1.21/0.75	201/339	0.50/0.41	70/87
		0.18	709/296	0.48/0.24	207/219	0.34/0.26	182/142
		0.3	437/430	0.54/0.38	213/265	0.42/0.29	133/206

(table continues)

Rat	Delay pair (Left/right)	PPX (mg/kg)	Left lever Responses	Left lever Local rate	Right lever Responses	Right lever Local rate	Changeover events
R1B2	7.5 s/7.5 s	Saline	547/700	1.00/1.35	404/406	1.14/1.31	55/52
		0.03	723/669	1.15/1.01	431/292	1.34/1.00	50/41
		0.1	405/612	0.82/1.00	304/274	0.71/0.93	52/33
		0.18	331/532	0.64/0.78	324/294	0.71/0.89	47/39
		0.3	328/363	0.6/0.39	387/231	0.48/0.42	42/42
	12 s/3 s	Saline	594/488	1.31/1.41	453/587	1.08/1.08	58/43
		0.03	488/383	1.25/1.04	478/514	0.92/0.91	42/43
		0.1	401/314	0.82/1.00	444/492	0.80/0.90	44/37
		0.18	363/285	0.83/0.76	449/445	0.72/0.73	44/44
		0.3	283/239	0.54/0.76	287/418	0.55/0.64	33/39
	3 s/12 s	Saline	974/1074	1.55/1.58	274/208	1.06/1.13	53/38
		0.03	816/796	1.24/0.97	243/210	1.02/1.04	42/39
		0.1	684/603	0.91/0.80	208/223	0.92/0.98	35/38
		0.18	613/455	0.80/0.60	171/231	0.77/0.49	33/62
		0.3	288/419	0.48/0.43	233/168	0.46/0.49	36/57
R1B3	7.5 s/7.5 s	Saline	706/536	2.27/2.45	698/873	2.26/2.53	57/59
		0.03	520/663	1.81/1.99	882/739	1.94/2.14	65/55
		0.1	550/444	1.65/1.76	695/653	1.57/1.25	64/57
		0.18	444/520	1.30/1.45	507/622	1.21/1.17	55/66
		0.3	376/377	0.96/1.36	501/504	0.82/0.92	49/41
	3 s/12 s	Saline	989/1101	2.47/2.54	430/326	2.75/2.71	39/38
		0.03	874/1098	1.61/1.79	523/290	2.20/2.14	53/30
		0.1	719/761	1.48/1.19	483/351	1.58/1.57	52/38
		0.18	586/641	1.19/0.79	319/294	1.15/1.15	46/40
		0.3	512/698	0.98/0.57	278/304	0.81/0.27	45/41
	12 s/3 s	Saline	403/350	4.00/3.57	1016/1068	3.77/3.50	27/27
		0.03	468/387	2.45/2.26	945/1008	2.40/2.06	36/42
		0.1	519/481	1.65/1.76	707/907	1.17/1.84	55/48
		0.18	388/490	0.51/0.93	687/674	0.56/0.87	60/70
		0.3	251/347	0.79/0.62	511/482	0.79/0.55	42/64
P2	7.5 s/7.5 s	Saline	380/427	1.05/1.00	611/609	1.18/1.32	61/65
		0.03	461/545	0.76/0.91	360/414	0.94/0.99	65/50
		0.1	269/269	0.75/0.54	305/242	0.70/0.66	47/37
		0.18	264/256	0.58/0.53	307/354	0.68/0.68	54/71
		0.3	229/196	0.20/0.16	244/309	0.23/0.19	60/64
	3 s/12 s	Saline	721/818	1.42/1.27	566/428	1.55/1.70	55/49
		0.03	537/469	0.70/0.77	202/344	1.13/1.24	32/47
		0.1	395/345	0.60/0.36	302/251	0.65/0.89	59/47
		0.18	264/436	0.42/0.49	230/288	0.23/0.50	61/101
		0.3	239/391	0.09/0.26	196/200	0.24/0.33	36/48

(table continues)

Rat	Delay pair (Left/right)	PPX (mg/kg)	Left lever Responses	Left lever Local rate	Right lever Responses	Right lever Local rate	Changeover events
	12 s/3 s	Saline	599/503	1.56/1.97	776/834	2.27/2.22	59/47
		0.03	423/283	1.21/0.76	573/354	1.31/0.82	48/54
		0.1	286/249	0.75/0.54	398/408	0.57/0.61	58/104
		0.18	240/219	0.30/0.52	271/318	0.44/0.55	53/80
		0.3	210/221	0.18/0.42	285/312	0.20/0.34	57/43
B1R1	7.5 s/7.5 s	Saline	535/465	1.43/1.81	735/876	1.73/1.85	73/61
		0.03	447/505	1.49/1.54	619/790	1.36/1.51	56/60
		0.1	404/416	1.02/1.02	396/405	0.87/0.87	64/63
		0.18	350/441	0.59/1.09	337/535	0.64/1.02	82/67
		0.3	293/210	0.29/0.24	208/341	0.39/0.58	81/62
	3 s/12 s	Saline	1167/1238	1.76/2.08	240/180	1.28/1.89	73/39
		0.03	1145/1030	1.46/1.24	249/259	1.77/1.38	31/53
		0.1	704/752	0.89/0.96	286/219	0.92/1.01	64/55
		0.18	415/552	0.56/0.62	191/270	0.53/0.82	54/84
		0.3	556/467	0.54/0.35	157/251	0.47/0.58	59/93
	12 s/3 s	Saline	631/550	2.15/2.03	762/840	2.12/2.17	58/65
		0.03	406/418	0.96/1.28	700/776	1.36/1.54	66/70
		0.1	341/271	1.02/1.02	549/677	1.04/0.96	63/57
		0.18	314/235	0.63/0.79	442/555	0.49/0.95	100/49
		0.3	502/207	0.52/0.76	228/243	0.21/0.31	133/51
B1R2	7.5 s/7.5 s	Saline	520/573	1.13/1.27	282/416	0.84/1.20	88/115
		0.03	369/415	0.91/0.92	283/306	0.82/0.87	67/75
		0.1	230/335	0.24/0.65	150/264	0.04/0.57	54/64
		0.18	280/290	0.44/0.71	191/235	0.09/0.33	82/61
		0.3	339/222	0.57/0.26	183/162	0.12/0.40	61/57
	3 s/12 s	Saline	686/824	1.23/1.49	354/405	1.42/1.87	83/71
		0.03	712/692	1.15/1.35	238/373	1.08/1.54	56/70
		0.1	450/504	0.79/0.53	174/325	0.82/0.95	44/66
		0.18	403/418	0.54/0.85	139/186	0.58/0.82	42/44
		0.3	385/431	0.32/0.28	310/203	0.36/0.70	61/54
	12 s/3 s	Saline	543/532	1.74/1.89	835/848	2.05/2.02	81/80
		0.03	504/348	1.78/1.31	876/924	1.73/1.84	69/59
		0.1	409/481	0.24/0.65	598/627	1.28/1.51	71/61
		0.18	386/472	0.97/1.36	651/682	0.65/1.47	78/58
		0.3	272/369	0.72/0.58	365/535	0.76/0.49	44/54
B1R3	7.5 s/7.5 s	Saline	834/969	2.04/2.42	558/448	2.04/2.53	65/49
		0.03	847/990	1.90/2.23	556/419	2.04/2.25	51/37
		0.1	674/720	1.61/1.44	652/647	1.92/1.72	45/45
		0.18	390/790	0.91/1.56	533/552	1.16/1.70	69/51
		0.3	286/525	0.64/0.90	403/478	0.85/1.31	65/65

(table continues)

Rat	Delay pair (Left/right)	PPX (mg/kg)	Left lever Responses	Left lever Local rate	Right lever Responses	Right lever Local rate	Changeover events
	3 s/12 s	Saline	1054/1205	2.21/2.63	363/214	2.38/2.51	42/28
		0.03	1153/1172	2.29/2.33	264/243	2.18/1.85	38/31
		0.1	984/1056	1.49/1.56	403/332	1.60/1.62	44/33
		0.18	608/819	0.67/1.11	292/402	0.44/1.28	73/41
		0.3	807/552	0.86/0.59	331/187	1.07/1.19	61/27
	12 s/3 s	Saline	352/267	1.91/2.11	1046/1128	2.74/2.60	53/37
		0.03	306/395	1.34/1.61	1082/983	1.85/2.05	58/58
		0.1	437/430	1.61/1.44	927/755	1.74/1.64	53/70
		0.18	495/404	1.24/0.86	677/668	1.37/1.15	65/86
		0.3	309/315	0.79/0.75	456/385	1.02/0.91	82/50

Note. Left and right lever response output, left and right local response rates, and changeover events in the first/second administration of each acute PPX dose for individual rats in each delay condition.

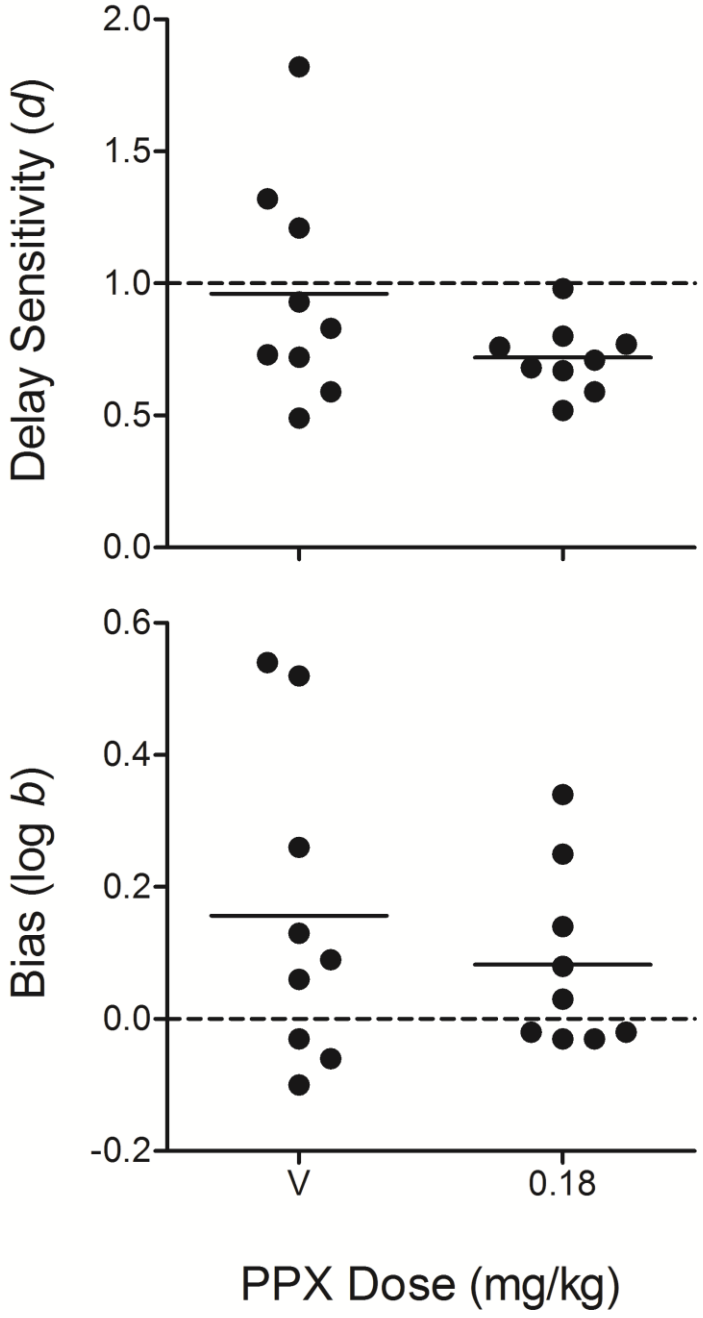

Figure 3-2. Parameters of best-fitting linear regressions of individual-subject initial-link response allocation from the chronic PPX assessment of Experiment 1. Each point corresponds to an individual subject's sensitivity to relative reinforcer delays (*d*) or bias (log *b*) estimate with solid lines representing group averages.

Table 3-4

Behavioral Measures from the Chronic PPX Assessment of Experiment 1

			Left lever		Right lever		
Rat	Delay pair (Left/right)	PPX (mg/kg)	Responses	Local rate	Responses	Local rate	Changeover events
G1	3 s/12 s	Saline	1245.75	2.59	165.25	1.74	27.75
			(18.94)	(0.05)	(20.04)	(0.07)	(3.11)
		0.18	1019.00	1.17	221.50	1.23	55.25
			(70.59)	(0.07)	(9.06)	(0.08)	(4.17)
	12 s/3 s	Saline	920.50	2.57	470.75	1.44	64.50
			(18.97)	(0.04)	(18.88)	(0.05)	(1.89)
		0.18	479.50	1.17	497.00	1.13	64.75
			(48.64)	(0.11)	(30.19)	(0.06)	(4.42)
	7.5 s/7.5 s	Saline	1013.75	2.79	379.50	1.30	81.00
			(10.67)	(0.08)	(10.94)	(0.05)	(0.87)
		0.18	620.75	1.05	267.00	0.79	60.25
			(40.15)	(0.12)	(14.47)	(0.07)	(3.09)
G2	3 s/12 s	Saline	1229.50	1.54	176.50	1.55	32.50
			(19.69)	(0.08)	(22.14)	(0.05)	(3.01)
		0.18	928.25	1.13	231.75	1.08	53.00
			(57.94)	(0.04)	(25.86)	(0.13)	(6.53)
	12 s/3 s	Saline	128.25	1.53	1278.00	1.61	32.00
			(10.33)	(0.08)	(13.99)	(0.13)	(1.90)
		0.18	275.00	1.08	673.25	0.91	66.25
			(16.63)	(0.02)	(29.20)	(0.11)	(4.55)
	7.5 s/7.5 s	Saline	585.25	1.45	537.50	1.49	68.75
			(24.67)	(0.04)	(12.70)	(0.04)	(0.96)
		0.18	325.50	0.62	301.50	0.54	98.25
			(24.07)	(0.10)	(12.77)	(0.07)	(19.44)
G4	3 s/12 s	Saline	1167.25	2.14	224.75	1.10	39.75
			(8.97)	(0.03)	(9.58)	(0.13)	(0.89)
		0.18	887.75	1.65	343.25	1.20	64.50
			(6.84)	(0.04)	(25.74)	(0.05)	(2.36)
	12 s/3 s	Saline	272.00	2.20	1125.75	2.03	28.50
			(29.29)	(0.05)	(28.31)	(0.05)	(1.92)
		0.18	323.75	1.24	741.00	1.29	60.00
			(35.14)	(0.12)	(49.79)	(0.09)	(3.52)
	7.5 s/7.5 s	Saline	389.00	1.32	912.50	1.75	50.00
			(33.12)	(0.09)	(30.47)	(0.08)	(2.03)
		0.18	346.00	0.78	432.75	1.01	108.00
			(30.75)	(0.10)	(38.93)	(0.10)	(14.95)

(table continues)

			Left lever		Right lever		
Rat	Delay pair (Left/right)	PPX (mg/kg)	Responses	Local rate	Responses	Local rate	Changeover events
R1B1	3 s/12 s	Saline	1169.50	1.67	184.25	0.98	55.75
			(14.95)	(0.02)	(8.17)	(0.02)	(2.61)
		0.18	863.00	1.18	212.50	0.79	79.75
			(57.61)	(0.12)	(16.78)	(0.05)	(8.58)
	12 s/3 s	Saline	302.50	1.12	428.50	0.78	75.25
			(12.00)	(0.08)	(15.61)	(0.02)	(7.13)
		0.18	363.25	0.92	593.00	0.93	102.50
			(17.73)	(0.03)	(57.29)	(0.14)	(4.93)
	7.5 s/7.5 s	Saline	358.75	1.42	261.50	0.54	58.00
			(14.47)	(0.05)	(9.04)	(0.01)	(3.18)
		0.18	348.00	0.62	340.25	0.39	150.25
			(29.88)	(0.03)	(29.85)	(0.05)	(22.41)
R1B2	3 s/12 s	Saline	1180.75	1.81	190.75	1.05	42.50
			(13.24)	(0.01)	(6.70)	(0.03)	(1.60)
		0.18	725.50	0.80	158.00	0.92	28.50
			(41.56)	(0.02)	(13.02)	(0.03)	(1.68)
	12 s/3 s	Saline	795.00	1.72	412.00	1.26	60.00
			(19.46)	(0.02)	(11.97)	(0.01)	(2.26)
		0.18	362.75	0.94	417.50	0.69	40.50
			(14.90)	(0.02)	(8.26)	(0.01)	(1.25)
	7.5 s/7.5 s	Saline	946.50	1.92	312.00	1.06	58.00
			(17.34)	(0.04)	(5.09)	(0.03)	(1.70)
		0.18	414.75	0.89	298.75	0.81	36.25
			(20.49)	(0.03)	(13.52)	(0.03)	(4.64)
R1B3	12 s/3 s	Saline	305.25	3.19	1121.00	3.54	30.00
			(20.67)	(0.07)	(18.30)	(0.10)	(1.62)
		0.18	386.50	1.90	997.50	1.58	45.00
			(31.82)	(0.14)	(28.84)	(0.11)	(2.50)
	3 s/12 s	Saline	925.50	3.14	485.50	2.77	37.50
			(18.41)	(0.07)	(17.76)	(0.03)	(1.03)
		0.18	768.50	1.21	340.25	1.16	54.25
			(18.55)	(0.09)	(32.95)	(0.10)	(4.13)
	7.5 s/7.5 s	Saline	783.75	2.99	628.00	2.77	44.75
			(6.91)	(0.06)	(7.75)	(0.03)	(0.82)
		0.18	323.75	0.82	352.75	0.84	50.50
			(15.07)	(0.03)	(13.34)	(0.06)	(2.25)
B1R1	12 s/3 s	Saline	442.50	1.95	948.50	2.34	64.75
			(14.10)	(0.02)	(13.95)	(0.05)	(2.41)
		0.18	286.00	0.99	611.25	1.01	56.00
			(10.11)	(0.06)	(34.38)	(0.06)	(2.67)

(table continues)

Rat	Delay pair (Left/right)	PPX (mg/kg)	Left lever Responses	Left lever Local rate	Right lever Responses	Right lever Local rate	Changeover events
	3 s/12 s	Saline	1004.00	2.20	395.50	2.40	54.75
			(7.87)	(0.07)	(8.00)	(0.12)	(4.08)
		0.18	543.50	0.80	293.00	0.92	47.25
			(42.62)	(0.05)	(27.29)	(0.08)	(1.98)
	7.5 s/7.5 s	Saline	771.25	2.01	617.25	2.09	71.75
			(13.42)	(0.10)	(10.65)	(0.08)	(5.02)
		0.18	408.50	0.83	446.00	1.14	60.25
			(18.32)	(0.02)	(16.42)	(0.04)	(2.46)
B1R2	12 s/3 s	Saline	502.00	2.13	886.25	2.17	77.00
			(7.42)	(0.01)	(7.58)	(0.04)	(2.85)
		0.18	368.00	1.31	663.25	1.30	70.25
			(7.88)	(0.01)	(22.84)	(0.10)	(1.95)
	3 s/12 s	Saline	1047.50	2.16	340.25	1.50	62.25
			(12.42)	(0.08)	(10.68)	(0.10)	(5.25)
		0.18	492.00	1.06	265.00	1.03	63.75
			(42.33)	(0.05)	(21.60)	(0.05)	(5.13)
	7.5 s/7.5 s	Saline	825.25	2.57	568.00	1.84	82.00
			(7.35)	(0.08)	(7.06)	(0.05)	(2.52)
		0.18	327.25	0.90	282.00	0.89	64.00
			(26.82)	(0.17)	(25.79)	(0.05)	(3.52)
B1R3	12 s/3 s	Saline	305.25	1.90	1093.75	2.58	53.25
			(10.16)	(0.08)	(8.78)	(0.07)	(2.48)
		0.18	364.75	1.40	904.75	1.76	66.00
			(26.75)	(0.03)	(29.68)	(0.03)	(3.08)
	3 s/12 s	Saline	1158.25	2.64	251.25	2.04	48.50
			(15.86)	(0.03)	(16.13)	(0.06)	(4.25)
		0.18	825.00	1.47	427.00	1.51	73.50
			(17.51)	(0.05)	(6.31)	(0.02)	(3.88)
	7.5 s/7.5 s	Saline	835.25	2.49	562.00	2.37	78.75
			(17.20)	(0.08)	(17.12)	(0.04)	(2.13)
		0.18	485.00	1.05	421.75	1.30	86.00
			(14.39)	(0.09)	(15.32)	(0.07)	(11.59)

Note. Mean left and right lever response output, mean left and right local response rates, and mean changeover responses emitted in the final four sessions at each chronic PPX dose for individual rats in each delay condition. Standard error of the mean of the final four administrations per dose is in parentheses.

over the final four sessions at each chronic saline or PPX administration in each delay condition for each rat.

Figure 3-3 shows the effects of acute PPX on response perseveration. Overall, increasing the PPX dose decreased bout length; however, this effect depended on the terminal-link delay condition, significant dose x delay condition interaction, $F(2.45, 24.47) = 3.33$, $p < .05$, $\eta_G^2 = .07$. The simple main effect of dose was not investigated

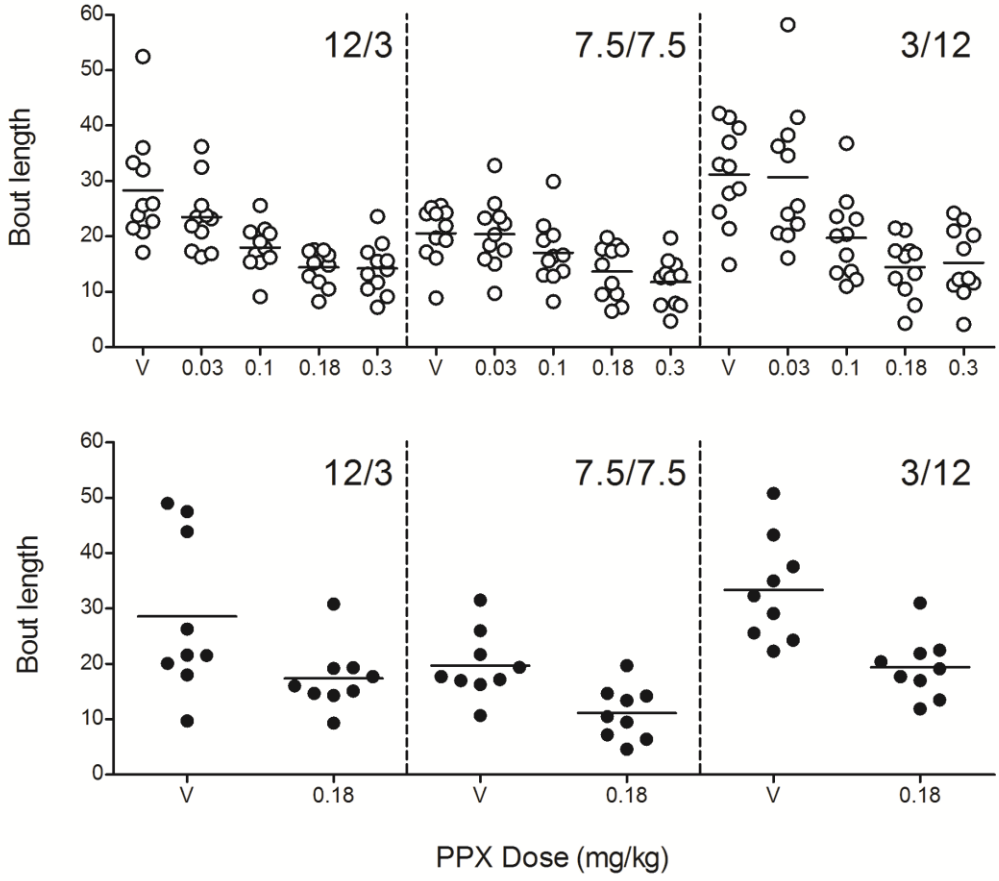

Figure 3-3. Bout length from each delay condition in the acute and chronic PPX assessments of Experiment 1. Acute and chronic data are shown in top and bottom panels, respectively. Each point represents an individual subject with solid lines representing group averages.

further because in only 11 out of 132 cases (9.84%) did PPX increase bout length above saline levels, many fewer instances than would have been expected had response perseveration influenced response allocation.

Relative to chronic saline, chronic PPX significantly reduced bout length, main effect of dose, $F(1, 8) = 22.09$, $p = .002$, $\eta_G^2 = .34$. Bout length did not differ significantly between acute and chronic PPX assessments ($p = .31$), although a significant interaction with delay condition was detected, $F(2, 16) = 5.33$, $p < .02$, $\eta_G^2 = .11$. Most importantly for the hypothesis that PPX increases the likelihood of response perseveration, in neither assessment did PPX significantly increase bout length. Thus, there was no evidence for a perseverative effect of PPX and the data were not analyzed further.

Figure 3-4 depicts left- and right-lever response rates, expressed as a proportion

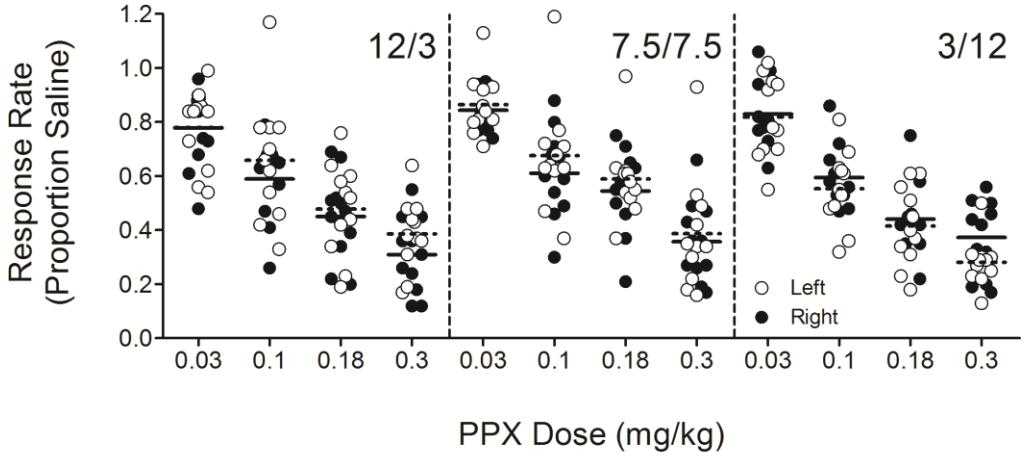

Figure 3-4. Left- and right-lever response rate (expressed as proportion of saline rate) from each delay condition in the acute PPX assessment of Experiment 1. Each point represents an individual subject, with dashed and solid lines representing group averages for left and right levers, respectively.

of saline rates, as a function of acute PPX dose. Regardless of the delay associated with either the left or right levers, acute PPX significantly reduced response rates, $F(3, 30) = 205.47$, $p < .001$, $\eta_G^2 = .59$; this effect was dose-dependent, significant linear contrast, $F(1, 10) = 678.37$, $p < .001$, $\eta_G^2 = .71$.

Discussion

Experiment 1 was designed to dissociate competing hypotheses regarding PPX-induced changes in sensitivity to relative reinforcer delay in studies previously assessing the drug effect in intertemporal choice procedures. Increased SS choice with acute PPX administration was observed by Madden et al. (2010) and, if sensitivity to relative reinforcer delay was affected, could have resulted from an increase in sensitivity to LL delays. Koffarnus et al. (2011) also observed an increase in SS choice at the highest PPX dose investigated (0.32 mg/kg), but the form of the drug effect in their study suggested a nonspecific impairment of stimulus control. In the present experiment, acute PPX administration dose-dependently decreased rats' sensitivity to relative terminal-link reinforcer delay in a concurrent-chains procedure. Chronic PPX (0.18 mg/kg) did not significantly affect sensitivity to relative reinforcer delay. Bias was also not significantly affected by the drug in either assessment. Alternative explanations for the drug's effects on previous intertemporal choice studies, namely response perseveration and rate dependent increases in selection of the SS reinforcer, were not supported.

That PPX decreased sensitivity to relative reinforcer delay is incompatible with the results of Madden et al. (2010). Decreased sensitivity to relative reinforcer delay is predicted to lead to more LL choices but Madden et al. (2010) reported the opposite. The

present findings are consistent with those of Koffarnus et al. (2011) and of the experiment presented in Chapter 2. In these studies, PPX flattened preference functions towards indifference in a manner resembling disruption of stimulus control of choice behavior. Impaired stimulus control could also manifest as a reduction in bias (log *b*), although biases were not apparent under nondrug conditions and therefore could not be reduced.

As noted in Chapter 2, poor discrimination of reinforcer delays in intertemporal choice situations should increase LL choice if sensitivity to differences in reinforcer amount remains intact. However, no previous study has reported that PPX increases LL choice. Thus, impaired delay discrimination does not alone provide a satisfactory explanation for the behavioral patterns exhibited across these studies. Perhaps PPX impairs discrimination of the response-reinforcer contingency (i.e., observing/ remembering which response fulfilled the reinforcer contingency). Disruption of this elementary discrimination may equalize response allocation in both intertemporal choice and concurrent-chains procedures and was therefore the focus of Experiment 2.

Experiment 2

Introduction

According to Davison and Nevin (1999), choice between two concurrently available alternatives is affected by the discriminability of the stimulus features that differentiate the alternatives. As a given stimulus feature (e.g., the color of cue lights that signal the two options), becomes increasingly similar along a shared dimension,

discriminability is reduced to chance levels. Essentially, as the confusability of two stimuli increases, choice should approach indifference, or 50% choice. The shared profile of the findings of Chapter 2 and of Experiment 1–namely, reduced sensitivity to relevant stimulus features (reinforcer amount and delay in Chapter 2 and terminal-link delays in Experiment 1)–suggests a critical discrimination was disrupted by PPX administration.

One discrimination which, if disrupted, is capable of producing the PPX-induced disruptions seen in previous experiments is discrimination of the source of reinforcement or, more specifically, the response-reinforcer contingency (Davison & Jenkins, 1985). Once reinforcement is earned, the organism must discriminate the relation between its own behavior and production of the reinforcer. If PPX disrupts this discrimination, then reinforcement earned via the just-productive alternative could be misattributed to an unproductive alternative. The degree to which reinforcers are misattributed may also be influenced by stimulus features whose discrimination remains intact (e.g., reinforcer amount) or variables which may degrade the response-reinforcer contingency (e.g., delay to reinforcement). Evidence for the latter hypothesis is provided by research in the areas of memory and forgetting which has established the deleterious effects of intervening delays on discrimination performance (Blough, 1959; Chrobak & Napier, 1992; Etkin & D'Amato, 1969; Jans & Catania, 1980; Roberts, 1972b; Savage & Parsons, 1997; Wallace, Steinert, Scobie, & Spear, 1980; White, 1985).

In the context of an intertemporal choice, if discrimination of response-reinforcer contingencies is compromised following choice of the LL reinforcer and further degraded by the intervening delay to reinforcement, the frequency of future SS choices may

increase because LL reinforcers are misattributed as the result of a response on the SS alternative. By this logic, because SS reinforcers are delivered immediately, one might predict greater fidelity in attribution to the SS alternative. This hypothesis may explain the pattern of results seen by Madden et al. (2010), in which PPX administration increased SS preference against a baseline preference for the LL reinforcer, but did not affect preference when the SS was highly preferred under baseline conditions, perhaps due to a ceiling effect. This hypothesis could also account for the indifference observed by Koffarnus et al. (2011): At longer delays to the LL reinforcer, differential misattribution of LL reinforcers to the SS response would shift preference away from LL choices and toward indifference.

This hypothesis does not, however, provide a coherent account of the results of Chapter 2. In that experiment, under saline conditions rats preferred SS reinforcers at longer LL delays. The differential-misattribution hypothesis predicts that following PPX administration, LL reinforcers should have been misattributed to the SS alternative, thereby further increasing SS preference. This was not observed. Instead, in this range of delays choice shifted toward indifference; a pattern of results consistent with nondifferential misattribution of reinforcers to responses (i.e., a disruption of stimulus control).

In order to examine the effects of PPX on discrimination of response-reinforcer contingencies, Experiment 2 incorporated a procedure used by researchers interested in signal detection (McCarthy & Davison, 1986), as well as memory and forgetting (Jones & Davison, 1998): the symbolic matching-to-sample (SMTS) procedure (see below for

full description and quantitative modeling). Additionally, Experiment 2 restricted investigation to chronic PPX, as previous research has suggested that chronic administration reduces the likelihood of interference from nonspecific drug effects (Maj et al., 2000), which were likely present in the acute assessments conducted in Chapter 2 and Experiment 1 of the present paper.

Methods

Subjects. Twelve experimentally naïve male Wistar rats served as subjects and were treated identically to subjects serving in Experiment 1. Animal use was in accordance with the Institutional Animal Care and Use Committee (IACUC) of Utah State University.

Apparatus. Sessions were conducted in standard operant conditioning chambers housed within sound-attenuating cubicles (Med Associates Inc., St. Albans, VT). Located on either side of the front wall were two retractable side levers with stimulus lamps located above each lever. Centered between the levers was a food receptacle into which a pellet dispenser (Med Associates Inc.) delivered 45 mg nutritional rodent pellets (Bio-Serv, Frenchtown, NJ). On the opposite wall were two nose-poke operanda (left and right sides). The nose pokes were separated by a food receptacle serviced by an additional 45-mg pellet dispenser (Coulbourn Instruments, Whitehall, PA). Chambers were equipped with a white noise speaker and ventilation fan. All experimental events were coordinated and recorded via a PC.

Behavioral procedure. Experimental sessions consisted of 40 trials. For the first part of each trial (sample period), one of the levers was selected randomly without

replacement and inserted into the chamber accompanied by illumination of its stimulus lamp (20 trials per lever). A single response on this lever retracted the lever, extinguished its stimulus lamp and resulted in the delivery of 1 food pellet to the front receptacle. If a sample response did not occur within 15 s of lever insertion, the trial was terminated and counted as an omission.

Immediately following reinforcer deliveries to the front receptacle, discrimination of the response that produced reinforcement was assessed (comparison period). First, the stimulus lights located within the rear nose pokes were illuminated. Next, a conditional discrimination was required such that the rat needed to make a single nose poke to the nose poke operandum symbolically associated with the sample response (e.g., if the pellet was earned on left lever, choose left nose poke). Failure to emit a comparison response within 15 s of illumination of the nose poke lights resulted in trial termination and the trial being counted as an omission.

Correct responses extinguished all stimuli and resulted in the delivery of 1 food pellet to the rear receptacle. Incorrect responses produced the same series of events with a 0.5-s blackout taking the place of pellet delivery. Following each trial, a 30-s ITI occurred during which all stimuli were in the off-state.

For the first 20 sessions of the experiment, a correction procedure was implemented. During this period, trials in which samples were not identified correctly were repeated indefinitely until the correct discrimination was made. Sessions ended once 40 correct discriminations were made or two hours had elapsed. The correction procedure

was then removed for 10 sessions, after which the chronic PPX assessment began regardless of baseline accuracy.

Drug procedure. PPX (0.18 mg/kg) or saline vehicle was administered subcutaneously 10 minutes prior to every session for 14 consecutive sessions. After a 6-day no-injection washout period, a second repeated dosing regimen was initiated with the compound not administered in the first regimen (order counterbalanced across subjects).

Data analysis. Accuracy of rats' discriminations of sample responses was calculated primarily as the percentage of correct discriminations. For reasons discussed below, accuracy was also calculated according to a signal-detection model forwarded by McCarthy, Davison, and Jenkins (1982):

$$\log d = 0.5 * \log\left(\frac{R_{LL}}{R_{LR}} * \frac{R_{RR}}{R_{RL}}\right), \quad (10)$$

where R_{LL} is the number of left nose pokes having just obtained a reinforcer from the left lever (correct discrimination) and R_{LR} is the number of right nose pokes having just obtained a reinforcer from the left lever (incorrect discrimination); the same criteria apply to reinforcers earned from the right lever. By comparing accuracy following both left and right samples, log *d*, a measure of the accuracy of response discrimination, was obtained. The calculation of log *d* included events from the final four sessions of each chronic dosing regimen (saline and PPX). Perfect discrimination between the contingencies (i.e., the correct nose poke was always chosen) was indicated by a ceiling log *d* value of 2.51; chance responding resulted in a log *d* of 0. A correction to Equation 10 suggested by Brown and White (2005) in which 0.25 is added to each response count was adopted. Compared to a percent correct measure, log *d* expresses accuracy proportionately and is,

therefore, less likely to be influenced by the total number of trials considered in the calculation. Bias (i.e., favoring a particular comparison response over another due to non-experimenter programmed variables) was calculated as log *b*:

$$\log b = 0.5 * \log\left(\frac{R_{LL}}{R_{LR}} * \frac{R_{RL}}{R_{RR}}\right), \quad (11)$$

Because data failed to satisfy assumptions of normality, related-samples Wilcoxon signed-rank tests (nonparametric equivalent of paired-samples *t* test) were used to test for PPX-induced differences in the accuracy with which rats discriminated response-reinforcer contingencies (log *d*), bias (log *b*), and omissions recorded during sessions. Effect sizes were calculated according to the method described by Field (2009).

Results

Behavioral measures are displayed in Table 3-5. Figure 3-5 (top left) shows that the accuracy with which rats correctly discriminated the sample response during the chronic saline regimen approached the maximum log *d* value (M = 2.20, SD = 0.33); 6 out of 12 rats discriminated the sample response with maximum accuracy. Chronic PPX (0.18 mg/kg) administration significantly reduced rats' accuracy on the discrimination task (M = 0.89, SD = 0.33), z = -3.06, $p < .01$, ES = .62. When calculated as the percentage of trials with correct discriminations (Figure 3-5, top right), mean accuracy corresponded to 99.27% (SD = 0.84) and 85.66% (SD = 7.21) for the saline and PPX regimens, respectively. Thus, chronic PPX administration reduced the accuracy with which rats discriminated the response-reinforcer contingencies by an average of 13.62% (SD = 7.27). PPX did not reduce accuracy on left- (M = 12.67, SD = 8.71) or right-lever (M = 14.51, SD = 8.43) trials differentially (not shown; $p > .5$).

Table 3-5

Parameter Estimates from Experiment 2

Rat	PPX (mg/kg)	Log *d*	Log *b*	Percent correct (%)	Percent left correct (%)	Percent right correct (%)	Omissions per session
B1	Saline	2.51	0.00	100.00	100.00	100.00	0.00 (0.00)
	0.18	0.84	0.00	88.41	87.69	87.50	5.75 (3.25)
B2	Saline	2.15	0.35	99.38	100.00	98.75	0.00 (0.00)
	0.18	0.86	0.03	88.13	88.75	87.50	0.00 (0.00)
B3	Saline	1.80	0.00	98.75	98.75	98.75	0.00 (0.00)
	0.18	0.89	-0.21	88.44	82.81	92.98	9.75 (5.45)
B4	Saline	2.51	0.00	100.00	100.00	100.00	0.00 (0.00)
	0.18	1.07	0.19	91.84	95.00	88.61	0.25 (0.25)
B5	Saline	1.80	0.00	98.75	98.75	98.75	0.00 (0.00)
	0.18	1.06	0.48	88.59	97.50	79.49	0.50 (0.29)
B6	Saline	2.02	-0.48	98.75	97.50	100.00	0.00 (0.00)
	0.18	1.07	0.42	89.22	97.22	81.82	2.75 (1.11)
G1	Saline	2.51	0.00	100.00	100.00	100.00	0.00 (0.00)
	0.18	1.65	-0.84	93.20	87.01	100.00	1.50 (1.50)
G2	Saline	2.51	0.00	100.00	100.00	100.00	0.00 (0.00)
	0.18	0.34	-0.01	59.65	68.42	69.57	19.00 (5.80)
G3	Saline	2.51	0.00	100.00	100.00	100.00	0.00 (0.00)
	0.18	0.43	0.02	72.84	73.91	72.22	19.50 (4.66)
G4	Saline	1.88	-0.63	97.50	95.00	100.00	0.00 (0.00)
	0.18	0.65	0.00	82.16	82.35	82.14	24.50 (3.77)
G5	Saline	1.67	0.13	98.13	98.75	97.50	0.00 (0.00)
	0.18	0.73	0.01	83.80	84.85	84.42	4.25 (1.70)
G6	Saline	2.51	0.00	100.00	100.00	100.00	0.00 (0.00)
	0.18	1.07	-0.07	92.24	91.14	93.42	1.25 (0.63)

Note. Overall accuracy (calculated as log *d* and percentage correct), bias (log *b*), accuracy on left and right sample trials, and mean number of omissions per session at each chronic PPX dose for individual rats. Standard error of the mean of the final four administrations per dose is in parentheses.

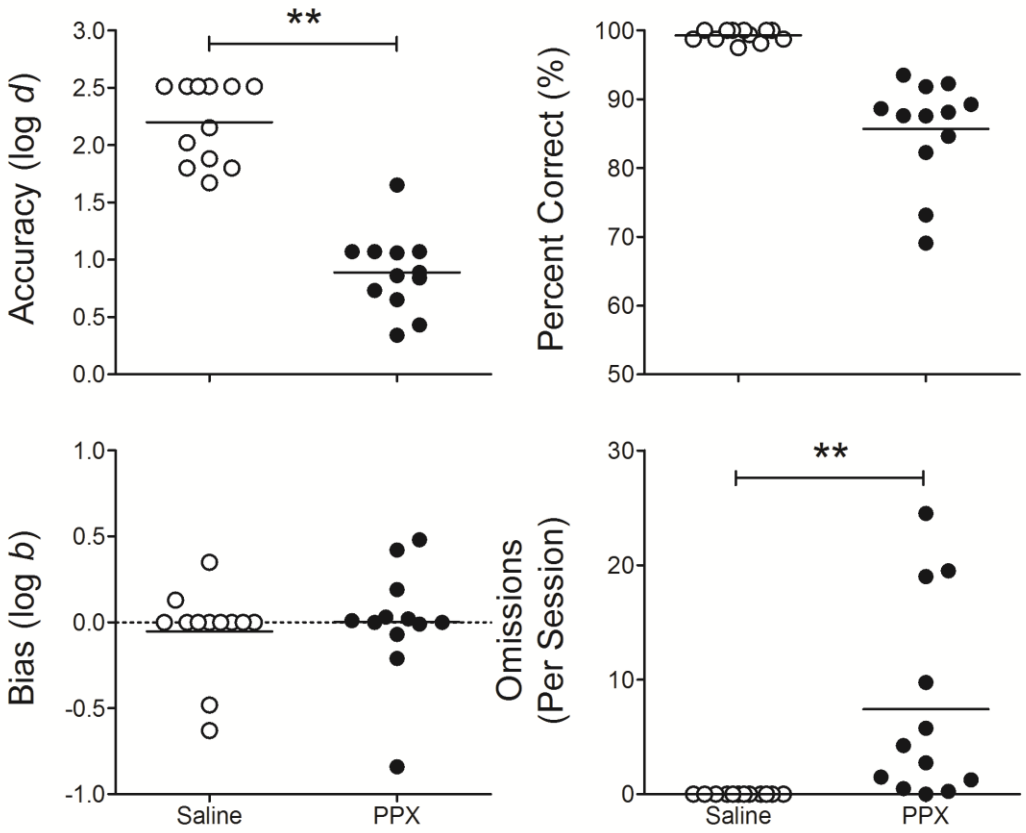

Figure 3-5. Effects of chronic saline and PPX administration on behavioral measures in Experiment 2. Top left: Accuracy of rats' discrimination of the response-reinforcer contingencies as log *d* (see text). Top right: The same accuracy data calculated as percentage of correct discriminations. Bottom left: Bias for a given comparison response independent of experimenter-programmed variable calculated as log *b* (see text). Bottom right: Mean number of omissions per session. Double asterisks identify behavioral measures significantly affected by PPX administration at the $p < .01$ level.

The bottom left graph in Figure 3-5 shows that bias, measured as log *b*, was minimal (i.e., near zero) during the chronic saline (M = -0.05, SD = 0.25) and PPX (M = 0.00, SD = 0.32) regimens and was not significantly affected by drug administration.

Figure 3-5 (bottom right) also depicts the mean number of omissions recorded per session. During the last four sessions of the chronic saline regimen, no omissions

occurred. Conversely, the frequency of omissions increased significantly during the chronic PPX regimen (M = 7.42, SD = 8.36), z = -2.93, p < .01, ES = .60.

Discussion

Experiment 2 explored the possibility that PPX reduces rats' discrimination of response-reinforcer contingencies. Rats were trained to symbolically relate samples (left or right levers) to arbitrary comparisons (left or right nose poke operanda). Accuracy of rats' discrimination of the response-reinforcer contingencies was perfect for half of the subjects and nearly so for other subjects under chronic saline conditions. At the group level, chronic PPX (0.18 mg/kg) administration reduced accuracy of the discrimination and increased the frequency of omitted trials.

Perfect accuracy of the discrimination of the source of reinforcement in the SMTS task indicates that subjects correctly attend to and identify contingencies relating the productive response to the reinforcer delivered to the centralized food receptacle. Conversely, the decrements observed with PPX administration suggest that during drug sessions subjects occasionally misattributed reinforcement obtained from the just-productive response to the nonproductive response. Impairment of the discrimination, however, was not so severe as to completely disrupt discrimination (i.e., a log d value of 0, or 50% accuracy). Instead, accurate discriminations decreased by approximately 14%.

Moderately impaired discrimination of response-reinforcer contingencies observed in Experiment 2 may in part explain the results of Experiment 1. Procedural differences between the two experiments, however, suggest that this discrimination might be less impaired in Experiment 1 than in Experiment 2. First, a COD was programmed in

Experiment 1 to discourage rapid switching between the left and right levers. As a result, rats tended to engage in response bouts on a single lever prior to being granted terminal-link access. When tasked with discriminating response-reinforcer contingencies, extended exposure to the ultimately-productive response (in this case, by means of a response bout) may facilitate accuracy, as reported in nonhuman studies of memory in which sample repetition or duration was manipulated (Grant, 1976; Roberts, 1972a; White & Wixted, 1999). Second, upon earning terminal-link access in Experiment 1, the stimulus lamp above the productive alternative (left or right lever) remained illuminated, providing a stimulus that bridged the delay to reinforcement that might otherwise impair discrimination of the response-reinforcer contingency. Indeed, a small literature suggests that the effects of *d*-amphetamine, an indirect dopamine agonist, on intertemporal choice are modulated by the presence or absence of a stimulus during the LL delay (Cardinal, Robbins, & Everitt, 2000; but see, Helms, Reeves, & Mitchell, 2006). By comparison, the deficit in accuracy may have been more pronounced in the SMTS procedure in Experiment 2 because only a single sample response was required and there were no stimuli programmed that could have bridged the response and reinforcer delivery, the combination of which predicts a greater likelihood for disrupted discrimination.

The present findings suggest that PPX-induced changes in intertemporal choice (Chapter 2; Koffarnus et al., 2011; Madden et al., 2010) may have been affected by disruptions in response-reinforcer contingency discrimination. As discussed above, the context in which this discrimination occurs may determine the severity of disruption. One variable known to affect the accuracy of discrimination is the extent to which differential

outcomes are provided for each response (Jones & White, 1994; Nevin, Ward, Jimenez-Gomez, Odum, & Shahan, 2009; Savage & Parsons, 1997). Therefore, by virtue of differences in reinforcer delay and amount provided for each choice response (i.e., differential outcomes), the accuracy of response-reinforcer contingency discrimination in intertemporal choice should be less prone to disruption than accuracy in Experiment 1, which featured only differences in delay to reinforcement. Moreover, the degree to which stimulus features differ from one another along a common dimension (i.e., discriminability) should influence the extent of disruption. Because reinforcer delays in Experiment 1 were more similar (3 vs. 12 s) than reinforcer delays in Chapter 2 (0.01 s vs. 10, 20, or 30 s), performance in Experiment 1 may have been more easily disrupted than intertemporal choice in Chapter 2.

According to the differential-outcomes effect, differences in reinforcer amount may facilitate response-reinforcer contingency discrimination in an intertemporal choice situation (e.g., 3 pellets always follow a right-lever response). However, amount discrimination could also be impaired by PPX administration. As outlined in Figure 1-4, if a drug disrupts amount sensitivity in an intertemporal choice task, then according to Equation 8, response allocation will not as strongly favor the larger of the two reinforcer amounts. As sensitivity to relative reinforcer amount is increasingly impaired, intertemporal choice should become increasingly determined by differences in reinforcer delays and preference should shift toward the more immediate (SS) reward. Furthermore, if PPX disrupts amount discrimination, then the differential outcomes that may have otherwise facilitated discrimination of the source of reinforcement may be rendered

ineffective. In such a scenario, disruption of amount discrimination may exacerbate the disruption of response-reinforcer contingencies. For these reasons, examining the effects of chronic PPX on amount discrimination was the goal of Experiment 3.

Experiment 3

Introduction

In the absence of delays to reinforcement, organisms exhibit natural preferences for larger over smaller reinforcer amounts (e.g., initial-block choice in Chapter 2 and Koffarnus et al., 2011). In an intertemporal choice, however, preference for a larger amount of reinforcement competes with preference for immediate over delayed reinforcement. If small and large reinforcer amounts are perfectly discriminated in an intertemporal choice, then the difference in reinforcer amounts will have its maximal effect on choice. If, however, amount discrimination is compromised, the ratio of the two reinforcer amounts may appear subjectively less than is objectively the case as reflected in response allocation. With differences in reinforcer amount effectively minimized, intertemporal choice is free to be governed almost entirely by differences in reinforcer delay. Under these circumstances, choice for the more immediate SS reinforcer would be expected to increase. Additionally, poor amount discrimination may further impair other discriminations germane to intertemporal choices, such as the contingency relating which response produced a particular amount of reinforcement (i.e., response-reinforcer contingency).

Impaired amount discrimination provides an additional and perhaps complementary explanation for the findings of PPX-induced increased SS choice in intertemporal choice experiments. For instance, in Koffarnus et al. (2011) and in Chapter 2 of the present research, high PPX doses (0.1-0.32 mg/kg) increased SS choice in the initial trial block in which rats chose between small and large reinforcer amounts, both available immediately. Because nondrug choice favored almost exclusively the larger reinforcer in both cases, the direction of the PPX-induced shift in preference for this alternative suggests that discrimination of reinforcer amounts may have been compromised. Diminished amount discrimination could also explain the results of the Madden et al. (2010) study in which PPX increased preference for the SS reinforcer in a dose-dependent manner. This increase in impulsive choice could be due to increased sensitivity to relative reinforcer delay (a hypothesis not supported by Experiment 1) or a diminished ability to discriminate large from small reinforcers. If PPX impaired amount discrimination and thus made subjectively more equal the reinforcer amounts (1 and 3 food pellets), then choice would be more strongly influenced by the intact difference in reinforcer delay and favor the SS reinforcer. The same could be said for Madden and others' (2010) "impulsive" baseline, although a ceiling effect on SS choice may have prevented the detection of this effect.

To investigate the hypothesis that PPX impairs rats' discrimination of different reinforcer amounts, Experiment 3 used the SMTS procedure employed in Experiment 2. The experimental question could not be evaluated using the concurrent-chains procedure of Experiment 1 because diminished amount discrimination is predicted to flatten the

matching function in a manner formally identical to a general impairment of stimulus control, an outcome which would fail to dissociate the two accounts. As discussed below, the SMTS procedure does not require rats to discriminate the source of reinforcement–only the reinforcer amount obtained–and is therefore less confounded by impairments of other relevant discriminations. In our experiment, rats received response-independently either small or large food amounts (1 or 3 food pellets), which served as the sample stimulus. Following consumption, rats selected a left or right lever to report which sample was provided. The resulting measures of accuracy provided an individualized baseline performance against which the effects of chronic PPX were then compared.

Methods

Subjects and apparatus. The subjects and apparatus were those used in Experiment 2. A head entry detector (ENV-254-CB, Med Associates Inc., St. Albans, VT) was installed in the front pellet receptacle between Experiments 2 and 3 to precisely coordinate the onset of comparison stimuli. Animal use was in accordance with the Institutional Animal Care and Use Committee (IACUC) of Utah State University.

Behavioral procedure. Experimental sessions consisted of 40 trials. For the first part of each trial, one of two food reinforcer amounts (1 or 3 pellets) was selected randomly without replacement to be delivered response-independently into the front receptacle (20 trials per reinforcer amount; sample period). Following consumption and an exit response from the food receptacle, an SMTS task was used to assess discrimination of the 1- and 3-pellet reinforcer amounts (comparison period). First, the left and right levers were inserted and their associated stimulus lights were illuminated.

Next, a conditional discrimination was required such that the rat needed to press the lever symbolically associated with the sample reinforcer amount (e.g., if 3 pellets were delivered, choose left lever); symbolic relations were counterbalanced across rats. Correct responses extinguished all stimuli and resulted in the delivery of 1 food pellet to the front receptacle. Incorrect responses produced the same series of events with a 0.5-s blackout taking the place of pellet delivery. Following each trial, a 30-s ITI occurred during which all stimuli were in the off-state. Failure to emit a comparison response within 15 s of lever activation resulted in trial termination and the trial being counted as an omission.

For the first 10 sessions of the experiment, a correction procedure was implemented. During this period, trials in which samples were not identified correctly were repeated indefinitely until the correct discrimination was made. Sessions ended once 40 correct discriminations were made or 2 hours had elapsed. The correction procedure was then removed for 10 sessions, after which the chronic PPX assessment began regardless of baseline accuracy.

Drug procedure and data analysis. With the exception of the order of saline and PPX regimens (opposite those experienced in Experiment 2), drug procedures and analytical techniques were identical to those used in Experiment 2. Log *d* and log *b* calculations were modified from Equations 10 and 11 to yield amount-specific formulations:

$$\log d = 0.5 * \log\left(\frac{R_{SS}}{R_{SL}} * \frac{R_{LL}}{R_{LS}}\right), \quad (12)$$

$$\log b = 0.5 * \log\left(\frac{R_{SS}}{R_{SL}} * \frac{R_{LS}}{R_{LL}}\right). \quad (13)$$

In Equations 12 and 13, R_{SS} and R_{LL} correspond to trial counts for correct discriminations of small and large samples, respectively; R_{SL} and R_{LS} are trials on which subjects reported incorrectly small and large samples. Statistical comparisons used Wilcoxon signed-ranks tests with an alpha level of .05. Effect sizes were calculated according to the method described by Field (2009).

Results

Behavioral measures are displayed in Table 3-6. Figure 3-6 (top left) shows that chronic PPX (0.18 mg/kg) administration significantly reduced the accuracy of rats' discrimination of the different reinforcer amounts (log *d*; M = 0.77, *SD* = 0.26), *z* = -2.63, $p < .01$, ES = .54. Calculated as the percentage of trials on which a correct amount discrimination occurred, rats reported the sample correctly on 93.3% (*SD* = 2.99) and 84% (*SD* = 7.09) of trials in the chronic saline and PPX regimens, respectively. Thus, PPX reduced accuracy of the discrimination from nondrug levels by an average of 9.23% (*SD* = 8.40).

When considered separately, the accuracy with which rats reported small reinforcer sample trials (*M* = 95.11, *SD* = 4.20) was significantly higher than accuracy on large reinforcer sample trials (*M* = 91.47, *SD* = 3.66), *z* = -2.25, $p < .03$, ES = .46 (data not shown). PPX administration reduced accuracy from nondrug levels by 11.26% (*SD* = 8.44) and 7.76% (*SD* = 11.74; $p > .13$) to 83.95% (*SD* = 7.57) and 83.49% (*SD* = 11.86) in small and large sample trials, respectively.

As shown in Figure 3-6 (bottom left), rats were biased in favor of reporting that the sample reinforcer was small (i.e., positive bias) under saline conditions. Chronic PPX

Table 3-6

Parameter Estimates from Experiment 3

Rat	PPX (mg/kg)	Log *d*	Log *b*	Percent correct (%)	Percent left correct (%)	Percent right correct (%)	Omissions per session
B1	Saline	1.16	0.00	93.75	93.75	93.75	0.00 (0.00)
	0.18	0.74	-0.18	84.08	78.75	89.61	0.75 (0.65)
B2	Saline	1.12	0.42	90.63	97.50	83.75	0.00 (0.00)
	0.18	0.94	0.21	89.24	93.75	84.62	0.50 (0.43)
B3	Saline	1.72	0.78	95.00	100.00	90.00	0.00 (0.00)
	0.18	0.30	0.26	69.91	78.67	52.63	11.75 (2.10)
B4	Saline	0.89	0.00	88.75	88.75	88.75	0.00 (0.00)
	0.18	0.90	0.10	89.03	91.25	86.67	1.25 (0.65)
B5	Saline	1.25	0.00	95.00	95.00	95.00	0.00 (0.00)
	0.18	1.21	-0.05	94.38	93.75	95.00	0.00 (0.00)
B6	Saline	1.04	-0.04	91.88	91.25	92.50	0.00 (0.00)
	0.18	0.63	-0.11	80.67	76.92	84.72	2.50 (0.83)
G1	Saline	1.13	0.24	92.50	96.25	88.75	0.00 (0.00)
	0.18	1.12	0.04	93.13	93.75	92.50	0.00 (0.00)
G2	Saline	1.83	0.68	96.88	100.00	93.75	0.00 (0.00)
	0.18	0.66	-0.07	82.07	79.75	84.85	3.75 (0.54)
G3	Saline	1.25	0.00	95.00	95.00	95.00	0.00 (0.00)
	0.18	0.68	-0.12	82.35	78.48	86.49	1.75 (0.89)
G4	Saline	1.31	0.06	95.63	96.25	95.00	0.00 (0.00)
	0.18	0.50	-0.08	75.95	72.50	79.49	0.50 (0.43)
G5	Saline	1.76	0.75	95.63	100.00	91.25	0.00 (0.00)
	0.18	0.58	0.21	79.85	86.25	70.37	6.50 (0.90)
G6	Saline	0.86	0.03	88.13	88.75	87.50	0.00 (0.00)
	0.18	0.96	-0.27	87.39	83.54	95.00	10.25 (1.71)

Note. Overall accuracy (calculated as log *d* and percentage correct), bias (log *b*), accuracy on small and large sample trials, and mean number of omissions per session at each chronic PPX dose for individual rats. Standard error of the mean of the final four administrations per dose is in parentheses.

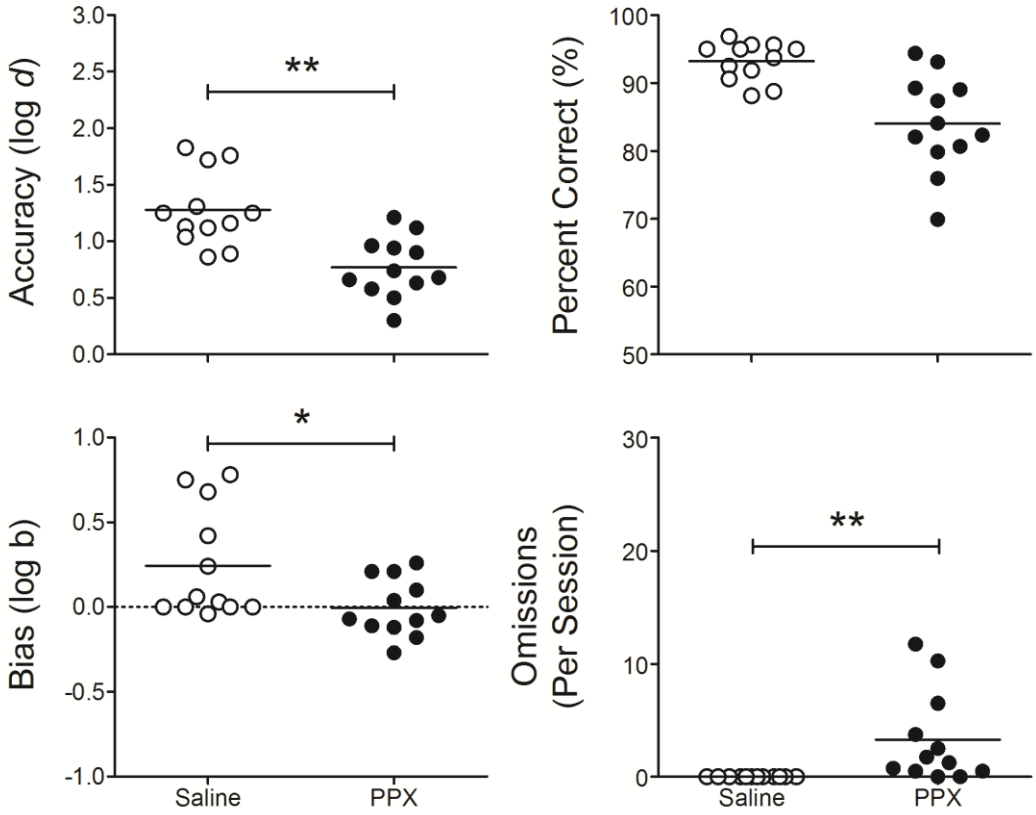

Figure 3-6. Effects of chronic saline and PPX administration on behavioral measures in Experiment 3. Top left: Accuracy of rats' discrimination of the reinforcer (i.e., sample) amount calculated as log *d* (see text). Top right: The same accuracy data calculated as percentage of correct discriminations. Bottom left: Bias for a given comparison response independent of experimenter-programmed variable calculated as log *b* (see text). Bottom right: Mean number of omissions per session. Single and double asterisks identify behavioral measures significantly affected by PPX administration at the $p < .05$ and $p < .01$ level, respectively.

administration significantly reduced this bias (M = -0.01, SD = 0.17), z = -2.82, $p < .01$, ES = .58.

As in Experiment 2, rats completed trials reliably under chronic saline conditions. The bottom right graph in Figure 3-6 shows that the frequency of omissions per session

increased significantly with chronic PPX administration (M = 3.29, SD = 4.06), z = -2.81, p < .01, ES = .57.

Discussion

Experiment 3 was conducted to assess the effects of chronic PPX administration on rats' discrimination of small and large reinforcer amounts. Chronic PPX administration reduced rats' discrimination of the reinforcer amounts, affecting the percentage of small-sample trials matched correctly to a greater extent than large-sample trials. PPX also reduced nondrug bias, but increased the frequency of omitted trials.

That PPX reduced discrimination of different reinforcer amounts in the present experiment suggests an additional behavioral mechanism by which the drug might influence intertemporal choice. As discussed above, if an organism perceives smaller and larger reinforcer amounts as subjectively more similar following PPX administration, and discrimination of reinforcer delays is preserved, then choice is predicted to increasingly favor the SS reinforcer because this alternative is delivered immediately. Compared to the magnitude of the disruptions in choice observed by Madden et al. (2010), Koffarnus et al. (2011), and in Chapter 2–that is, disruptions sufficient to shift choice toward 50% or indifference–the disruption of amount discrimination in Experiment 3 was modest. That a disruption of this magnitude alone accounts for the collective results is unlikely, although differences in the duration of PPX administration (acute vs. chronic) may partially account for the discrepancy. It could also be the case that poor amount discrimination exacerbates the discrimination of response-reinforcer contingencies in intertemporal choice situations. That is, if reinforcer amounts serve discriminative functions that aid the

organism in relating reinforcement earned to the response that produced reinforcement, then the absence of differential stimuli may further reduce accurate discrimination of operative contingencies. Even so, the formal manner in which disruption of amount discrimination interacts with disruption of response-reinforcer contingency discrimination is unclear and remains a point of speculation.

General Discussion

Across three experiments, putative behavioral mechanisms underlying the effects of acute and chronic PPX on intertemporal choice were investigated in an effort to provide a unified explanation for the divergent findings of Madden et al. (2010), Koffarnus et al. (2011), and Chapter 2. Those divergent findings are as follows:

1. Madden et al. (2010) reported that PPX (0.1-0.3 mg/kg) increased SS choice in a baseline condition of nondrug LL reinforcer preference, but not in a control condition of nondrug SS reinforcer preference;
2. Koffarnus et al. (2011) and Chapter 2 reported that PPX (0.1., 0.18, 0.3, and 0.32 mg/kg) increased preference for the SS reinforcer primarily when the larger reinforcer was not delayed (0 s trial block of the increasing-delay procedure) and generally shifted preference toward indifference (50% choice) in subsequent trial blocks.

In Chapter 3, behavioral processes relevant to intertemporal choice were experimentally isolated to quantify the effect of PPX on each process independently. To the extent that the effects observed across these experiments generalize to the more complex procedural arrangements characterizing intertemporal choice studies, the present

research may be in a position to explain why PPX produces the divergent profile of behavioral outcomes summarized above.

The logic outlined in Figure 1-3 suggests that Finding 1 could be the product of increased sensitivity to relative reinforcer delays to the LL and SS reinforcers. That is, increased delay sensitivity means the value of the LL reinforcer would be discounted more severely, resulting in increased preference for the SS reinforcer. This account was not supported by the results of Experiment 1. Instead, sensitivity to relative reinforcer delay was *decreased* by acute PPX, whereas chronic PPX did not affect sensitivity. Thus, no evidence was obtained to suggest that Finding 1 is the product of hypersensitivity to reinforcer delay. Rather, the manner in which delay sensitivity was affected by PPX suggests a disruption of stimulus control over choice behavior, an account consistent with Finding 2.

Experiments 2 and 3 were designed to investigate specific components of stimulus control that may have been disrupted by chronic PPX. Discriminated performance requires that the organism accurately characterize the contingency relating the response and the reinforcer it produces. If the accuracy of this discrimination was impaired in Experiment 1 (as well as in previous intertemporal choice studies), some reinforcers would be attributed falsely to the other programmed operant responses. This hypothesis was supported in Experiment 2 as chronic PPX administration modestly decreased the accuracy of rats' discrimination of a simple response-reinforcer contingency. Theoretically, the magnitude of such a disruption should depend upon the initial discriminability of the response alternatives. In Experiment 1, wherein the delays

to reinforcement were more similar (e.g., 3 vs. 12 s) than in traditional intertemporal choice studies (e.g., 0.01 vs. 10 s), it seems likely that misattribution was undifferentiated and therefore responsible for the progressive flattening of the matching function (although this effect was not seen with chronic PPX). Impairments in response-reinforcer contingency discrimination might also be accentuated by the presence of a delay separating the response from the reinforcer, as is the case with LL reinforcers. As a result, it may be more likely that LL reinforcers are misattributed to the SS choice response than vice versa. Differential misattribution of LL reinforcers could explain Findings 1 and 2. In both cases, SS choice was increased by PPX, although with Finding 2 the drug-induced shift was more indicative of a loss of stimulus control as the preference functions of Koffarnus et al. (2011) and Chapter 2 shifted toward indifference. The upward shift in LL choice at longer LL delays in Chapter 2 is not, however, consistent with the differential-misattribution hypothesis and instead suggests that reinforcers were misattributed with greater equality across the response alternatives.

An alternative explanation for Findings 1 and 2 was that rats' discrimination of differences in reinforcer amounts was disrupted by PPX, and the results of Experiment 3 revealed such a disruption. If reinforcer amounts are discriminated imperfectly, then intertemporal choice should be governed increasingly by differences in reinforcer delay (i.e., shifting preference toward the SS alternative, Finding 1), assuming this discrimination remains unaffected by the drug. Poor amount discrimination should also shift choice between a small and a large reinforcer toward indifference (Finding 2). Poor amount discrimination could also complement and exacerbate impairments in other

critical discriminations. For example, through the removal of discriminative stimuli (i.e., differences in reinforcer amount) the discrimination of response-reinforcer contingencies could be increasingly impaired in the absence of amount-related cues.

Across three experiments, the effects of PPX administration were most consistent with an account based on impaired stimulus control. That is, two behavioral processes likely to be recruited during intertemporal choice were negatively affected by acute and chronic PPX administration. Impairment of one these processes, amount discrimination, not only predicts greater SS choice but may also interact with and further impair another process, discrimination of response-reinforcer contingencies, through the removal of critical discriminative stimuli (i.e., differences in reinforcer amount). Confidence in this account should be tempered by five limitations of the present line of research. First, the procedures using in Experiments 1-3 were designed to isolate single behavioral processes; as such, the results of these experiments may not reveal the interactions between these processes that contributed to the findings of previous studies.

Second, the concurrent-chains procedure used in Experiment 1 was designed to isolate the effects of relative reinforcer delays on response allocation, but as demonstrated in Experiment 2 was likely also influenced by negative effects of PPX on discrimination of response-reinforcer contingencies. As such, the procedure may not have provided a valid index of the drug effect on delay sensitivity independent of other behavioral perturbations. Use of an SMTS procedure with delays as sample stimuli or a temporal bisection task (Church & Deluty, 1977) could have addressed this procedural shortcoming and resulted in an unadulterated measure of delay discrimination. Third, the

interpretation of previous findings based on impairments in discrimination processes involved in intertemporal choice provided above assumes in part that rats' discrimination of reinforcer delays remains intact to influence SS choice. Delay discrimination, however, was not explicitly assessed in the present study. Evidence to suggest that delay discrimination was not disrupted by PPX may come from Experiment 1, in which the same chronic PPX dose used in Experiments 2 and 3 did not significantly affect delay sensitivity. The lack of an effect on delay sensitivity, a behavioral process presumably based on an organism's ability to discriminate differences in reinforcer delays, suggests that delay discrimination may have remained intact following PPX administration. Despite this reasoning, if future studies reveal delay discrimination to be comparably impaired by PPX, then an interpretation based solely on impairment of amount and response-reinforcer contingency discriminations should be reconsidered, as global impairment of all discriminations predicts shifts in choice toward indifference in not only the increasing-delay procedure, but also the fixed-delay procedure used by Madden et al. (2010). Fourth, the chronic PPX dose of 0.18 mg/kg was chosen for examination because this dose produced behavioral effects in previous studies and with fewer omissions than the highest PPX dose (0.3 mg/kg). Investigation of chronic PPX is important for its resemblance to the regimens of clinical patients and should be parametrically examined across a wider dose range to accurately describe its effects at both low and high doses. Finally, Experiments 2 and 3 were conducted using the same subjects, a decision which may have reduced baseline accuracy in the amount discrimination task which was completed after the contingency discrimination task. Within-subject manipulations allow

researchers to reduce the number of subjects used, but may also compromise behavioral performances if historical variables are prone to interference.

Acute and chronic PPX affected behavioral processes potentially involved in intertemporal choice. Disruptions in two discrimination processes, response-reinforcer contingency and amount discrimination, were implicated as candidate behavioral mechanisms that could have produced the effects of PPX observed in previous intertemporal choice studies. An interpretation of the drug effect based on poor stimulus control may prove satisfactory for nonhuman experiments, but is unfortunately silent with respect to the occurrence of ICDs in clinical populations taking DA agonist medications like PPX. The procedures incorporated herein could easily be exported for use in humans and as such may further elucidate the generality of the behavioral mechanisms identified in the present work.

CHAPTER 4

SUMMARY AND CONCLUSIONS

The present set of experiments was designed to address two research questions related to the effects of the dopamine agonist medication PPX on rats' intertemporal choices as reported in Madden et al. (2010) and Koffarnus et al. (2011). Given the contradictory nature of these two findings, the first research question targeted the conditions under which the drug increased impulsive choice, but also nonspecifically disrupted behavior (as in Koffarnus et al., 2011). The second research question was aimed more broadly at the elucidation of behavioral mechanisms underlying the PPX effect on intertemporal choice. The ultimate goal of the research was to identify a behavioral process or processes affected by the drug that was capable of providing a common explanation for the mixed PPX literature.

Contrary to the report by Madden et al. (2010), Koffarnus et al. (2011) suggested that in addition to increasing the probability of SS choice, acute PPX might also disrupt choice behavior vis-à-vis stimulus control. To address this interpretation, the experiment presented in Chapter 2 attempted to systematically replicate the behavioral profile of PPX in an increasing-delay procedure similar to the one employed by Koffarnus et al. (2011). In an effort to decrease the likelihood that rats' choices were based on the passage of time within the session (rather than LL delays) or that choice reflected idiosyncratic lever biases, intermittent no-delay sessions and a centering response were added to the experimental protocol of Chapter 2. The results were formally consistent with those reported by Koffarnus et al. (2011): At high doses (0.1-0.3 mg/kg), acute PPX shifted

preference functions toward indifference, even in the initial trial block in which both 1- and 3-pellet reinforcers were available immediately. Furthermore, lower PPX doses (0.01 and 0.03 mg/kg) did not significantly affect choice. Relative to acute PPX, chronic PPX (0.1 and 0.3 mg/kg) did not disrupt initial-block choice, suggesting that repeated administration of the drug may ameliorate some of its disruptive effects on behavior.

Chapter 3 outlined an approach for identifying behavioral processes critical for intertemporal choice which, if affected by PPX, could have produced the pattern of PPX effects as reported by Madden et al. (2010), Koffarnus et al. (2011), and in Chapter 2. Experiment 1 tested the hypothesis that PPX increased rats' SS choice in the Madden et al. (2010) experiment by increasing their sensitivity to relative reinforcer delay. By examining response allocation in a concurrent-chains procedure and by modeling choice using the generalized matching law, Experiment 1 revealed that acute, but not chronic, PPX *decreased* rats' delay sensitivity, a finding inconsistent with an outcome of greater SS choice. An alternative explanation of these findings suggested that PPX disrupted the accuracy with which rats discriminated the response-reinforcer contingencies in the concurrent-chains procedure and possibly in intertemporal choice procedures as well. Experiment 2 used a symbolic matching-to-sample task to assess the chronic drug effect on rats' reporting of which response (left or right lever press) produced reinforcement. PPX decreased the accuracy of rats' discrimination of response-reinforcer contingencies. Experiment 3 evaluated an alternative but potentially complementary behavioral mechanism, specifically rats' discrimination of different reinforcer amounts (1 vs. 3 pellets) under chronic PPX conditions. In a similar manner to the way in which PPX

negatively affected the discrimination in Experiment 2, PPX decreased rats' accuracy with respect to amount discrimination. Collectively, these experimental findings emphasize the potential for PPX to impair discrimination processes thought to be critical in intertemporal choice.

Based on the results of Chapter 3, an explanation for the behavioral patterns induced by PPX as observed in previous intertemporal choice studies was provided based on impaired discrimination processes. Recall that in an intertemporal choice an organism's "default" preferences for immediate and greater quantities of reinforcement are set in conflict with one another by virtue of the SS and LL choice alternatives. An important consequence of this conflict is that if PPX impairs an organism's ability to discriminate differences in any one of these stimulus dimensions, then choice should become increasingly determined by any discrimination that remain unaffected by the drug. For instance, if PPX were to impair the discrimination of reinforcer amounts and delay discrimination remained intact (as suggested by the nonsignificant results of chronic administration on delay sensitivity in Experiment 1), then choice should increasingly favor the SS reinforcer because it is delivered relatively sooner than the LL reinforcer. However, if PPX *globally* impairs discrimination of the choice alternatives (i.e., subjects cannot discriminate relative amounts, delays, or other relevant differences), then choice should trend toward indifference (i.e., 50% choice). Empirically, although a dose-dependent trend toward indifference was observed by Koffarnus et al. (2011) and in Chapter 2, Madden et al. (2010) reported that only choice in one of two baseline conditions was affected by PPX. This latter finding suggests that if PPX does disrupt

choice behavior by impairing a discrimination required for intertemporal choice then at least one discrimination must remain intact to govern choice.

According to the results of Experiment 2, PPX negatively affects the discrimination of response-reinforcer contingencies in a manner that would appear to partially explain the decrease in delay sensitivity observed in Experiment 1. Research in nonhuman memory using similar matching-to-sample procedures demonstrates that by introducing a delay (i.e., retention interval) between the sample stimulus to be remembered and the comparison stimulus the accuracy of a discrimination is diminished (e.g., Chrobak & Napier, 1992; White, 1985). By extension, in an intertemporal choice, the LL delay separating the choice response from reinforcer delivery may decrease the likelihood that LL reinforcers are attributed correctly to the LL choice response. Alternatively, because SS reinforcers are delivered almost immediately after the choice response, the response-reinforcer contingency is unlikely to be as negatively affected by an intervening delay and SS reinforcers are putatively attributed with greater accuracy. As a result, a hypothesized outcome of impaired discrimination of response-reinforcer contingencies (i.e., misidentification of the source of obtained reinforcement) is that LL reinforcers are differentially misattributed to the SS choice response, but not vice versa. Once misattributed, perhaps in the course of experiencing forced-choice trials, misattributed LL reinforcers may artificially inflate the frequency of SS choice.

Along with delay to reinforcement, the amount of reinforcement delivered for each alternative also differs in an intertemporal choice. If an organism poorly discriminates response-reinforcer contingencies as the results of Experiment 2 suggest,

then intact discrimination of the different reinforcer amounts may provide a supplemental discriminative stimulus to guide future choices. That is, in the event that a LL delay decreases the likelihood that an organism correctly attributes the LL reinforcer to the LL choice response, then the intact discrimination of the LL reinforcer amount (e.g., 3 pellets) upon its delivery may counteract the impairment in contingency discrimination. However, as was demonstrated in Experiment 3, PPX also disrupted rats' discrimination of reinforcer amount (1 vs. 3 pellets). Such a drug effect has two apparent consequences on choice behavior. First, if reinforcer amounts are less than perfectly discriminated in an intertemporal choice, then choice may become increasingly dependent upon differences in reinforcer delay. Assuming that organisms prefer reinforcement to be delivered sooner rather than later, choice in drug sessions should increasingly favor the SS reinforcer. Second, if PPX impairs amount discrimination, then reinforcer amount differences cannot serve their discriminative function to aid the attribution of reinforcers to responses. As a result, given the predicted effects of LL delays on discriminated performance, occasional misattribution of LL reinforcers may further exacerbate an organism's tendency to select the SS choice alternative.

The above interpretation of PPX's effects on discrimination processes underlying intertemporal choice accords not only with the findings presented herein but also with previous reports of increased SS choice (Madden et al., 2010) and nonspecific disruption (Chapter 2; Koffarnus et al., 2011) following PPX administration. In the study by Madden et al. (2010), acute PPX significantly increased rats' choice for the SS reinforcer in a nondrug baseline condition of predominantly LL reinforcer choice. The opposite

effect (i.e., a decrease in SS choice) was not observed in a control baseline condition of predominantly SS reinforcer choice, a finding that indicated the absence of any nonspecific effects (e.g., poor discrimination between the choice alternatives). How do the results of Madden and others' (2010) study conform to an interpretation of the drug effect in terms of impaired discrimination processes? In the "self-control" baseline condition (i.e., predominant LL choice), a PPX-induced disruption of response-reinforcer contingency and amount discriminations is predicted to produce an increase in SS choice, which was observed as an increasing function of PPX dose. In the "impulsive" baseline condition (i.e., predominant SS choice), the same disruptions are also predicted to increase SS choice. However, because baseline preference already favored this alternative, the lack of a PPX effect on SS choice may have represented a ceiling effect. Thus, in both baseline conditions, SS choice is increased by the drug as a result of impaired contingency and amount discrimination as well as by intact discrimination of reinforcer delays.

Koffarnus et al. (2011) and Chapter 2 found that acute PPX shifted preference functions toward indifference, regardless of whether a LL delay was in effect or not. In the initial trial block, rats chose between 1 or 3 pellets delivered immediately. In saline sessions, data from this initial block reflected a near exclusive preference for the 3-pellet reinforcer. Following PPX administration, this preference was disrupted and trended toward indifference as a function of increasing PPX dose. Decreased preference for a larger over a smaller reinforcer in the absence of any delay is consistent with an interpretation involving some impairment of amount discrimination. If discrimination of

differences in reinforcer amounts was the only discrimination disrupted by the drug, then one might predict a shift in only the y-intercept of the preference functions. However, these researchers observed a progressive flattening of the preference function toward indifference. In the case of Koffarnus et al. (2011), SS choice increased following acute PPX (0.32 mg/kg) administration but only to the point of near indifference (i.e., 50% choice) in each trial block. Assuming that an impairment in the integrity of rats' discrimination of response-reinforcer contingencies may have also been present in their study, the misattribution of LL reinforcers would be expected to increase with longer duration LL delays. If misattributed to the SS choice response, future SS choice may result and shift the preference function toward indifference. Although this explanation is in agreement with the Koffarnus et al. (2011) findings, differential misattribution of LL reinforcers to the SS choice response cannot fully explain the results of Chapter 2. Contrary to the saline preference function generated by Koffarnus et al. (2011) which remained above indifference regardless of LL delay, the saline preference function generated in Chapter 2 was relatively steeper, achieving approximate indifference at a LL delay of 20 s and approaching 20% LL choice at a LL delay of 30 s. If delayed LL reinforcers are more likely to be misattributed to the SS choice response than vice versa, then an increase in SS choice should have been visible. Instead, preference functions became increasingly shallow and moved closer to indifference: At short LL delays, SS choice increased, while at longer LL delays, LL choice increased. Such an outcome is incompatible with an explanation based on the proposed interaction between contingency

discrimination and reinforcer delay and suggests instead that misattribution of reinforcers was undifferentiated (i.e., occurred at the same frequency for SS and LL reinforcers).

Several shortcomings and limitations of the present set of experiments are noteworthy. First, interpretation of the effects of PPX in the context of intertemporal choice and matching-to-sample procedures as unique to the particular drug may be unwarranted as a reference compound was not used for comparative purposes. Although research investigating less specific dopamine agonists (e.g., *d*-amphetamine) has demonstrated drug-related increases in SS choice (Cardinal et al., 2000; Evenden & Ryan, 1996; Hand, Fox, & Reilly, 2008) and disruption of stimulus control (Bizot, 1997; Çevik, 2003; Odum & Ward, 2007; Slezak & Anderson, 2009), there are reports of the same drug class exerting opposite behavioral effects (e.g., decrease in SS choice; Cardinal et al., 2000; Wade, de Wit, & Richards, 2000). Moreover, because PPX has affinity for both D_2 and D_3 receptor subtypes, the neurobiological specificity of the behavioral effects documented herein remains to be elucidated. Administration of D_2- or D_3-selective antagonists prior to PPX administration may facilitate this pursuit. Second, although not reported in the results, locomotor-slowing effects of PPX were evident in each of the experiments. Consistent with this finding, Johnson et al. (2011), Koffarnus et al. (2011), and Madden et al. (2010) all reported longer choice latencies in PPX sessions compared to the same measure in saline sessions. There has been some evidence to suggest that chronic PPX administration reduces the degree of locomotor effects (Chernoloz et al., 2009; Maj et al., 2000), which was the primary rationale for the incorporation of chronic dosing into the present set of experiments. However, even

repeated drug administration produced longer latencies to emit a centering response and select a choice alternative (Chapter 2) or report a sample stimulus (Experiments 2 and 3) than those recorded during saline sessions (data not shown). Despite measures taken to reduce its influence, this nonspecific drug effect may have interfered with or confounded behavioral measures of processes that may have contributed to intertemporal choice independent of hypolocomotor effects. Experimental preparations that minimize nonspecific effects of PPX may permit the investigation of relevant behavioral processes in the absence of any impairment in responding. Finally, an interpretation of the present findings based on impaired discrimination processes requires that the discrimination of relative reinforcer delays remains unaffected by PPX administration. Unfortunately, an evaluation of the drug effect on delay discrimination was not included in the research agenda and therefore the assertion that this discrimination is preserved under drug conditions lacks empirical support. As a proxy measure, sensitivity to, but not discrimination of, relative reinforcer delays was examined in Experiment 1 of Chapter 3. Although the extent to which sensitivity and discriminability of environmental stimuli are related constructs is beyond the scope of the present discussion (see Sutton, Grace, McLean, & Baum, 2008 for some consideration of this topic), future research could resolve the question by administering PPX prior to a task in which temporal intervals must be discriminated.

By attempting to isolate and describe the drug effect on individual behavioral processes in rats, the generality of the research findings is limited with respect to clinical populations prescribed the drug and reports of impulsive behavior (e.g., pathological

gambling, hypersexuality). Based on the nature of the clinical occurrences, it was assumed that they were behaviorally and theoretically consistent with the phenomenon of impulsive choice. As was mentioned in Chapter 1, however, impulsive choice represents but one facet of impulsivity. Impulsive *action*, the inability to inhibit a prepotent response, may capture just as easily the functional relations present in clinical instances of PPX-induced impulsivity. The inter-changeability of these constructs serves only to underscore the complexity and ambiguity inherent in the clinical setting.

A systematic program of research was designed and undertaken to identify the behavioral effects of the dopamine agonist medication PPX on intertemporal choice in rats. Quantitative analyses based on models of choice (generalized matching law), impulsivity (delay discounting), and discriminated performance (signal detection) proved useful in demonstrating PPX-related deficits in behavioral processes thought to be critical to decision-making. Based on the findings, it was concluded that disruptions in rats' discriminations of response-reinforcer contingencies and reinforcer amounts were primarily responsible for the effects of acute and chronic PPX in intertemporal choice experiments with rats (Koffarnus et al, 2011; Madden et al., 2010). Despite several shortcomings, the research findings emphasize the importance of elucidating behavioral mechanisms of drug action in an effort to understand complex clinical behavior.

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APPENDICES

Appendix A

Copyright Clearance for Koffarnus et al. (2011)

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Volume Number	22
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Type of Use	Dissertation/Thesis
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Title of your thesis / dissertation	Behavioral mechanisms of pramipexole-induced impulsivity: Discrimination processes underlying decision-making
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Appendix B

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- Madden, G. J., Johnson, P. S., Brewer, A. T., Pinkston, J. W., & Fowler, S. C. (2010). Effects of pramipexole on impulsive choice in male wistar rats. Experimental and Clinical Psychopharmacology, 18(3), 267-276. doi:10.1037/a0019244

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Appendix C

Permission Letters from Madden et al. (2010) co-authors

February 5, 2012

Patrick S. Johnson
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pastejohn@gmail.com

Dear Adam:

I am in the process of preparing my dissertation in the Department of Psychology at Utah State University. I am writing to seek permission to reuse data from a published article of which you are a co-author. The article is titled, "Effects of pramipexole on impulsive choice in male Wistar rats," and was published in *Experimental and Clinical Psychopharmacology* in June, 2010. Your co-authorship will be acknowledged in a footnote preceding the relevant dissertation chapter.

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Signature Adam Brewer

Printed Name Adam Brewer

Date 2-21-12

February 5, 2012

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Dear Jon:

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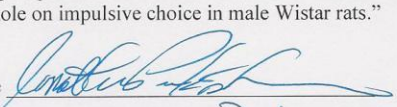
Signature 

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If you have any questions, please call me at the number above or send me an e-mail at the above address. Thank you for your assistance.

Patrick

I hereby give permission to Patrick Johnson to reuse data presented in the article, "Effects of pramipexole on impulsive choice in male Wistar rats."

Signature Stephen C. Fowler

Printed Name STEPHEN C. FOWLER

Date FEB. 5, 2012

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Patrick S. Johnson

April, 2012

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Ph.D. in Psychology (Emphasis: Behavior Analysis), April, 2012
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Dissertation Title: *Behavioral mechanisms of pramipexole-induced impulsivity: Discrimination processes underlying decision-making*

University of Kansas (2006-2010):

M.A. in Applied Behavioral Science, July 2009
Thesis Advisor: Gregory J. Madden, Ph.D.
Thesis Title: *Effects of acute pramipexole on preference for gambling-like schedules in male Wistar rats*

University of Florida (2002-2006):

B.S. in Psychology (Emphasis: Behavior Analysis), May 2006
Thesis Advisor: Timothy D. Hackenberg, Ph.D.
Thesis Title: *Risky choice: Measuring delay sensitivity using an adjusting procedure and video clip reinforcers with adult humans*
B.A. in Anthropology, May 2006

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2011 Walter R. Borg Scholarship for Scholarship and Research Productivity ($2,500), Department of Psychology, Utah State University
2009 Experimental Analysis of Behavior Fellowship ($2,000), Society for the Advancement of Behavior Analysis (SABA)
2007 2nd Place, Sigma Xi Graduate Student Research Paper Competition
2006 Summa cum laude, Psychology, University of Florida
Cum laude, Anthropology, University of Florida

RESEARCH

PEER-REVIEWED PUBLICATIONS

Johnson, P. S., Madden, G. J., & Stein, J. S. (2012). Effects of acute pramipexole on male rats' preference for gambling-like rewards II. *Experimental and Clinical Psychopharmacology*.

Johnson, P. S., Madden, G. J., Brewer, A. T., Pinkston, J. W., & Fowler, S. C. (2011). Effects of acute pramipexole on preference for gambling-like schedules of reinforcement in rats. *Psychopharmacology (Berl), 213, 11-18.*

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MANUSCRIPTS UNDER REVIEW OR IN PREPARATION (data collection completed)

Brewer, A. T., Madden, G. J., Pinkston, J. W., **Johnson, P. S.,** & Williams, D. C. (in preparation). Negative incentive contrasts in Lewis and Fischer 344 rats.

Johnson, P. S., Madden, G. J., & Stein, J. S. (in preparation). Behavioral mechanisms of pramipexole-induced impulsivity: Effects of acute and chronic administration on delay sensitivity and discrimination processes.

BOOK CHAPTERS

Madden, G. J., & **Johnson, P. S.** (2010). A delay discounting primer. In G. J. Madden & W. K. Bickel (Eds.), *Impulsivity: The behavioral and neurological science of discounting.* Washington, DC: American Psychological Association.

CONFERENCE PRESENTATIONS

Stein, J. S., **Johnson, P. S.**, Brewer, A. T., Smits, R. R., Francisco, M. T., & Madden, G. J. (May, 2011). *Training self-control choice in Lewis rats: Assessments of generality across novel procedures*. In D. Reed (Chair), Contemporary Approaches to the Analysis of Choice, Preference, and Decision Making. Symposium conducted at the annual meeting of the Association for Behavior Analysis International, Denver, CO.

Brewer, A. T., Stein, J. S., **Johnson, P. S.,** Francisco, M. T., Williams, D. C., Saunders, K., & Madden, G. J. (May, 2010). *Pausing following rich-to-lean transitions under variable-ratio schedules: Effects of schedule configuration*. In J. Everly (Chair), Recent Findings on the Disruptive Effects of Transitions Between Favorable and Unfavorable Schedules of Reinforcement. Symposium conducted at the annual meeting of the Association for Behavior Analysis International, San Antonio, TX.

Brewer, A. T., Smits, R. R., **Johnson, P. S.,** Francisco, M. T., Stein, J. S., & Madden, G. J. (May, 2010). *A touch-screen apparatus using Visual Basic in the animal laboratory*. In M. Perone (Chair), Advances in Computer Technology to Conduct Laboratory Experiments. Symposium conducted at the annual meeting of the Association for Behavior Analysis International, San Antonio, TX.

Johnson, P. S., Stein, J. S., Brewer, A. T., Francisco, M. T., & Madden, G. J. (May, 2010). *Effects of acute pramipexole on delay sensitivity in a concurrent-chains procedure*. In A. A. Keyl (Chair), Quantitative Analysis of the Effects of Drugs on Behavior. Symposium conducted at the annual meeting of the Association for Behavior Analysis International, San Antonio, TX.

Stein, J. S., Pinkston, J. W., Francisco, M. T., Brewer, A. T., **Johnson, P. S.,** & Madden, G. J. (May, 2010). *Delay discounting in Lewis and Fischer 344 rats: Implications for the use of an adjusting-amount procedure to detect between-strains differences*. In P. L. Soto (Chair), Recent Studies of Variables Affecting Discounting and Demand. Symposium conducted at the annual meeting of the Association for Behavior Analysis International, San Antonio, TX.

Brewer, A. T., **Johnson, P. S.,** Stein, J. S., Francisco, M. T., Williams, D. C., & Madden, G. J. (May, 2009). *Pre-ratio pausing following rich-to-lean transitions on multiple schedules in Fischer 344 and Lewis rats*. In T. Wade-Galuska (Chair), Recent Topics on the Disruptive Effects of Negative Incentive Shifts. Symposium conducted at the annual meeting of the Association for Behavior Analysis International, Phoenix, AZ.

Johnson, P. S., Brewer, A. T., Pinkston, J. W., Stein, J. S., Francisco, M. T., & Madden, G. J. (May, 2009). *Delay discounting processes in pathological gambling: Pharmacological induction of impulsive behavior in the nonhuman laboratory*. In K. A. Saulsgiver (Chair), Delay Discounting, Substance Abuse, and Gambling. Symposium conducted at the annual meeting of the Association for Behavior Analysis International, Phoenix, AZ.

Madden, G. J., Brewer, A. T., **Johnson, P. S.,** Pinkston, J. W., & Woods, J. H. (May, 2009). *Behavioral economics in the lab: Delay discounting, drug taking, and pathological gambling*. In G. P. Hanley (Chair), Science Board Translational Series: History and Current Status of Translational Research in Behavioral Economics. Symposium conducted at the annual meeting of the Association for Behavior Analysis International, Phoenix, AZ.

Bullock, C. A., **Johnson, P. S.,** & Hackenberg, T. D. (May, 2007). *Human risky choice in an adjusting-delay procedure.* In W. Fisher (Chair), Translational Research on Choice Responding. Symposium conducted at the annual meeting of the Association for Behavior Analysis International, San Diego, CA.

Madden, G. J., **Johnson, P. S.,** Smith, N. G., & Brewer, A. T. (May, 2007). *Behavioral economics, impulsivity, and empirical findings from an animal model of gambling.* In C. M. Galuska (Chair), Recent Advances in Behavioral Economics and Delay Discounting. Symposium conducted at the annual meeting of the Association for Behavior Analysis International, San Diego, CA.

Johnson, P. S. (March, 2007). *Self-control choice in Lewis and Fischer 344 rats: Manipulating delay between rather than within sessions*. Paper presented at the second annual Sigma Xi Graduate Student Research Paper Competition.

Madden, G. J., Brewer, A., **Johnson, P.,** & Smith, N. (February, 2007). *Some thoughts and some data on delay discounting and gambling*. Paper presented at the annual meeting of the Winter Conference on Animal Learning and Behavior. Winter Park, CO.

CONFERENCE POSTERS

Johnson, P. S., Stein, J. S., Smits, R. R., & Madden, G. J. (May, 2012). *Pramipexole disrupts discrimination processes involved in intertemporal choice.* Poster presented at the annual meeting of the Society for the Quantitative Analysis of Behavior, Seattle, WA.

Stein, J. S., Smits, R. R., **Johnson, P. S.,** Renda, R., & Madden, G. J. (May, 2012). *Effects of prolonged exposure to delayed reinforcement on impulsive choice and alcohol consumption in rats.* Poster presented at the annual meeting of the Association for Behavior Analysis International, Seattle, WA.

Johnson, P. S., Madden, G. J., & Smits, R. R. (May, 2011). *Past-future discounting of non-monetary outcomes.* Poster presented at the annual meeting of the Association for Behavior Analysis International, Denver, CO.

Johnson, P. S., & Madden, G. J. (March, 2011). *Effects of acute and repeated pramipexole on delay sensitivity.* Poster presented at the 2011 Behavioral Economics Conference, Chicago, IL.

Stein, J. S., **Johnson, P. S.,** Francisco, M. T., Brewer, A. T., Tierney, S. L., & Madden, G. J. (May, 2010). *Experimental manipulation of delay discounting: Implications for subsequent gambling-like behavior.* Poster presented at the annual meeting of the Association for Behavior Analysis International, San Antonio, TX.

Johnson, P. S., Stein, J. S., Brewer, A. T., Francisco, M. T., & Madden, G. J. (October, 2009). *Effects of acute pramipexole on sensitivity to reward delay in concurrent-chains schedules*. Poster presented at the annual meeting of the Mid-American Association for Behavior Analysis, Davenport, IA.

Francisco, M. T., Brewer, A. T., Stein, J. S., **Johnson, P. S.,** & Madden, G. J. (May, 2009). *Impulsivity as a predictor of preference for gambling-like outcomes*. Poster presented at the annual meeting of the Association for Behavior Analysis International, Phoenix, AZ. (Also presented at the annual meeting of the Mid-American Association for Behavior Analysis, Davenport, IA.

Johnson, P. S., Brewer, A. T., Pinkston, J. W., Stein, J. S., Francisco, M. T., & Madden, G. J. (May, 2009). *Effects of pramipexole on choice for differential rewards using a within-session increasing-delay procedure*. Poster presented at the annual meeting of the Association for Behavior Analysis International, Phoenix, AZ.

Stein, J. S., **Johnson, P. S.,** Brewer, A. T., Francisco, M. T., & Madden, G. J. (May, 2009). *A percentile-like to teach delay tolerance in Wistar rats*. Poster presented at the annual meeting of the Association for Behavior Analysis International, Phoenix, AZ. (Also presented at the annual meeting of the Mid-American Association for Behavior Analysis, Davenport, IA.)

Brewer, A. T., **Johnson, P. S.,** Stein, J. S., Pinkston, J., Williams, D. C., & Madden, G. J. (May, 2008). *Pre-ratio pausing following rich-to-lean transitions on multiple schedules in Fischer 344 and Lewis rats.* Poster presented at the annual meeting of the Association for Behavior Analysis International, Chicago, IL.

Brewer, A. T., **Johnson, P. S.,** Stein, J. S., Smith, N. G., Williams, D. C., Pinkston, J., Woods, J., W., & Madden, G. J. (May, 2008). *Effects of pramipexole on choice for differential outcomes in a delay discounting paradigm.* Poster presented at the annual meeting of the Association for Behavior Analysis International, Chicago, IL.

Johnson, P. S., Brewer, A. T., Pinkston, J., Woods, J., W., & Madden, G. J. (May, 2008). *Effects of acute pramipexole on preference for gambling-like schedules.* Poster presented at the annual meeting of the Association for Behavior Analysis International, Chicago, IL. (Also presented at the annual meeting of the Mid-American Association for Behavior Analysis, Champaign-Urbana, IL.)

Brewer, A. T., **Johnson, P. S.,** Pyszczynski, A. D., Stein, J. S., Smith, N. G., Wu, H., Madden, G. J., Woods, J., Pinkston, J. W., & Williams, D. C. (May, 2007). *Preliminary effects of pramipexole on choice for differential outcomes in a delay discounting paradigm.* Poster presented at the annual meeting of the Association for Behavior Analysis International, San Diego, CA.

Brewer, A. T., Smith, N. G., **Johnson, P. S.,** & Madden, G. J. (October, 2006). *Self-control choice in Lewis and Fischer 344 rats: Manipulating delay between rather than within sessions*. Poster presented at the annual meeting of the Mid-American Association for Behavior Analysis, Carbondale, IL. (Also presented at the annual meeting of the Southeastern Association for Behavior Analysis, Greenville, SC).

PROFESSIONAL AFFILIATIONS

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- Society for the Quantitative Analysis of Behavior (2007 - present)
- Mid-American Association for Behavior Analysis (2006 - 2009)
- Southeastern Association for Behavior Analysis (2006)

TEACHING

COURSES TAUGHT

2012 (Spring)	**Instructor,** PSY 3460: Physiological Psychology, Utah State University, Logan, UT. Enrolled: 71
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2010 (Spring)	**Instructor,** ABSC 489: Directed Readings in Choice, University of Kansas, Lawrence, KS. Enrolled: 4
2009 (Fall)	**Instructor,** ABSC 100: Introduction to Applied Behavioral Science, University of Kansas, Lawrence, KS. Enrolled: 151
2009 (Summer)	**Instructor,** ABSC 100: Introduction to Applied Behavioral Science, University of Kansas, Lawrence, KS. Enrolled: 18
2009 (Spring)	**Instructor,** ABSC 499: Readings in the Experimental Analysis of Behavior, University of Kansas, Lawrence, KS. Enrolled: 4
2008 (Fall)	**Co-instructor,** ABSC 100: Introduction to Applied Behavioral Science, University of Kansas, Lawrence, KS. Enrolled: 160
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SERVICE

EDITORIAL

2011 Guest reviewer, *Pharmacology, Biochemistry, and Behavior*
2009 Guest reviewer, *Journal of Applied Behavior Analysis*
2009 Guest reviewer, *Behavioral Pharmacology*
2008 Guest reviewer, *Journal of the Experimental Analysis of Behavior*

DEPARTMENTAL

2011	**Student Search Committee Member,** Assistant/Associate Professor in Behavioral Neuroscience, Department of Psychology, Utah State University, Logan, UT
2011-2012	**Student Representative,** Experimental and Applied Psychological Science, Department of Psychology, Utah State University, Logan, UT
2010-2011	**Administrator,** Sona Human Subject Pool Database Utah State University, Logan, UT
2007-2009	**Secretary**, Applied Behavioral Science Graduate Student Organization University of Kansas, Lawrence, KS (2 terms)

REFERENCES

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