ASSESSING ANIMAL MODELS OF IMPULSIVE BEHAVIOR: INTER-MODEL CONGRUITY, RELATIONSHIP TO DEMAND FOR COCAINE, AND EFFECTS OF SELECTIVE DOPAMINERGIC COMPOUNDS

by

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CHAPTER 1

INTRODUCTION

Behaving in a way that maximizes short-term gain is adaptive under many circumstances. In an uncertain and competitive world, valuing immediate rewards and acting quickly to obtain those rewards will often be the optimal strategy. It is when such opportunistic strategies become excessive and disadvantageous that the behavior is deemed impulsive (Ainslie, 1975; Logue, 1995). Therefore, impulsive behavior patterns do not differ in form from normal behavior, only in degree. For example, occasionally enjoying celebratory drinks with friends despite the delayed consequence of a hangover may be considered normal. Drinking excessively on a daily basis, on the other hand, despite a delayed consequence of losing one's job and financial freedom may be considered impulsive. Simply observing a person drinking an alcoholic beverage does not necessarily convey whether that behavior is impulsive, it is the context of that drinking behavior in interaction with the consequences that result which determine if it is impulsive. Analogous examples of impulse control are central to a wide variety of daily behaviors. Failures in impulse control, depending on the specific context, have been implicated in psychological disorders as varied as substance abuse, conduct disorder, attention-deficit/hyperactivity disorder (ADHD), kleptomania, and pathological gambling

(*Diagnostic and statistical manual of mental disorders-IV-TR*, American Psychiatric Association, 2000).

Subtypes of Impulsivity

Given the broad brush that has been used to paint the construct of impulsivity, it is not surprising that researchers and theorists have identified multiple, distinct subtypes of impulsivity. Using answers given on self-report questionnaires as a basis, the Barratt Impulsivity Scale (BIS) and Eysenck Impulsiveness scales have both proposed multiple subtypes. Furthermore, these subtypes differ depending on the version of the scale used. The BIS-10 proposes cognitive impulsiveness, motor impulsivenss, and non-planning impulsiveness, while the BIS-11 includes attentional impulsiveness along with the motor and cognitive subtypes from version 10 (Patton, Stanford, & Barratt, 1995). Version 5 of the Eysenck Impulsiveness scale (I-5) proposes narrow impulsivity, risk taking, liveliness, and non-planning (Eysenck & Eysenck, 1977), while version 7 (I-7) proposes just two subtypes – impulsiveness and venturesomeness (Eysenk & Eysenck, 1978). One attempt to parse these and other self-report scales resulted in 15 distinct components of impulsivity, which were proposed to be separable into the three overarching components: spontaneous, not persistent, and carefree (Gerbing, Ahadi, & Patton, 1987).

Behavioral measures of impulsivity have been grouped into classes that seem to show less volatility than the subtypes of impulsivity as described by designers of self-report questionnaires. The existence of at least two subtypes of behavioral measures and corresponding behavioral patterns of impulsivity is widely agreed upon (for recent reviews, see Dalley, Mar, Economidou, & Robbins, 2008; de Wit, 2009; Evenden, 1999a; Perry & Carroll, 2008; Winstanley, Eagle, & Robbins, 2006). Impulsive action,

sometimes called motor impulsivity, behavioral inhibition, or behavioral disinhibition, refers to the inability to withhold or inhibit a prepotent response (i.e., a response the individual has prepared to emit). Impulsive choice, sometimes referred to more positively as self control, is defined by hypersensitivity to delays of reward. Impulsive preparation, also known as reflection impulsivity, is discussed less often in the animal literature, but has received much attention in the human literature. Impulsive preparation refers to the tendency to act before obtaining and processing relevant environmental stimuli (Evenden, 1999a). Finally, lapses in attention which do not necessarily coincide with poor attentional performance overall have also been proposed as a component of impulsivity (de Wit, 2009).

Impulsive Action

Impaired performance on a number of procedures has been labeled impulsive action. For each, a response is reinforced in one context while the same response is punished in another context, but the specific characteristics of the response and the stimuli that signal appropriate behavior are different. To perform optimally, the organism must inhibit responses when appropriate. Impulsive action is most often measured experimentally with one of five procedures, most of which have both human and animal variants: the go/no-go task, the stop signal reaction time (SSRT) task, the 5-choice serial reaction time (5-CSRT) task, differential reinforcement of low rates (DRL) schedules, and fixed consecutive number (FCN) schedules. The go/no-go task and SSRT task are very similar (for review, see Band & van Boxtel, 1999). On the go/no-go task, responding is reinforced in the presence of a stimulus (the "go" stimulus), but the same response is punished if a second stimulus (the "no-go" stimulus) is presented slightly before or

concurrently with the "go" stimulus. As with the go/no-go task, responding on the SSRT task is reinforced in the presence of a stimulus, but the same response is punished if followed by a "stop signal." In the go/no-go task, successful inhibition of responses in the presence of the "no-go" stimulus is measured, while in the SSRT task the reaction time of the subject on successful trials is typically the measure of interest. Since a successfully inhibited trial is defined by the absence of a response, reaction time is estimated using the shortest "stop signal" interval on incorrect trials. The 5-CSRT task was originally developed as an animal model of sustained attention similar to the continuous performance task (CPT) used to measure attentional processes in humans (Robbins, 2002). On both the CPT and 5-CSRT task, visual stimuli are briefly presented in distinct response locations, and a response at the signaled location is reinforced. On the 5-CSRT task, "premature" responses made prior to the presentation of stimuli are punished, and this type of response has been used as a model of impulsive action (Dalley et al., 2008). Premature responses on another visual discrimination task, the uncertain visual discrimination (UVD) task, have also been studied as a model of impulsive action in animals (Evenden, 1999b). DRL and FCN schedules are also measures of impulsive action that are conceptually similar (for review, see Monterosso & Ainslie, 1999). Responding is reinforced on a DRL schedule based on the time since the previous response. For example, responses are reinforced on a DRL 60-s schedule if a fixed 60-s interval has elapsed since the previous response. On a FCN schedule, responses on a "reinforcement lever" are reinforced based on the number of responses made on a "chain lever" since the previous reinforcement-lever response. For example, a single response on the reinforcement lever is reinforced on a FCN 8 schedule if at least 8 responses have

been recorded on the chain lever prior to the reinforcement-lever response. Responses made prior to the time interval on a DRL schedule, or prior to the response requirement on a FCN schedule, are punished with a timeout and interpreted as impulsive action. Evenden (1998) developed a variant of this FCN schedule, dubbed a paced FCN schedule, for use when assessing drug effects. A paced FCN schedule controls for the rate-increasing or rate-decreasing effects many drugs have on schedule-maintained behavior. By withdrawing the levers after every response and reinserting them into the chamber after a specified interval, the maximum response rate can be controlled and set to an arbitrarily low rate.

Impulsive Choice

Impulsive choice is typically measured using procedures that provide choice opportunities between a smaller amount of a reinforcer delivered after little or no delay and large amount of the same reinforcer delivered after a longer delay (Ainslie, 1975). Due to the financial and logistical challenges of delivering delayed rewards to human subjects, delay discounting (DD) is typically measured in people by offering choices between hypothetical immediate and hypothetical delayed consequences (for review, see Reynolds, 2006). Choices between actual reinforcers have been compared to choices between hypothetical rewards, however, finding sufficient concordance to justify the use of hypothetical rewards (Baker, Johnson, & Bickel, 2003; Madden, Begotka, Raiff, & Kastern, 2003; Madden et al., 2004; but see Heyman & Gibbs, 2006). Procedures to measure impulsive choice in animals subjects fall into two categories: those that make within-session adjustments the amount of one reinforcer or the delay to one reinforcer based on the subject's behavior (Mazur, 1987; Richards, Mitchell, de Wit, & Seiden,

1997), or those that arrange choices between a predefined set of delays and amounts (Evenden & Ryan, 1996).

In both types of DD procedures, the tendency to choose the smaller, more immediate reinforcer over the larger, delayed reinforcer is interpreted as impulsive choice. Results are often presented as a series of indifference points, or the amount of an immediate reinforcer that is subjectively equal to a delayed reinforcer. For example, if a subject's choices indicate indifference between $100 delayed one month and $90 delivered immediately, that individual can be said to value that $100 at 90% of its absolute value when delayed one month. A hyperbolic function fitted to a series of these indifference points quantifies impulsive choice (Figure 1-1). The hyperbolic nature of this function is important for theoretical purposes. Prominent early economists and psychologists assumed that present value of a reward is discounted exponentially as a function of delay (e.g., Fishburn & Rubinstein, 1982; Hull, 1943; Lancaster, 1963). A major interpretive problem with exponential delay functions, however, is presented by considering the phenomenon of preference reversals. Anecdotal evidence abounds for the existence of preference reversals, or the tendency to make a self-controlled choice when the consequences are remote, but reverse preference to the impulsive choice when the options are near. For example, women often choose to forego anesthesia when asked their preference many hours before giving birth, but switch their preference as time to childbirth approaches (Christensen-Szalanski, 1984). Preference reversals are illustrated by Figure 1-2 (right panel). When the present value of a delayed reward is discounted hyperbolically, plots measuring the present value through time of two differently-sized reinforcers often cross, such that small rewards are preferred when nearly immediate, but

large rewards are preferred if the delay to both the small and large reward is increased. In the hypothetical example illustrated in Figure 1-2 (right panel), the choice for $50 is preferred at T1, when both $50 and $25 are delayed substantially (e.g., a choice between $50 in six weeks versus $25 in five weeks). As time progresses preferences reverse, such that by T2 the smaller reward is chosen (e.g., a choice between $50 in one week versus $25 now), even though the time between the delays is constant (one week). Analogous preference reversals have been observed many times in both human participants choosing between a variety of reinforcers (Christensen-Szalanski, 1984; Kirby & Herrnstein, 1995; Millar & Navarick, 1984; Solnick, Kannenberg, Eckerman, & Walker, 1980) and animal subjects choosing between food reinforcers (Bradshaw & Szabadi, 1992; Green & Estle, 2003; Green, Fisher, Perlow, & Sherman, 1981; Navarick & Fantino, 1976; Rachlin & Green, 1972). Even before the currently-used hyperbolic function was confirmed experimentally (Mazur, 1987); a curve approximating this shape was proposed on theoretical grounds by both a psychologist (Ainslie, 1975) and economist (Thaler, 1981).

Impulsive Preparation

Impulsive preparation, often labeled reflection impulsivity or cognitive impulsivity by human-subjects researchers, refers to a tendency to act before obtaining and processing environmental stimuli relevant to optimal performance on a given task (for review, see Evenden, 1999a). On a number of laboratory tasks designed to measure some aspect of cognitive processing, there is often a trade-off between response speed and response accuracy (e.g., Yakir et al., 2007). A certain subset of individuals respond quickly, before fully considering and deciding upon optimal response patterns. Neither rapid responding nor poor accuracy alone defines impulsive responding on such tasks, it

is the combination of the both that is labeled impulsive. For example, the Tower of London task (Culbertson & Zillmer, 1998) presents participants with a series of objects arranged in a particular pattern within a series of wells or stacked into towers. A goal pattern that differs from the starting pattern is presented, and the participant has a predefined number of "moves" to rearrange the objects to match the goal pattern. Those subjects that perform poorly, not because they lack the cognitive abilities to perform the task but because they respond quickly, are labeled impulsive. An analogous pattern of responding is found on other tasks which have been used to measure impulsive preparation, such the Matching Familiar Figures Test (MFFT) (Kagan, 1966), the Porteus Maze Test (Porteus, 1973), the Trail Making Test (Lezak, 1995), and the Wisconsin Card Sorting Task (Heaton, Chelune, Talley, Kay, & Curtiss, 1993). On each, a pattern of responding described as impulsive preparation includes fast, inaccurate responding (Leshem & Glicksohn, 2007).

A single task has been proposed to model impulsive preparation in animals (Evenden, 1999b). The UVD task is a visual discrimination task similar in many respects to the 5-CSRT task, but with the visual stimuli probabilistically correlated with the correct response location. Stimuli are presented every 200 msec in a series of cycles, and with each cycle, the probability that the stimulus predicts the correct response location increases. Therefore, similar to impulsive preparation tasks used with human subjects, it is advantageous to wait and observe the stimuli prior to responding. Impulsive responding on this task is defined by rapid, relatively inaccurate responding.

Lapses of Attention

A fourth component of impulsivity characterized by lapses in attention has been proposed (de Wit, 2009). While sometimes cited as a component of impulsivity in self-report questionnaires (e.g., Patton et al., 1995), a specific behavioral measure of lapses in attention has only recently been proposed as a way to model a distinct subtype of impulsivity (de Wit, 2009). Lapses in attention are defined as long reaction times on a sustained attention task, and to date have not been modeled as a component of impulsivity in laboratory animals.

Behavioral and Psychiatric Correlates of Impulsivity

With such an expansive list of impulsivity measures, validating each is a daunting task. A common method of determining the validity of a given measure is associating performance on a task with an impulse control disorder. Such efforts face potential confounds, however, when it is not clear whether a person with a given impulse control disorder "should" be associated with any one subtype of impulsivity. Despite these qualms, it is notable that many of these impulsivity measures correlate with characteristics thought to be related to impulse control. For example, self-report measures of impulsivity differentiate criminals from controls (Eysenck & McGurk, 1980), persons with "high-risk" psychiatric disorders involving impulse-control deficits from those with "low-risk" psychiatric disorders (Crean, de Wit, & Richards, 2000), and gamblers from non-gamblers (Petry, 2001). Pathological gamblers also make more errors on the go/no-go task (Kertzman, Lowengrub, Aizer, Vainder, Kotler, & Dannon, 2008), and ADHD is correlated with impulsive responding on the Tower of London task (Culbertson & Zillmer, 1998), variants of the DD task (Schweitzer & Sulzer-Azaroff, 1995; Solanto et al., 2001; Sonuga-Barke, Taylor, Sembi, & Smith, 1992; Sonuga-Barke, Williams, Hall,

& Saxton, 1996), and the SSRT task (de Zeeuw et al., 2008; McAlonan et al., 2009; Tannock, Ickowicz, & Schachar, 1995; Tannock, Schachar, Carr, Chajczyk, & Logan, 1989).

Substance abuse is perhaps the most consistently and widely documented correlate with measures of impulsivity. Almost without exception, impulsivity is found to be more prevalent in substance abusers, regardless of substance of abuse. Eysenck and Eysenck's (1977, 1978) impulsivity scales positively correlate with smoking status (Bickel, Odum, & Madden, 1999, but see Mitchell, 1999), alcohol use (Bobova, Finn, Rickert, & Lucas, 2009; Sher, Bartholow, & Wood, 2000; Vuchinich & Simpson, 1998), cocaine use (Coffey, Gudleski, Saladin, & Brady, 2003), and opioid dependency (Madden, Petry, Badger, & Bickel, 1997). Opioid-dependent needle-sharers scored higher than those that did not share needles (Odum, Madden, Badger, & Bickel, 2000), and scores predicted who would become alcohol dependent up to six years prior to development of dependence (Sher et al., 2000). Similarly, the BIS (Patton et al., 1995) is positively correlated with cocaine use (Coffey et al., 2003), smoking status (Heyman & Gibbs, 2006; Mitchell, 1999; Reynolds, Patak, Shroff, Penfold, Melanko, & Duhig, 2007), and heroin use (Kirby, Petry, & Bickel, 1999). Scores on the BIS are also higher among early-onset alcoholics than among late-onset alcoholics (Dom, D'haene, Hulstijn, & Sabbe, 2006). On behavioral measures of impulsive action, cocaine dependent people (Lane, Moeller, Steinberg, Buzby, & Kosten, 2007; but see Li, Milivojevic, Hong, & Sinha, 2006) have been shown to make more errors. On the Tower of London model of impulsive preparation, smokers, amphetamine users, and opiate users have a more impulsive pattern of behavior (Ersche, Clark, London, Robbins, & Sahakian, 2006; Yakir

et al., 2007), as have amphetamine and opiate users on a novel model of impulsive preparation (Clark, Robbins, Ersche, & Sahakian, 2006). Animal models of impulsive action have also been shown to correlated with escalation of cocaine intake and continued cocaine use despite punishment (Belin, Mar, Dalley, Robbins, & Everitt, 2008; Dalley et al., 2007)

Greater impulsive choice on the DD task has also been associated with drug abuse, nearly without exception. The first account of greater discounting of delayed rewards among substance abusers was with a group of opioid-dependent participants (Madden et al., 1997). The opioid-dependent group in that study was found to discount hypothetical delayed money more than controls, such that delayed money was discounted to 50% of its absolute value when delayed approximately 37 months in the control group, but only 4.5 months in the opioid-dependent group. Opioid-dependent subjects were subsequently confirmed by others to discount delayed rewards more than controls (Kirby & Petry, 2004; Kirby et al., 1999; Madden, Bickel, & Jacobs, 1999; Odum et al., Odum, Madden, & Bickel, 2002), as were cocaine users (Coffey et al., 2003; Kirby & Petry, 2004), cigarette smokers (Audrain-McGovern, Rodriguez, Epstein, Cuevas, Rodgers, & Wileyto, in press; Baker et al., 2003; Bickel et al., 1999; Heyman & Gibbs, 2006; Johnson, Bickel, & Baker, 2007; Jones, Landes, Yi, & Bickel, in press; Mitchel, 1999; Reynolds, 2006; Reynolds et al., 2007), alcohol abusers (Bobova et al., 2009; Dom et al., 2006; Vuchinich & Simpson, 1998), and methamphetamine users (Monterosso, Ainslie, Xu, Cordova, Domier, & London, 2007). Furthermore, the DD task differentiates opioid users who share needles from those that do not, with the needle-sharers demonstrating greater discounting of delayed rewards (Odum et al., 2000). Opioid users that are mildly

deprived of opioids at the time of assessment discount delayed rewards to a greater degree (Giordano, Bickel, Goewenstein, Jacobs, Marsch, & Badger, 2002), and substance users that also exhibit problem gambling have greater impulsive choice than substance abusers not meeting criteria for problem gambling (Petry, 2001; Petry & Casarella, 1999). When discounting is measured at intake to a smoking-cessation treatment program, it has been shown that degree of discounting predicts which participants will remain abstinent at the end of treatment, with greater impulsive choice in those that relapse (Krishnan-Sarin et al., 2007; Yoon, Higgins, Heil, Sugarbaker, Thomas, & Badger, 2007). After an exhaustive search, the only report of any substance abusing population that did not demonstrate greater impulsive choice than matched controls was in a single group of alcoholics (Kirby & Petry, 2004).

Dopaminergic Neural Mechanisms Involved in Impulsivity

Dopaminergic pathways between the prefrontal cortex (PFC), anterior cingulate cortex (ACC), and basal ganglia are often implicated in ADHD and impulsive behavior (for recent reviews see Bickel, Miller, Yi, Kowal, Lindquist, & Pitcock, 2007; Dalley et al., 2008; Winstanley et al., 2006). Unmedicated adults with ADHD have less DOPA decarboxylase activity in the PFC, likely indicating fewer dopaminergic synapses in this area (Ernst, Zametkin, Matochik, Jons, & Cohen, 1998). Similarly, compared to control subjects, lower PFC activation was found in functional magnetic resonance imaging (fMRI) scans of adolescent boys with ADHD performing the SSRT task or a task involving delay to reinforcement (Rubia, Overmeyer, Taylor, Brammer, Williams, Simmons, & Bullmore, 1999). The ACC has also been implicated in ADHD, with lower activation in that region during attentional tasks (Bush et al., 1999; Zametkin et al.,

1990). Combined with the finding that striatal dopamine transporter (DAT) availability is increased in untreated adults with ADHD (Krause, Dresel, Krause, Kung, & Tatsch, 2000), the involvement in ADHD of the pathways connecting these areas is highly probable. Drug dependence also involves dysregulation of the same striatocortical pathways (Robinson & Berridge, 2003; Volkow, Fowler, & Wang, 2004); and like people with ADHD, methamphetamine users show lower PFC activity while making choices on the DD task (Monterosso et al., 2007).

In addition to differentiating brains of people with impulse-control disorders from control subjects, the same striatocortical pathways seem to be involved in impulsive behavior in healthy adults. fMRI scans taken while people make choices on the DD task often find activation of the PFC and striatum during choices. More PFC activation is found when making delayed or difficult choices, while ventral striatum is associated with immediate choices or reward amount (Ballard & Knutson, 2009; Hoffman et al., 2008; McClure, Laibson, Loewenstein, & Cohen, 2004; Tanaka, Doya, Okada, Ueda, Okamoto, & Yamawaki, 2004; Shamosh et al., 2008; Wittman, Leland, & Paulus, 2007). This pathway is not only activated during the DD task. Individual differences in impulsive choice are associated with different levels of activation in healthy adults, with greater ventral striatal activity and less medial and dorsolateral PFC activation associated with greater impulsive choice (Ballard & Knutson, 2009; Hariri, Brown, Williamson, Flory, & de Wit, 2006). Response inhibition on the go/no-go task utilizes the same pathways between the striatum and medial or dorsolateral PFC, with thalamic modulation (Stevens, Kiehl, Pearlson, & Calhoun, 2007; Tapert et al., 2007). However, dorsolateral PFC

activation only occurs if the stimuli used as "go" and "no-go" signals are complex (Simmonds, Pekar, Mostofsky, 2008).

Research in animal subjects has implicated the same striatocortical pathways. As in human subjects, the ventral striatum in rats appears to be related to reinforcer valuation and the PFC involved in sensitivity to delay. Rats making choices on the DD task after nucleus accumbens (NAc) core lesions choose the small reinforcer under all delay conditions, even when both the small and large reinforcers are delivered immediately (Bezzina et al., 2007; Cardinal, Pennicott, Sugathapala, Robbins, & Everitt, 2001). This counterintuitive finding seems to result from lesioned animals being unable to assess delay and amount under the rapidly-changing conditions present in the DD task used (Acheson et al., 2006). Increases in impulsive choice are seen with lesions of the orbital PFC (Kheramin et al., 2004) or disconnection of the orbital PFC from the NAc core by lesioning the orbital PFC on one side of the brain and the NAc core on the other side (Bezzina et al., 2008). Note that a contradictory report claims that orbital PFC lesions decrease impulsive choice (Winstanley, Theobald, Dalley, Cardinal, & Robbins, 2006), but the effect in this paper is primarily due to an increase in choice of the large reinforcer independent of delay. Increases in choice of the large reinforcer that are independent of delay are more accurately conceptualized as alterations in sensitivity to amount or disruptions in ability to discriminate or adapt to the consequences of responding, not an effect on impulsive choice (Acheson et al., 2006; Pitts & Febbo, 2004).

Animal models of impulsive action show similar sensitivity to dopaminergic pathways. ACC lesions in rats increase the number of premature responses emitted on the 5-CSRT task, but medial PFC, lateral PFC, and parietal cortex lesions had no effect

(Muir, Everitt, & Robbins, 1996). Dopamine levels are elevated in the PFC during 5-CSRT task performance, but this elevation is not related to task performance (Dalley, Theobald, Eagle, Passetti, & Robbins, 2002). D_2/D_3 receptor level in the ventral striatum is positively correlated with premature responses emitted on the 5-CSRT task (Dalley et al., 2007), but a D_2/D_3 agonist administered directly into this brain region only produced a small increase in premature responses that was not statistically significant (Pezze, Dalley, & Robbins, 2007).

Brain circuitry has not been explicitly associated with levels of impulsive responding in models of impulsive preparation. However, the PFC is critical for responding on these tasks (Crews & Boettiger, 2009), such as the Tower of London task (Schall et al., 2003; van den Heuvel, Groenewegen, Barkhof, Lazeron, van Dyck, & Veltman, 2003; Wagner, Kock, Reichenback, Sauer, & Schlösser, 2006).

Specific Aims

While impulsivity and impulsive behavior are studied extensively in both animals and people, relatively little is known about the ability of commonly employed animal models to accurately capture and provide insight into the human condition. When modeling cognitive disorders, three primary evaluative areas have been proposed for determining the quality of the model: face validity, construct validity, and predictive validity (Sagvolden, Russell, Aase, Johansen, & Fashbaf, 2005; Sarter, Hagan, & Dudchenko, 1992). Face validity refers to the degree to which a model resembles the clinical condition being modeled, with consideration for species-specific behavior and limitations. A model with construct validity should share underlying theoretical and neural mechanisms with the clinical condition being modeled. To have predictive

validity, pharmacological and behavioral manipulations should affect performance on a model in an analogous way in the clinic, including for previously-unknown manipulations. Evaluating models is difficult if the modeled disorder is not well understood, but such attempts are necessary if the goal is to discover treatments relevant to the clinic (Sarter et al., 1992). The experiments described within represent steps toward the evaluation of selected animal-subjects behavioral models of impulsivity used in laboratory experiments.

Specific Aim 1: Determine if Individual Differences in Impulsive Choice Are Associated With Demand for Sucrose or Self-Administered Cocaine

Human participants who misuse drugs of abuse, almost without exception, have been shown to be more impulsive than their non-using counterparts. This relationship is especially well-documented for impulsive choice, the subtype of impulsivity referring to the tendency to be hypersensitive to delays to rewards (e.g., Madden et al., 1997, 1999). While the drug-using status of human subjects can be ascertained with simple questioning and verified with physiological measures (e.g., breathalyzer for alcohol, carbon monoxide readings for tobacco-smoking, urinalysis for other drugs) modeling drug abuse in animals poses its own set of challenges. It is known that individual differences in impulsive choice predict acquisition of cocaine self-administration in female rats (Perry, Larson, German, Madden, & Carroll, 2005), as well as level of nicotine self-administration and reinstatement to extinguished nicotine self-administration in male rats (Diergaarde et al., 2008). It is not clear, however, whether animals that discount delayed rewards steeply value these drug reinforcers to a greater extent, as response-rate-based measures of drug reinforcement have many shortcomings (for recent reviews, see Bergman & Peronis,

2006; Hursh & Silberberg, 2008). Two of the critical issues associated with measuring drug value in experimental animals lie with dose effects and direct effects that many drugs have on behavior. When self-administered, different doses of the same drug support different amounts of behavior, with moderate doses typically supporting more behavior than both high and low doses (e.g., Collins & Woods, 2007; for review, Bergman & Peronis, 2006). This feature makes dose an influential variable when assessing reinforcer value, with no clear method of choosing which dose of a given drug best represents the reinforcing value of that drug. In addition, many self-administered drugs function to increase or decrease general activity, confounding the independent variable being assessed (e.g., drug A versus drug B) and the dependent measure (e.g., lever presses maintained by drug A versus drug B).

Behavioral economics, the application of economic terms, concepts, and analytical tools to the study of the behavior of individual organisms (Bickel, Green, & Vuchinich, 1995), provides a system of assessing reinforcer value that is independent of drug dose (Hursh & Silberberg, 2008). In such an analysis, total consumption of a reinforcer is the dependent measure instead of response rate, and this determined at a variety of prices (response requirements). As price increases, consumption decreases in a curvilinear fashion such that a unit increase in price will result in a small reduction in consumption initially, but a progressively larger reduction in consumption as price increases. The rate at which consumption declines is termed the elasticity of demand, and this measure reflects the reinforcer value. If price and consumption are both normalized to relatively unrestrained consumption levels, elasticity of demand can be used to rank order reinforcer value across different reinforcers (e.g., Hursh & Winger, 1995) or across

different environmental conditions with responding maintained by the same reinforcer (e.g., Hursh, 1991). Note that elasticity of demand only depends on the rate of decline in consumption, and does not depend on total level of responding, total consumption, or the dose of the drug being self-administered. Elasticity of demand therefore avoids many of the potential confounds introduced by response-rate-based measures when assessing value of self-administered drugs.

To assess one aspect of the construct validity of the DD model of impulsive choice in animals, individual differences in choices on this task were used to predict demand elasticity for sucrose pellets and self-administered cocaine injections. If the DD task and drug demand are adequate models of impulsive choice and drug abuse, respectively, two predictions can be made regarding these comparisons. First, it is hypothesized that individual differences in impulsive choice will predict individual differences in drug demand. Second, individual differences in impulsive choice should fail to predict individual differences in sucrose demand.

Specific Aim 2: Determine if Receptor-Selective Dopamine Agonists and Antagonists Improve Performance on Models of Three Subtypes of Impulsivity

Dopaminergic pathways are known to be influential in impulsive behavior, and both $D_{1\text{-like}}$ (D_1 and D_5) and $D_{2\text{-like}}$ (D_2, D_3, and D_4) dopamine receptors, as well as DAT, are known to exist in the dopaminergic pathways connecting the striatum to the PFC (Ciliax et al., 1995; Gaspar, Bloch, & Le Moine, 1995; Lévesque et al., 1992; Mrzljak, Bergson, Pappy, Huff, Levenson, & Goldman-Rakic, 1996; Muly III, Szigeti, & Goldman-Rakic, 1998; Revay, Vaughan, Grant, & Kuhar, 1996; Wędzony, Chocyk, Maćkowiak, Fijał, & Czyrak, 2000). DAT, important to the effects of clinically-used

ADHD drugs amphetamine and methylphenidate, is present in higher levels in the NAc and striatum than in the PFC (Ciliax et al., 1995; Revay et al., 1996). Despite this, methylphenidate has been shown to increase dopamine in the PFC to a greater extent and at lower doses than in the NAc (Berridge et al., 2006). D_2 and D_3 receptors are located in higher concentrations in the striatum and NAc than in the PFC (Lévesque et al., 1992; Bouthenet, Souil, Martres, Sokoloff, Giros, & Schwartz, 1991), while $D_{1\text{-like}}$ and D_4 receptors are the most prevalent dopamine receptor subtypes in the PFC (Fare, Halldin, Stone-Elander, & Sedvall, 1987; Lidow, Goldman-Rakic, Gallager, & Rakic, 1991; Mrzljak et al., 1996). Since these areas are highly connected, it is difficult to make predictions regarding the actions of systemically-administered, selective dopamine agonists and antagonists on behavior. In accordance with the research discussed above regarding the role of brain pathways in impulsive behavior in people, receptor subtypes with preferential locations in the basal ganglia (D_2, D_3) are expected to be involved in modulating impulsive action, while receptor subtypes with preferential location in the PFC ($D_{1\text{-like}}$, D_4) are expected to be more involved in modulating impulsive choice.

With the abundance of tasks available to model impulsive behavior in animals, choosing specific tasks for evaluation is not trivial. Evenden (1999a) proposed a theoretical framework for classifying impulsivity tasks which appears to be based on Skinner's (1953) three-term contingency. Skinner's three-term contingency, consisting of a discriminative stimulus, a behavior, and a consequence, describes the interrelationship of behavior and environment. A discriminative stimulus sets the occasion for behavior, the organism engages in that behavior, and a consequence is delivered that either increases or decreases the likelihood of that behavior occurring in the future in the

presence of that discriminative stimulus. Evenden (1999a) envisioned impulsive behavior as behavior that is abnormal with respect to one of these terms, with each of three subtypes of impulsivity corresponding to abnormalities with one component of the three-term contingency. He proposed that abnormal integration of discriminative stimuli characterizes impulsive preparation, abnormal execution of the behavior characterizes impulsive action, and abnormal evaluation of the consequences of behavior characterizes impulsive choice (Evenden, 1999a). This framework is appealing for conceptualizing the vast field of impulsivity research, and a behavioral task proposed to fit within each of these subtypes was chosen for further evaluation. The DD task (Evenden & Ryan, 1996) was chosen as a model of impulsive choice, a paced FCN schedule (Evenden, 1998) was chosen as a model of impulsive action, and the UVD task (Evenden, 1999b) was chosen as a model of impulsive preparation and impulsive action.

Subaim 2.1. Determine the effects of selective dopaminergic compounds on a delay discounting task. Given the extensive role of dopamine in impulsive choice, the selective dopaminergic compounds listed in Table 1-1 were evaluated for potential therapeutic effects on the chosen model of impulsive choice, the DD task (Evenden & Ryan, 1996). As the organization of dopamine receptors within the pathways involved in impulsive behavior are complex, the role of specific systemically-administered compounds is difficult to predict *a priori*. However, given the critical role of the PFC in impulsive choice and the relatively greater concentration of $D_{1\text{-like}}$ and D_4 receptors in this area (see above), it is hypothesized that compounds binding preferentially to these receptor subtypes will be influential in modulating impulsive choice.

Subaim 2.2. Determine the effects of selective dopaminergic compounds on a paced fixed consecutive number schedule. Dopaminergic pathways are also critically involved in impulsive action. To determine the potential therapeutic effects of receptor-specific compounds on impulsive action, the selective dopaminergic compounds listed in Table 1-1 were evaluated for effects on the chosen model of impulsive action, a paced FCN schedule (Evenden, 1998). As the organization of dopamine receptors within the pathways involved in impulsive behavior are complex, the role of specific systemically-administered compounds is difficult to predict *a priori*. However, given the critical role of the striatum and NAc in impulsive action and the relatively greater concentration of D_2 and D_3 receptors in this area (see above), it is hypothesized that compounds binding preferentially to these receptor subtypes will be influential in modulating impulsive action.

Subaim 2.3. Determine the effects of selective dopaminergic compounds on an uncertain visual discrimination task. Little is known about the neural pathways involved in impulsive behavior on tasks that measure impulsive preparation. While it is known that the PFC is important for the cognitive processes involved in these tasks (Crews & Boettiger, 2009), it is not known which pathways are important for impulsive behavior patterns on these tasks. Therefore, Subaim 2.3 is largely exploratory. Given the critical role of dopaminergic pathways in impulsivity, and for comparison purposes with Subaim 2.1 and Subaim 2.2, the selective dopaminergic compounds listed in Table 1-1 were evaluated for effects on the chosen model of impulsive preparation, the UVD task (Evenden, 1999b). It is hypothesized that dopaminergic compounds will be active on this

task, but specific predictions with specific compounds would be highly speculative and of little value.

Specific Aim 3: Assess Inter-Model Congruity of Animal Models of Impulsive Behavior

The theoretical framework proposed by Evenden (1999a) relating subtypes of impulsivity to behavioral contingencies is appealing, but remains speculative until tested empirically. Some environmental and pharmacological manipulations have been assessed across models of impulsivity, allowing for comparisons of effects between tasks. For example, *d*-amphetamine has been tested on the DD task, a paced FCN schedule, and on the UVD task. On the DD task with intact animals, *d*-amphetamine has been shown to reduce impulsive choice (Floresco, Tse, & Chods-Sharifi, 2008; van den Bergh, Bloemarts, Groenink, Olivier, & Oosting, 2006; van Gaalen, van Koten, Schoffelmeer, & Vanderschuren, 2006; Wade, de Wit, & Richards, 2000; Winstanley, Theobald, Dalley, & Robbins, 2005), increase impulsive choice (Evenden & Ryan, 1996; Helms, Reeves, & Mitchell, 2006), or have no significant effect (Stanis, Avila, White, & Gulley, 2008; Uslaner & Robinson, 2006). On a paced FCN schedule, *d*-amphetamine increases impulsive action (Evenden, 1998; Evenden & Myerson, 1999), as it does on the UVD task (Evenden, 1999b) and 5-CSRT task (Cole & Robbins, 1987; van Gaalen, Brueggeman, Bronius, Schoffelmeer, & Vanderschuren, 2006). On the UVD task, *d*-amphetamine has no effect on impulsive preparation, as defined by this task (Evenden, 1999b). Analyzing group effects for differences such as these does not definitively determine whether different tasks are measuring the same subtype of impulsivity. Since there are generally only three results possible on these tasks (increase, decrease, or no effect), observing the same overall result with *d*-amphetamine, for example, on two

models does not determine if these models are measuring the same construct or whether *d*-amphetamine is affecting behavior on each through different mechanisms.

The three tasks chosen for assessment of the effects of dopaminergic compounds in Specific Aim 2 were also chosen for comparison in Specific Aim 3 with a within-subjects comparison technique. After completion of Specific Aim 2, the same subjects were retrained on a new task. A subset of the drugs listed in Table 1-1 were reassessed, such that baseline performance levels and drug effects could be directly compared among the three tasks on a within-subject basis. The rationale for this experiment depends on the hypothesis that individual differences in performance on these tasks and individual differences in reactions to drugs on these tasks will correlate across measures that rely on the same underlying behavioral and neural processes, while they will not necessarily correlate if different behavior and neural processes are at work. For example, *d*-amphetamine increases premature responses (increases impulsive action) on the UVD task (Evenden, 1999b) and decreases chain length (increases impulsive action) on a paced FCN schedule (Evenden, 1998; Evenden & Myerson, 1999). As with most any behavioral measure, however, individual differences exist in this effect. It is hypothesized that if both of these tasks measure impulsive action as purported, those rats that show the largest response to *d*-amphetamine on the UVD task should also show the largest response to *d*-amphetamine on a paced FCN schedule. Conversely, if these measures are mediated through distinct processes, the effects of *d*-amphetamine on these measures should not necessarily correlate on a within-subject basis. Specific Aim 3 tests such correlations with baseline performance and selected drug effects on the DD task, a paced FCN schedule, and the UVD task.

Table 1-1. Compounds assessed in Specific Aim 2, including the mechanism of action and selectivity profile of each. Selectivity refers to the difference in affinity between the first receptor or transporter listed and the second.

Compound	Mechanism	Selectivity	Reference(s)
d-Amphetamine	DAT/NET blockade	NET/DAT: 9-fold NET/SERT: 549-fold DAT/SERT: 60-fold	Han & Gu, 2006 Han & Gu, 2006 Han & Gu, 2006
GBR 12909	DAT blockade	DAT/SERT: 59-fold DAT/NET: 281-fold	Cao et al., 2008 Cao et al., 2008
Apomorphine	$D_1/D_2/D_3/D_4/D_5$ agonist	D_2/D_1: 7-fold D_4/D_2: 12-fold D_3/D_2: 2-fold	Millan et al., 2002 Millan et al., 2002 Millan et al., 2002
SKF 81297	$D_{1\text{-like}}$ agonist	D_1/D_2: 670-fold	Neumeyer et al., 2004
Sumanirole	$D_{2\text{-preferring}}$ agonist	D_2/D_3: 215-fold D_2/D_4: >240-fold D_2/D_1: >790-fold	McCall et al., 2005 McCall et al., 2005 McCall et al., 2005
Pramipexole	$D_{3\text{-preferring}}$ agonist	D_3/D_2: 170-fold D_3/D_2: 122-fold D_3/D_4: 57-fold D_3/D_1: >954-fold	Newman-Tancredi et al., 2002 Millan et al., 2002 Newman-Tancredi et al., 2002 Millan et al., 2002
ABT-724	D_4 partial agonist	D_4/D_2: >157-fold	Brioni et al., 2004
SCH 23390	$D_{1\text{-like}}$ antagonist	D_1/D_2: >10,000-fold	Neumeyer et al., 2004
L-741,626	$D_{2\text{-preferring}}$ antagonist	D_2/D_3: 15-fold D_2/D_4: 136-fold	Grundt et al., 2007a Grundt et al., 2007a
PG01037	$D_{3\text{-preferring}}$ antagonist	D_3/D_2: 133-fold D_3/D_4: 540-fold	Grundt et al., 2007b Grundt et al., 2007b
L-745,870	D_4 antagonist	D_4/D_2: 2050-fold	Ericksen et al., 2009
Haloperdol	$D_{2\text{-like}}$ antagonist	D_2/D_1: 53-fold	Tice et al., 1994

DAT: dopamine transporter, NET: norepinephrine transporter, SERT: serotonin transporter

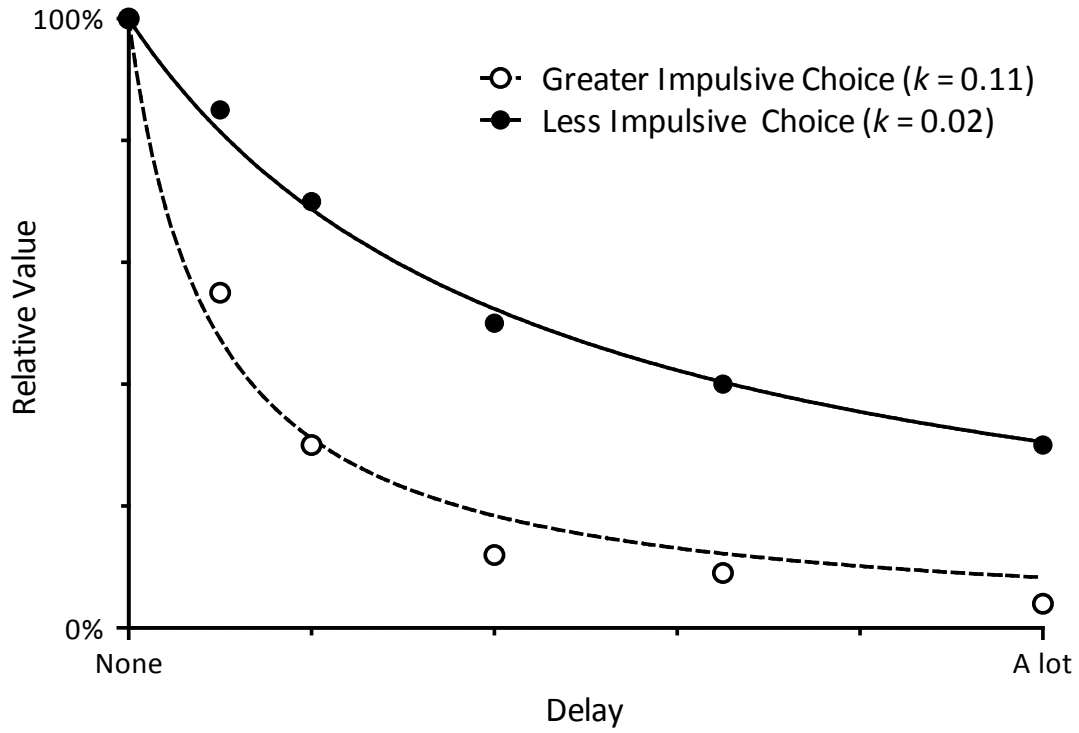

Figure 1-1. Indifference points for two hypothetical groups making choices on a delay discounting task. Each point represents an indifference point from a series of choices between two amounts when delay to the larger amount is varied. Relatively greater impulsive choice is represented by the open symbols and dashed line, while relatively less impulsive choice is represented by filled symbols and a solid line. The hyperbolic function $V = A / (1 + kD)$ typically fits the data well. The k value from this equation indicates the degree of impulsive choice, with a higher k signifying more impulsive choice.

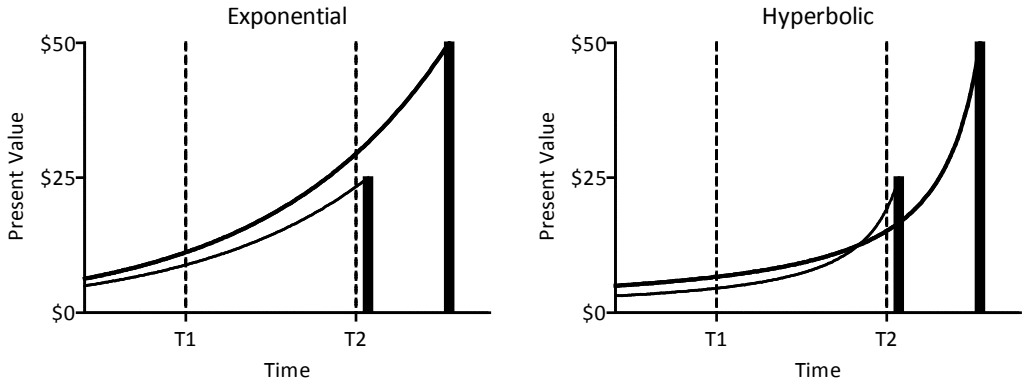

Figure 1-2. Hypothetical discounting curves representing the theoretical importance of hyperbolic discounting. Each graph shows the present subjective value of two delayed rewards, $25 and $50, with the $50 is delayed more than the $25. Exponential curves predict that a choice made at any time point relative to the delivery of the rewards with result in the same preference, and $50 will be chosen in the example. Hyperbolic curves are able to cross, predicting preference reversals. In the example, $50 is preferred when both options are delayed by a large amount (T1), but $25 is preferred if the choice is made near to the availability of the $25 option (T2). Note that this is true even though the delay separating the two choices remains constant. This figure adapted from Ainslie (1975) and Madden et al. (1999).

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CHAPTER 2

INDIVIDUAL DIFFERENCES IN DISCOUNT RATE ARE ASSOCIATED WITH DEMAND FOR SELF-ADMINISTERED COCAINE, BUT NOT SUCROSE

Impulsivity and self control are constructs used to describe what is increasingly apparent to be more than one class of behaviors. Based on operant and neurobiological experiments in humans and animals, a growing consensus largely agrees on at least two types of impulsive behavior: impulsive choice and what is termed impulsive action or behavioral inhibition (Dalley, Mar, Economidou, & Robbins, 2008; de Wit, 2009; Evenden, 1999; Perry & Carroll, 2008; Winstanley, Eagle, & Robbins, 2006). Impulsive choice is the tendency to be hypersensitive to delays of reward, while impulsive action refers to the inability to withhold or inhibit a prepotent response.

Impulsive choice is typically measured using procedures that provide choice opportunities between a smaller amount of a reinforcer delivered after little or no delay and large amount of the same reinforcer delivered after a longer delay (Ainslie, 1975). Impulsive choice on these procedures is defined as the tendency to tolerate only small delays to the larger reinforcer before switching to choose the smaller reinforcer, while self-control is defined as the tendency to tolerate relatively long delays to the larger reinforcer. Variants of this task are used in both humans and animals, and in humans extensive evidence links delay discounting to substance abuse. Substance abusers demonstrate a higher degree of impulsive choice than do matched controls, including

users of cocaine (Coffey, Gudleski, Saladin, & Brady, 2003; Kirby & Petry, 2004), cigarettes (Audrain-McGovern, in press; Baker, Johnson, & Bickel, 2003; Bickel, Odum, & Madden, 1999; Heyman & Gibbs, 2006; Johnson, Bickel, & Baker, 2007; Jones, Landes, Yi, & Bickel, in press; Mitchel, 1999; Reynolds, 2006; Reynolds, Patak, Shroff, Penfold, Melanko, & Duhig, 2007), alcohol (Bobova, Finn, Rickert, & Lucas, 2009; Dom, D'haene, Hulstijn, & Sabbe, 2006; Vuchinich & Simpson, 1998; but see Kirby & Petry, 2004), opioids (Kirby & Petry, 2004; Kirby, Petry, & Bickel, 1999; Madden, Bickel, & Jacobs, 1999; Madden, Petry, Badger, & Bickel, 1997; Odum, Madden, Badger, & Bickel, 2000; Odum, Madden, & Bickel, 2002), and methamphetamine (Monterosso, Ainslie, Xu, Cordova, Domier, & London, 2007). Discounting of delayed rewards is increased further in substance users who also meet criteria for problem gambling (Petry, 2001; Petry & Casarella, 1999), in opioid users that share needles relative to those that do not share needles (Odum et al., 2000), and in opioid users that are deprived of opioids at the time of assessment (Giordano, Bickel, Goewenstein, Jacobs, Marsch, & Badger, 2002). Degree of discounting is also able to predict which people enrolled in smoking-cessation treatment programs will remain abstinent at the end of treatment, with those that exhibit greater impulsive choice more likely to relapse (Krishnan-Sarin et al., 2007; Yoon, Higgins, Heil, Sugarbaker, Thomas, & Badger, 2007).

Despite the robust relationship between delay discounting and substance abuse in people, relatively little research has examined the analogous relationship between delay discounting and drug self-administration in animals. Animal-subjects research offers many opportunities not available in human-subjects research, including the ability to

determine cause-and-effect relationships through environmental manipulation. Delay discounting is modeled straightforwardly in animals. Procedures to measure impulsive choice fall into two categories: adjusting procedures that make within-session adjustments of the amount of one reinforcer or the delay to one reinforcer based on the subject's choices (Mazur, 1987; Richards, Mitchell, de Wit, & Seiden, 1997), or those that arrange choices between a predefined set of delays and amounts (Evenden & Ryan, 1996). In both types of procedures, the tendency to choose the smaller, more immediate reinforcer over the larger, delayed reinforcer is interpreted as impulsive choice. Noncontingent exposure to cocaine has been shown to produce lasting (Simon, Mendez, & Setlow, 2007) or transient (Logue, Tobin, Chelonis, Wang, Geary, & Schachter, 1992; Paine, Dringenberg, Olmstead, 2003) increases in impulsive choice. Individual differences in impulsive choice also predicted acquisition of cocaine self-administration in female rats (Perry, Larson, German, Madden, & Carroll, 2005), as well as level of nicotine self-administration at high response requirements and reinstatement to extinguished nicotine self-administration in male rats (Diergaarde et al., 2008). It is not clear, however, whether animals that discount delayed rewards steeply value these drug reinforcers to a greater extent, as response-rate-based measures of drug reinforcement have many shortcomings (for recent reviews, see Bergman & Peronis, 2006; Hursh & Silberberg, 2008). Two of the critical issues associated with measuring drug reinforcement or value in experimental animals lie with dose effects and direct effects that many drugs have on behavior. When self-administered, different doses of the same drug support different amounts of behavior, with moderate doses typically supporting more behavior than both high and low doses (Bergman & Peronis, 2006). This feature

makes dose an influential variable when assessing reinforcer value, with no clear method of choosing which dose of a given drug best represents the reinforcing value of that drug. In addition, many self-administered drugs function to increase or decrease general activity, confounding the independent variable being assessed (e.g., drug A versus drug B) and the dependent measure (e.g., lever presses maintained by drug A versus drug B).

Behavioral economics, the application of economic terms, concepts, and analytical tools to the study of the behavior of individual organisms (Bickel, Green, & Vuchinich, 1995), provides a system of assessing reinforcer value that is independent of drug dose (Hursh & Silberberg, 2008). In such an analysis, total consumption of a reinforcer is the dependent measure instead of response rate, and this determined at a variety of prices (response requirements). As price increases, consumption decreases in a curvilinear fashion such that a unit increase in price will result in a small reduction in consumption initially, but a progressively larger reduction in consumption as price increases. The rate at which consumption declines is termed the elasticity of demand, and this measure reflects the reinforcer value. If price and consumption are both normalized to relatively unrestrained consumption levels, elasticity of demand can be used to rank order reinforcer value across different reinforcers (e.g., Hursh & Winger, 1995) or across different environmental conditions with responding maintained by the same reinforcer (e.g., Hursh, 1991). Note that elasticity of demand only depends on rate of decline in consumption, and does not depend on total level of responding, total consumption, or on the dose of the self-administered drug. Elasticity of demand therefore avoids many of the potential confounds introduced by rate of responding measures when assessing value of self-administered drugs.

In the current experiment, individual differences in impulsive choice were related to individual differences in valuation of sucrose pellets and cocaine injections. Individual differences in impulsive choice were measured by a slight modification of the delay discounting task described by Evenden & Ryan (1996), and were associated with elasticity of demand for sucrose pellets and elasticity of demand for self-administered cocaine injections. Based on the strong relationship between drug abuse and impulsive choice in humans, a similar relationship was hypothesized between delay discounting and demand for cocaine in rats. Delay discounting measures were also assessed for stability over the course of the experimental procedure with a delay discounting reassessment after demand determination.

Method

Subjects

Twenty-four male Sprague Dawley rats served as subjects (Harlan, Indianapolis, IN). Rats were approximately 10 weeks old at the start of the experiment. A food restriction protocol was in place to maintain the rats at approximately 325 g throughout the experiment. This weight was chosen as it is approximately 85% of the mean adult weight supplied by the manufacturer for this strain, and this weight was not changed once established. When not in session, rats were housed in accordance with institutional animal care and use guidelines in polycarbonate cages with fresh water continuously available. The lights in the housing colony were on from 7:00 AM to 7:00 PM, and sessions were conducted between 9:00 AM and 5:00 PM. These protocols were approved by the University of Michigan Committee on the Use and Care of Animals and

conformed to the guidelines established by the NIH Guide for the Use of Laboratory Animals.

Apparatus

Sessions were conducted in rodent operant conditioning chambers with an area of 30.5 cm x 24.1 cm x 21.0 cm and stainless steel grid floors (ENV-008; Med-Associates Inc., St. Albans, VT). Both sides of the front panel of the chamber held a retractable lever (ENV-112CM). Between the levers was a food tray connected to a 45 mg pellet dispenser (ENV-200R1AM and ENV-203M-45). Above both of the levers and the food tray were triple stimulus lights containing a red, green, and yellow LED (ENV-222M). Centered on the opposite wall was a nose-poke response device containing a yellow LED (ENV-114BM) and a houselight near the top of the wall to provide illumination to the chamber (ENV-215M). The houselight was unused in the current procedure. A syringe pump was located outside the chamber for drug deliveries (PHM-107). Chambers were connected to a computer running Med-PC IV software (Med-Associates, Inc.) to control experimental events and record data.

Procedure

Response and magazine training. Rats were trained to respond on a mixed fixed-time 60 s FR 1 schedule of reinforcement, with the active lever alternating each session between the left and right levers. This schedule arranged one sucrose pellet to be delivered every 60 s independent of behavior, with every lever press also producing a pellet. This was continued for four sessions, at which point the schedule was switched to a FR 1 with no response-independent pellet deliveries. Rats were allowed to respond on

this schedule until 80 responses or more were recorded on two consecutive 20-min sessions.

Delay discounting. The sessions were then extended to 75 min and split into five components of ten discrete-choice trials each. Total trial duration was 90 s and began with one or both levers extending into the chamber. If a single response was made within 20 s, the levers retracted and the consequence programmed for that lever was delivered. If no response was made within 20 s, that trial was recorded as an omission and the levers retracted for the remaining 70 s of that trial. The first two trials of each component were always forced-choice trials where only one lever was extended into the chamber, forcing the subject to sample the contingencies for that component. The remaining eight trials were free-choice trials where both levers were extended into the chamber, allowing the rat to respond on either. The red stimulus light above each lever was lit whenever that lever was inserted in the chamber, with the left light constant and the right light flashing. The green and yellow stimulus lights above the pellet tray were lit during sucrose-pellet deliveries. Initially, the consequences for the left and right levers were immediate deliveries of either one or three 45-mg sucrose pellets, respectively. This condition was continued until rats chose the three-pellet option on at least 85% of free-choice trials. At this point, delays were introduced between responses made on the 3-pellet lever and the delivery of the 3 pellets. The delays to the three-pellet option were 0, 10, 20, 40, or 60 s and were always presented in ascending order with one delay in effect in each of the five 10-trial components. Rats were exposed to this procedure for 48 sessions.

Sucrose pellet demand. Demand for 45-mg sucrose pellets was then determined. Levers remained retracted throughout this procedure and the nose-poke on the back wall

of the chamber was the active response device. At the start of the 30-min sessions, the nose-poke device was lit and reinforcers were delivered on an FR schedule. The same FR schedule remained in effect for the entire session, but the FR schedule value changed between sessions. The consequence of each completed FR was a brief flash of the yellow and green stimulus lights above the pellet tray, the nose-poke light extinguishing, and a single 45-mg sucrose pellet delivered to the tray. After a 5-s timeout period, the nose-poke was illuminated and the FR schedule was again active. FR values of 1, 3, 10, 32, and 100 were examined in an ascending order. This sequence was repeated three times with an extra FR-1 session before the first sequence only, for a total of 16 sessions.

Catheter surgery. Each rat was then implanted with an indwelling femoral catheter for intravenous infusion of cocaine. Rats were surgically prepared with chronic indwelling femoral catheters in either the right or left femoral vein under ketamine (100 mg/kg, i.m.) and xylazine (5 mg/kg, i.m.) anesthesia. The surgical field was shaved and cleaned with betadine, and lacrilube was applied to the eyes prior to the beginning of the surgery. A small incision was made just above the femoral vein, and the overlying tissue was dissected to allow for implantation of catheters into the femoral vein. The wound was closed using 5-0 Ethilon suture, and the catheters were tunneled under the skin and attached to stainless steel tubing, exiting the back through a Dacron mesh tether button which was sutured to the muscle between the scapula. Rats were allowed five to seven days to recover from surgery prior to the resumption of the experiment. Catheters were flushed with 0.25 ml of heperanized saline (100U/ml) daily to promote catheter patency.

Cocaine demand. Rats were initially allowed to respond for contingent infusions of 0.56 mg/kg/infusion cocaine (National Institute on Drug Abuse, Bethesda, MD) on the

nose-poke device on an FR 1 schedule. This continued until rats self-administered at least 20 infusions of cocaine in a 60-min session. The dose of cocaine was then lowered to 0.1 mg/kg/infusion and rats were allowed to self-administer this dose for two sessions on an FR 1 schedule. The session length was then shortened to 30 min and cocaine demand determination began. Rats responded for cocaine in a similar manner as for sucrose pellets, with the FR increasing between sessions. The FR sequence for cocaine demand was 1, 3, 10, 18, 32 and this sequence was repeated three times for most rats. Fewer repetitions were conducted for some rats that experienced catheter patency problems before three repetitions were complete. The mean number of total self-administration sessions was 28.15 (*SD* = 3.59).

Delay discounting redetermination. Rats were then allowed to respond on the delay discounting procedure as described above for 43 sessions.

Data Analysis

Choice data from each rat, expressed as percent choice of three pellets at each delay to three pellets, was analyzed in GraphPad Prism 5 (La Jolla, CA). To be included in the data for group analysis, delay had to significantly affect choices. This criterion included a significant main effect of delay to three pellets on choices, determined by a one-way repeated measures analysis of variance (ANOVA) over the last five delay discounting sessions. In addition, three-pellet choice in the 60-s delay condition had to be significantly lower than in the 0-s delay condition, as measured by a planned *post hoc* comparison test. For purposes of group formation, choice data were then fit to the hyperbolic equation

$$V = \frac{A}{1+k*D} \quad (2\text{-}1)$$

where *V* is the percent choice of three pellets at *D* delay, and *A* and *k* are fit parameters. *A* is the derived percent choice of three pellets when delayed 0 s, and *k* is a measure of the effect of delay on choices.

Demand functions for sucrose pellets and cocaine infusions were plotted as reinforcers earned as a function of response requirement and analyzed using procedures described previously (Hursh & Silverberg, 2008; Hursh & Winger, 1995). Number of reinforcers was reported as total responses divided by FR value. This value was used instead of reinforcer deliveries so the responses that occurred at the end of sessions that did not completely fulfill the response requirement were included in the analyses. Plotted in this manner, data were then fit with non-linear regression techniques in Prism 5 to the exponential equation

$$Y = \log\left(L^{-aX}\right) \tag{2-2}$$

where *Y* is reinforcer consumption at *X* price and *L* and *a* are fit parameters. *L* represents the derived level of unconstrained consumption under the experimental conditions, and is typically nearly equal to consumption at an FR 1. The *a* parameter indicates the elasticity of the curve, or the rate that consumption declines with increases in price.

To better isolate the elasticity parameter, normalized demand curves were also compared. Consumption data were normalized to consumption at an FR 1 with the equation

$$Q = 100 * \frac{Y_n}{Y_1} \tag{2-3}$$

where normalized consumption (*Q*) was equal to consumption at FR *n* (Y_n) divided by consumption at FR 1 (Y_1), expressed as a percent. Price was normalized with the equation

$$P = \frac{\mathrm{FR} * Y_1}{100} \tag{2-4}$$

where P is normalized price, FR is the fixed ratio value, and Y_1 is consumption at an FR 1. These normalized data were then fit to Equation 2-2, with L set to 100 since all data were transformed to be expressed as a percent. This left a single free parameter (a) that quantified elasticity of demand, the proposed measure of reinforcer value. The price that supported the most overall responding was also computed. This value, P_{max}, is directly related to elasticity and can be derived from the a parameter of Equation 2-2 with the equation

$$P_{max} = \frac{0.29}{a} \tag{2-5}$$

To compare correlations between two parameters that were both subject to experimental variability, Pearson product-moment correlations and Deming regressions were conducted in Prism 5. The distribution of k values was not normal in the current experiment, so k values were log transformed when used as the basis of statistical comparisons, an often-required step (e.g., Yoon et al., 2007). The best-fit parameters of demand functions were compared between groups using non-linear regression analyses in Prism 5 which are mathematically equivalent to an Analysis of Covariance (Motulsky & Christopoulos, 2003).

Results

At the end of the initial discounting assessment, 20 of the 24 rats met the statistical criteria for inclusion in a discounting group. These 20 rats were split into three groups based on the k parameter from Equation 2-1 fitted to their choice data: High (n = 7), Medium (n = 6), and Low (n = 7). The percent choice of three pellets at each delay to

three pellets is shown for the last five sessions of the initial discounting assessment in Figure 2-1 (top panel). A two-way ANOVA revealed an overall main effect of delay on choice ($F_{4,72} = 61.42$, $p < .001$) and a main effect of discounting group ($F_{2,72} = 5.72$, $p = .012$). The choices of the three groups were similar when the delay to three pellets was 0 s, with a difference among the groups emerging at higher delays. This pattern resulted in a significant delay by discounting group interaction ($F_{8,72} = 7.35$, $p < .001$). Individual discounting functions were generally well described by Equation 2-1, with median $r^2 = 0.828$ (interquartile range = 0.151) for subjects meeting criteria (Figure 2-1, bottom panel).

Demand for sucrose pellets was then assessed in all 24 rats, with the 20 rats that made up the three discounting groups analyzed in detail. Demand for sucrose pellets did not differ among the three groups when either the *L* parameter ($F_{2,94} = 0.59$, $p = .557$) or *a* parameter ($F_{2,94} = 0.04$, $p = .964$) was compared with curve-fitting procedures (Figure 2-2, top panel). The corresponding P_{max} values for each of the three groups (Figure 2-2, top panel) were nearly identical. Note that individual differences in demand curves for sucrose pellets were relatively small, and curves for subjects from each of the discounting groups overlapped a great deal (Figure 2-2, bottom panel). Normalized demand curves were also similar among the discounting groups (Figure 2-3, top panel), with no significant difference in the best-fit *a* parameter ($F_{2,97} = 0.53$, $p = .588$). Individual variability in these normalized curves was also minimal (Figure 2-3, bottom panel).

Unlike demand for sucrose pellets, demand for intravenous infusions of 0.1 mg/kg/infusion cocaine did differ as a function of group (Figure 2-4, top panel). The High discounting group had less elastic demand than the Low or Medium group, which

was reflected by a significant difference in the *a* parameter of Equation 2-2 fit to these data ($F_{2,73} = 3.53$, $p = .034$). The *L* parameter was not different between groups, however, indicating this group difference was restricted to higher FR values ($F_{2,73} = 0.21$, $p = .808$). The corresponding P_{max} value for the High group (6.37) was considerably higher than the Low (3.26) and Medium (3.43) groups. Note that there were more individual differences in the demand for cocaine than in demand for sucrose pellets (Figure 2-4, bottom panel). Although there was a significant group effect, there was still substantial overlap in the individual-subject data. When cocaine demand curves were normalized, demand in the High group was still less elastic than in the Low and Medium groups ($F_{2,76} = 5.2$, $p = .007$; Figure 2-5, top panel). A great deal of overlap existed in the individual normalized curves, although the rats in the High group tended to have less elastic demand than the rats in the other two groups (Figure 2-5, bottom panel).

Discounting was then reassessed in the 21 rats that were still alive at the end of the cocaine demand determination. Of these rats, 18 met the statistical criteria for inclusion in a second set of discounting groups. Two of the rats that failed to meet criteria also didn't meet criteria in the initial assessment. The other rat met criteria in the original assessment, but failed to meet criteria in the reassessment. The other two of the four rats that failed to meet criteria in the original assessment did meet criteria in the reassessment. The 18 rats that met criteria in the reassessment were split into three groups of six rats each, using *k* from Equation 2-1 fit to the individual choice data. Many of the rats stayed in the same discounting group in both assessments, although the performance of some switched enough to cause a change in group composition. Analyzed by group in these 18 subjects, there was a main effect of delay ($F_{4,60} = 24$, $p < .001$) and discounting group

($F_{2,60} = 48$, $p < .001$) on choices of three pellets (Figure 2-6, top panel). These differences also tended to be larger at the higher delays, leading to a significant group by delay interaction ($F_{8,60} = 3.8$, $p = .001$). Note that in the discounting reassessment, the groups were not equal with respect to sensitivity to amount, with significant differences among the groups in the 0-s delay component. A large amount of individual variability can be noted in examination of the individual discounting curves (Figure 2-6, bottom panel). These discounting curves, in general, also appeared to be steeper than those in the initial discounting assessment (see Figure 2-1, bottom panel). This was confirmed by a paired *t* test on the log *k* values from the individual curves in the initial assessment and reassessment ($t_{15} = 2.8$, $p = .013$). The *A* values from Equation 2-1 did not differ between discounting assessments ($t_{15} = 1.1$, $p = .306$). Any changes noted between the initial discounting assessment and reassessment did not depend on initial discounting group for log *k* values ($F_{2,13} = 0.78$, $p = .480$) or *A* values ($F_{2,13} = 0.43$, $p = .662$). In those rats that completed and met significance criteria in both discounting assessments, the respective *k* and *A* values from Equation 2-1 were significantly correlated across assessments (Figure 2-7; log *k* correlation $r = .698$, $n = 16$, $p = .003$; *A* correlation $r = .770$, $n = 16$, $p < .001$). In addition, the discounting groups remained similar (Figure 2-8). When discounting choices in the reassessment were plotted as a function of the groups determined by choices in the initial discounting assessment, a significant difference among groups remained (delay main effect $F_{4,52} = 39$, $p < .001$, discounting group main effect $F_{2,52} = 2.6$, $p = .109$, delay by group interaction $F_{8,52} = 2.3$, $p = .034$).

Using performance on the discounting reassessment as a basis for group selection, the effect of discounting group on demand for cocaine remained (Figure 2-9). Elasticity

of demand (*a* from Equation 2-2) for injections of 0.01 mg/kg/injection cocaine differed among the three discounting groups as determined by the discounting reassessment ($F_{2,69}$ = 3.2, p = .047), but the demand level (*L* from Equation 2-2) did not differ ($F_{2,69}$ = 0.01, p = .986; Figure 2-9, top panel). The P_{max} value derived from each of these curves was highest in the High discounting group and lowest in the Low discounting group. When normalized, this relationship between discounting and demand elasticity was more clear ($F_{2,72}$ = 5.8, p = .005; Figure 2-9, bottom panel).

Despite the significant and consistent relationship between demand for cocaine and discounting, a great deal of individual variability exists in these data. This is exemplified by performing a Pearson correlation analysis on the log *k* parameters from Equation 2-1 with the log P_{max} value derived from Equation 2-2 fit to the normalized individual cocaine demand curves. This correlation, using both the initial discounting assessment (Figure 2-10, top panel; r = .215, n = 16, p = .424) or the discounting reassessment as a basis (Figure 2-10, bottom panel; r = .213, n = 15, p = .447) was positive, but did not approach statistical significance. Examination of Figure 2-10 reveals a great deal of variability, and the relatively low-power statistical test of a Pearson product-moment correlation in this situation (relative to curve-fitting procedures employed by Prism 5) did not find these positive correlations statistically significant.

Discussion

Subjects appeared to learn the contingencies of the operative schedule of reinforcement during each phase of the current experiment, with data largely following the expected patterns. Individual differences in delay discounting did not predict level or elasticity of demand for sucrose, but did predict elasticity of demand for self-

administered cocaine injections. This relationship occurred whether delay discounting was measured prior to or after demand assessments.

Sizeable individual differences in sensitivity to delay produced discounting groups that significantly differed from one another in their choices of immediate and delayed rewards (Figure 2-1). These assessments were reasonably stable, with individual log *k* and *A* values correlating between the initial discounting assessment and reassessment (Figure 2-7, Figure 2-8). Overall, discounting was steeper in the second assessment, however. It should be noted that Equation 2-1, used here to differentiate subjects based on sensitivity to delay, is not typically used to analyze data obtained from the Evenden & Ryan (1996) procedure. For *k* to be a true representation of discounting rate as proposed by Mazur (1987), a series of indifferent points assessed with distinct amount and delay comparisons should first be obtained. Only one amount comparison was included in the current experiment (i.e., one versus three sucrose pellets), and therefore only one indifference point could be obtained from any subject's choice data. Curve-fitting with a single datum point is of little use. Rather, this hyperbolic function was used because it happened to describe the choice data in the current experiment well, and provided a simple one-parameter assessment of sensitivity to delay (*k*) and amount (*A*). To determine if the findings of the current experiment were a byproduct of the specific equation chosen to summarize obtained data, the slope and y-intercept of linear regression analyses drawn through choice data were also obtained and used as measurements of sensitivity to delay (slope) and amount (y-intercept). While this method of grouping subjects did not result in the same composition of the High, Medium, and Low groups, statistical conclusions of data described in this manner were not appreciably

different, and did not lead to different logical conclusions (i.e., the Linear Regression High group had significantly less elastic demand for cocaine than the Linear Regression Low group, with no difference in sucrose demand).

Individual differences in discounting were associated with elasticity of demand for cocaine (Figure 2-4, Figure 2-5), suggesting that impulsive choice differentiates assessments of cocaine value. An analogous relationship was not found between impulsive choice and demand for sucrose (Figure 2-2, Figure 2-3), indicating that differences in cocaine demand were not simply due to differences in propensity to respond for reinforcers of any type. Instead, a specific relationship seems to exist between cocaine demand and impulsive choice. Previous research has suggested a relationship between impulsive choice and acquisition of cocaine self-administration in female rats (Perry et al., 2005). The current research extends this finding by relating elasticity of cocaine demand in male rats to impulsive choice, with a sucrose demand control condition. It is notable that level of cocaine demand (L from Equation 2-2), which approximates responding on an FR 1, did not differ between delay discounting groups. Only elasticity of demand differed, which agrees with the finding that delay discounting is associated with nicotine self-administration at high FR values only (Diergaarde et al., 2008).

In humans, a clear relationship between substance abuse and delay discounting has been demonstrated, including with cocaine abusers as subjects (Coffey et al., 2003; Kirby & Petry, 2004). Due to the inherent limitations of human-subjects research, however, the causal direction, if any, of this correlation has not been conclusively determined. Four explanations for this observed correlation are plausible: inborn

variability in impulsive choice predisposes an individual to an increased likelihood of abusing cocaine, cocaine exposure and the life experiences associated with procuring and consuming cocaine increase impulsive choice, both characteristics cause the other in a positive-feedback loop, or both impulsive choice and cocaine abuse vulnerability are caused by an unknown third variable and do not otherwise interact. Limited evidence exists demonstrating that impulsivity, as measured by personality questionnaires and behavioral assessments, predicts development of drug abuse in human subjects (for review, see de Wit, 2009). Perhaps most relevant to impulsive choice is a single study finding that individual differences in delay discounting assessed at grade 10 predicts initiation of smoking within the following four years (Audrain-McGovern et al., in press). Also, ratings by nursery school teachers of nursery school children on a behavioral assessment item "Is unable to delay gratification," was associated with likelihood of using marijuana at age 14 (Block, Block, & Keys, 1988). However, a similar study found that the same assessment item measured at age 7 to 11 did not predict drug use at age 18; although the authors conclude that an overall psychological profile of impulsivity did predict drug use (Shedler & Block, 1990). The results of the current experiment, to the extent that the models employed capture the human condition, suggest that such a positive relationship does occur between impulsive choice and later propensity to self-administer cocaine.

Whether the act of abusing a substance increases discounting has not been studied experimentally in humans, for obvious reasons. However, acute drug effects have been shown to affect impulsive choice (for review, see de Wit, 2009) and recent opioid intake influences level of discounting in opioid abusers (Giordano et al., 2001). However, ex-

smokers and never-smokers discount delayed rewards similarly and less than current-smokers, suggesting that if smoking alters impulsive choice, it does so temporarily (Bickel et al., 1999). Delay discounting assessments conducted before and after the initiation of smoking also did not find evidence that smoking altered discounting of delayed rewards (Audrain-McGovern et al., in press), despite discounting in smokers being higher (Baker et al., 2003; Bickel et al., 1999; Heyman & Gibbs, 2006; Johnson et al., 2007; Jones et al., in press; Mitchel, 1999; Reynolds, 2006; Reynolds et al., 2007). These results suggest that impulsive choice may cause smoking, but not vice versa. The current study was not designed optimally to determine if cocaine self-administration influences discounting, but an increase in impulsive choice was measured from the initial discounting assessment to the discounting redetermination assessed after a period of cocaine self-administration. Increased impulsive choice with age is not typical, as impulsive choice typically negatively correlated with age in people (Green, Fry, & Myerson, 1994) and in rats (Simon et al., in press). An appropriate control group that experienced all the behavioral and surgical components of the current experiment without cocaine self-administration was not included, however. While noncontingent injections of cocaine are known to increase impulsive choice (Logue et al., 1992; Paine et al., 2003; Simon et al., 2007), further research is needed to determine the effects of self-administered cocaine on impulsive choice.

In conclusion, individual differences in impulsive choice are associated with elasticity of cocaine demand, a measure of reinforcer value. This relationship holds if impulsive choice is measured before or after cocaine demand is determined, and sucrose demand is not differentiated by individual differences in impulsive choice. Impulsive

choice was increased following cocaine self-administration, but the cause of this increase cannot be determined by the current experiment.

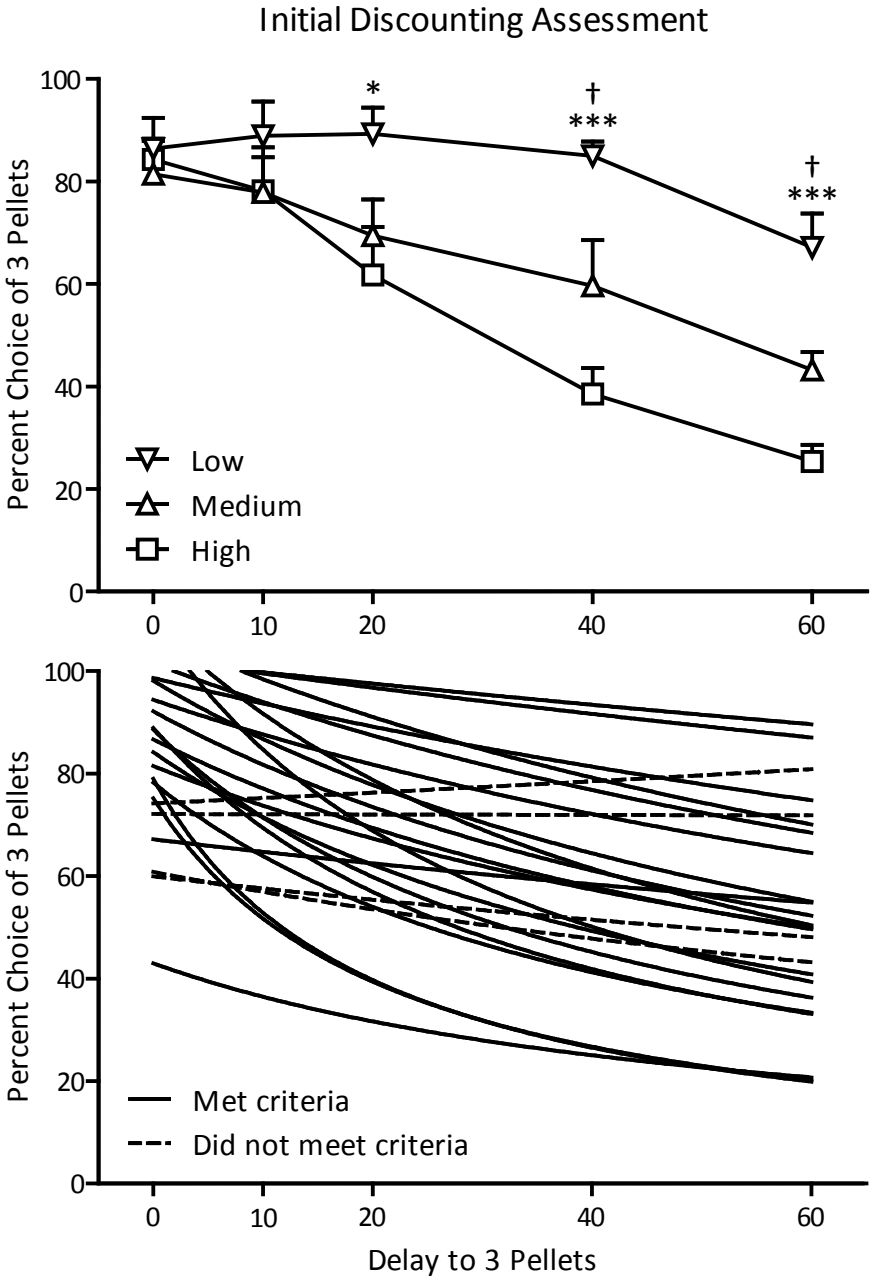

Figure 2-1. Choice data from the initial delay discounting assessment. Top panel: Groups of rats divided based on the *k* parameter from Equation 2-1 fit to the individual subject data. Data are presented as percent choice of 3 pellets as a function of the delay to 3 pellets for the High (□), Medium (△), and Low (▽) groups. Symbols near points indicate that point is significantly different from the corresponding point in the High (* $p < .05$, ** $p < .01$, *** $p < .001$) or the Med group († $p < .05$), as measured by a Bonferroni-adjusted *post hoc* test. Bottom panel: The fit curves obtained by fitting Equation 2-1 to the individual subject data. Curves in solid lines represent the 20 rats for which delay significantly affected their choice behavior, as described in the Data Analysis section. Curves in broken lines represent the four rats for which delay did not significantly reduce choice behavior. These four rats are not included in the groups in the top panel.

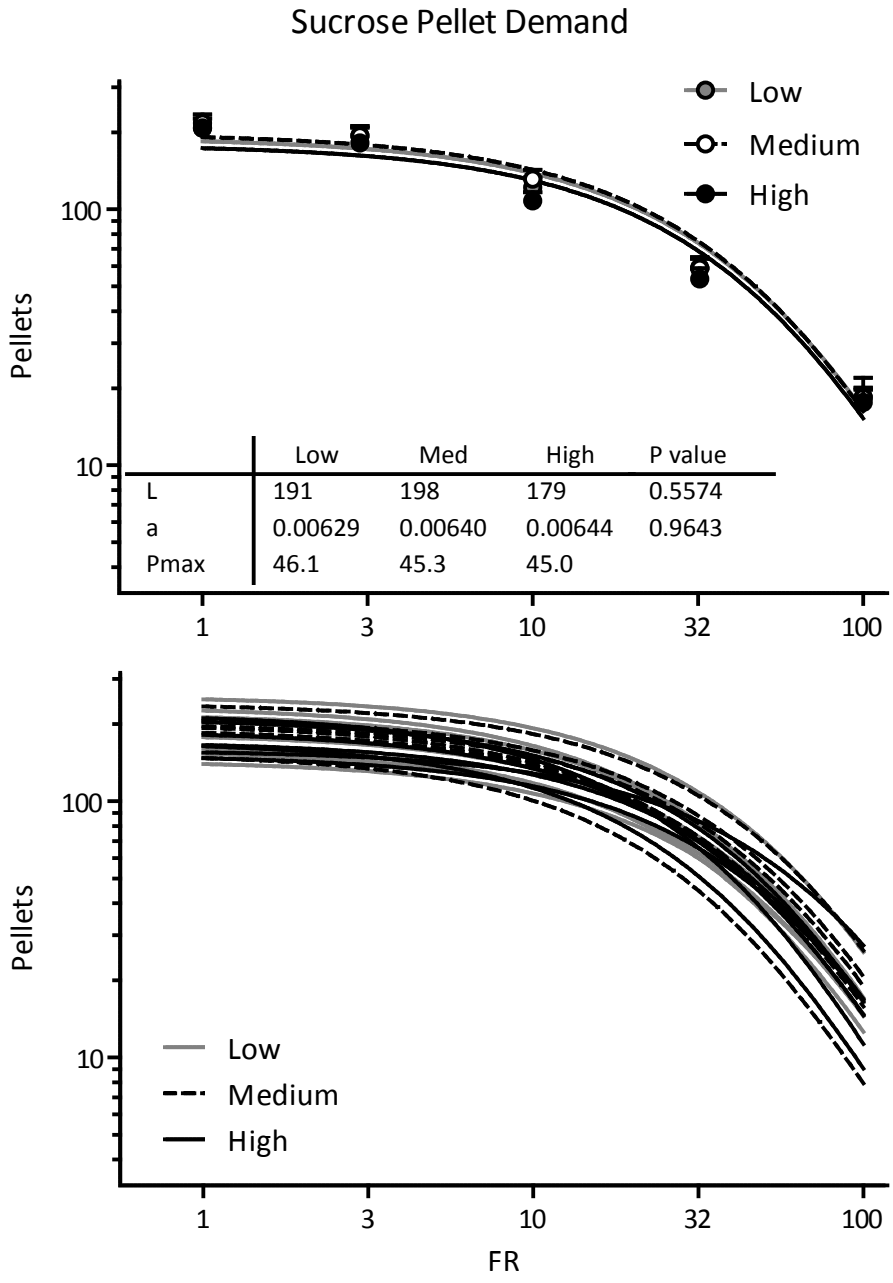

Figure 2-2. Demand for sucrose pellets. Top panel: Demand for sucrose pellets graphed as a function of discounting group. Data are plotted as consumption of sucrose pellets as a function of FR value. The best-fit parameters from the non-linear regression analyses are shown in the inset table for each group. The *p* value for the statistical comparison of those groups is also included for each parameter. P_{max}, derived from *a*, is also included. Bottom panel: The same data as in the top panel with individual-subject curves shown. The style of line indicates the discounting group in which that rat belongs.

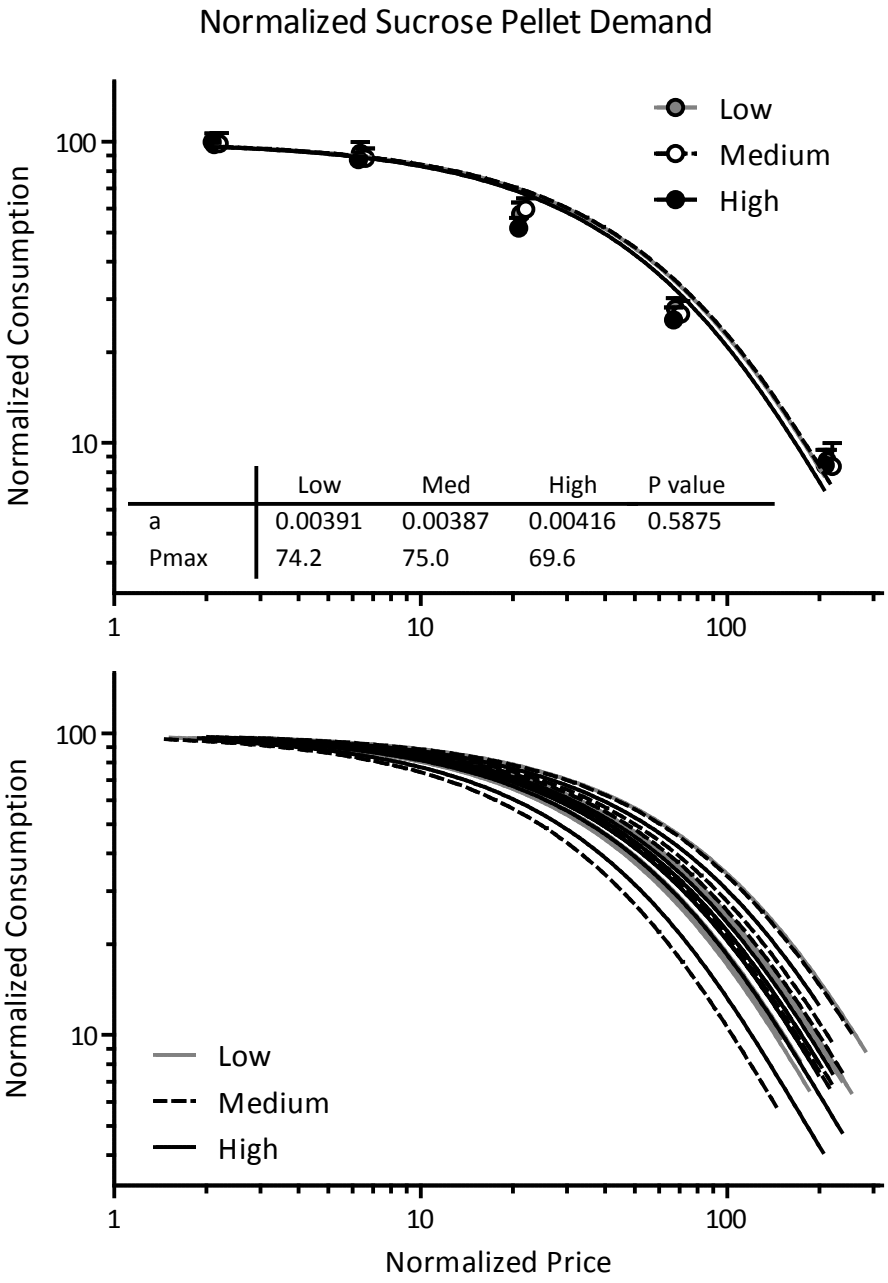

Figure 2-3. Normalized demand for sucrose pellets. Top panel: Normalized demand for sucrose pellets as a function of discounting group. Data are plotted as normalized consumption of sucrose pellets as a function of normalized price. The *L* parameter of Equation 2-2 is set to 100, and the best-fit *a* parameter is shown in the inset table with associated *p* value of the group comparison. P_{max}, which for these comparisons is in arbitrary normalized units, is also displayed. Bottom panel: The same data as in the top panel with the individual-subject curves shown. The style of the line indicates the discounting group in which that rat belongs.

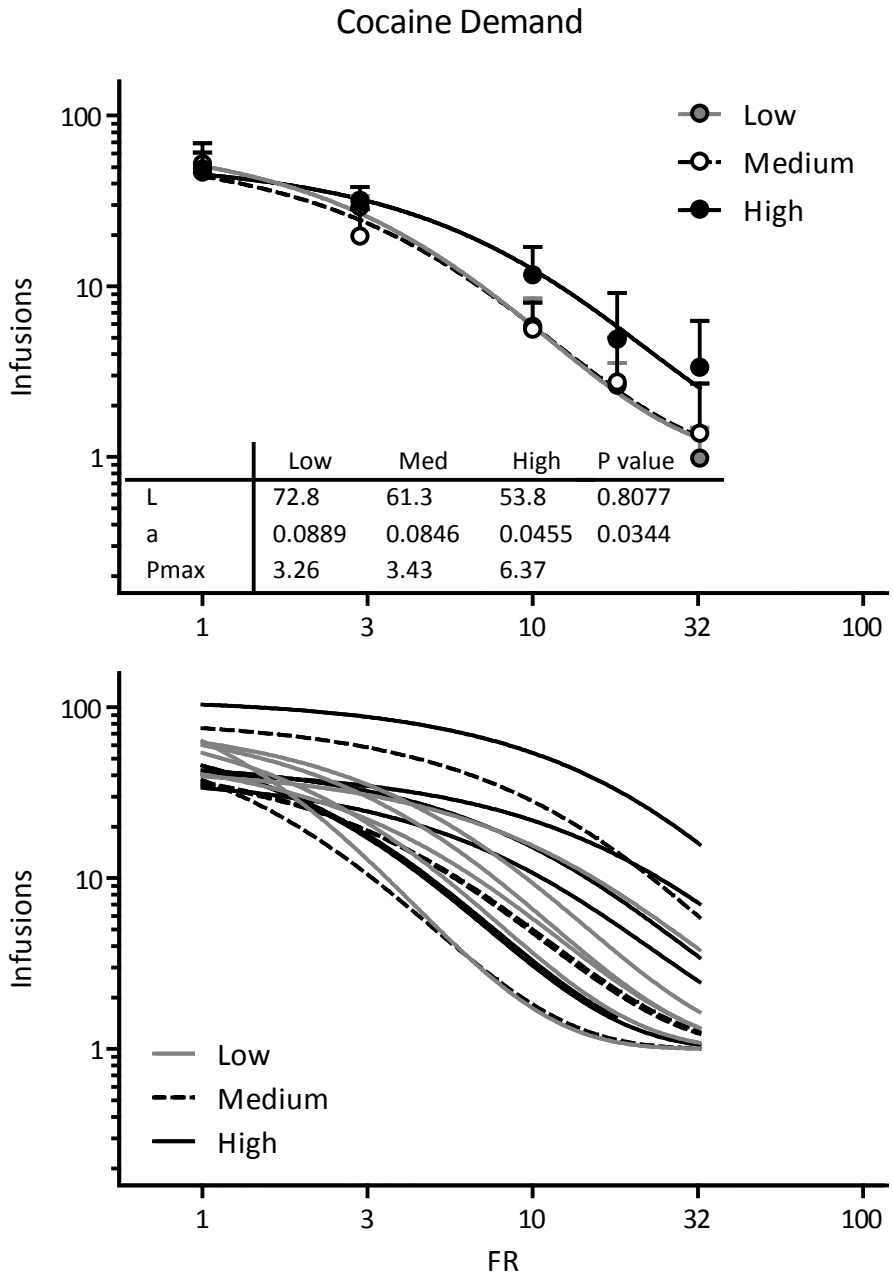

Figure 2-4. Demand for cocaine injections. Top panel: Demand for injections of 0.1 mg/kg/injection cocaine graphed as a function of discounting group. Data are plotted as consumption of cocaine as a function of FR value. The best-fit parameters from the non-linear regression analyses are shown in the inset table for each group. The *p* value for the statistical comparison of those groups is also included for each parameter. P_{max}, derived from *a*, is also included. Bottom panel: The same data as in the top panel with individual-subject curves shown. The style of line indicates the discounting group in which that rat belongs.

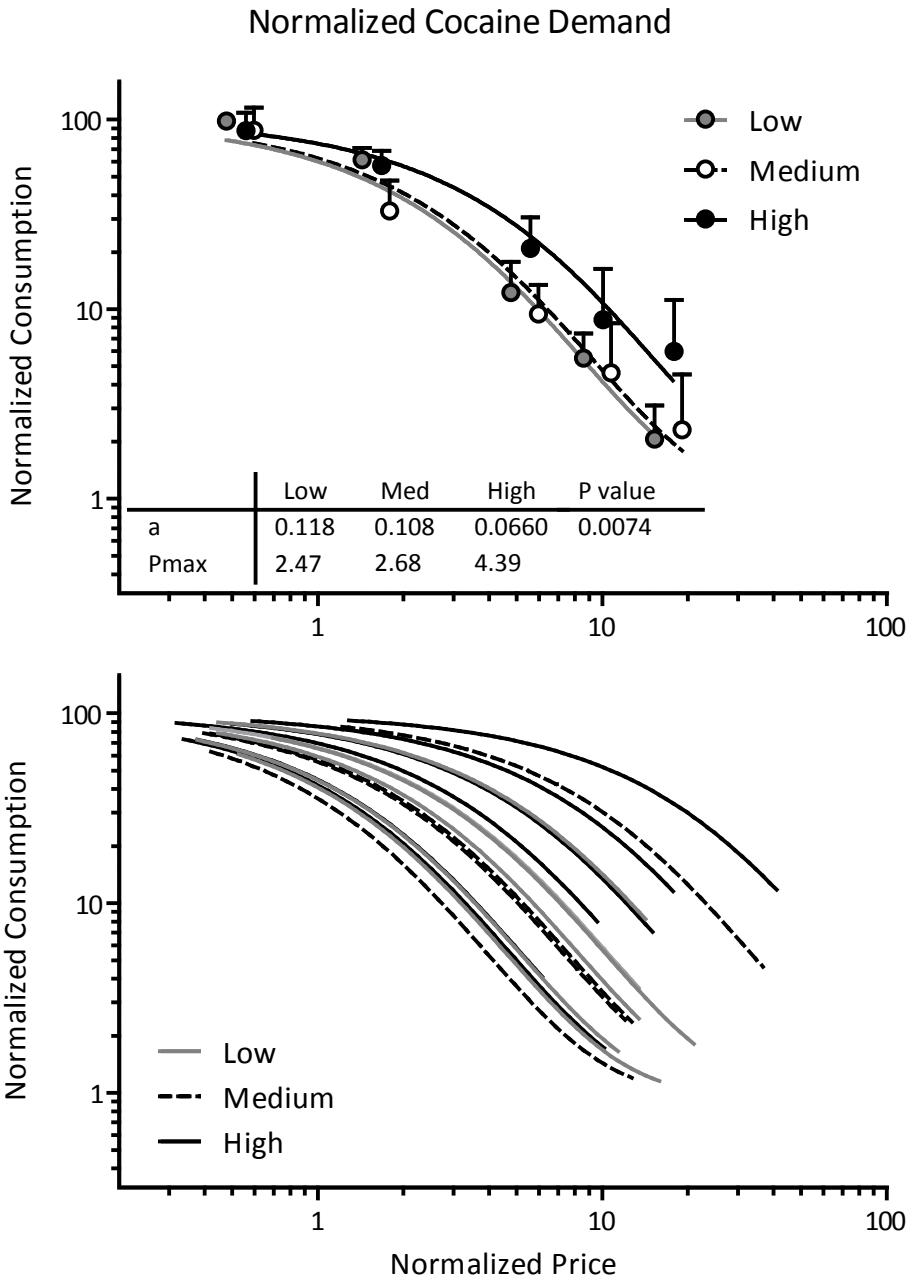

Figure 2-5. Normalized demand for cocaine injections. Top panel: Normalized demand for injections of 0.1 mg/kg/injection cocaine as a function of discounting group. Data are plotted as normalized consumption of cocaine as a function of normalized price. The *L* parameter of Equation 2-2 is set to 100, and the best-fit *a* parameter is shown in the inset table with associated *p* value of the group comparison. P_{max}, which for these comparisons is in arbitrary normalized units, is also displayed. Bottom panel: The same data as in the top panel with the individual-subject curves shown. The style of the line indicates the discounting group in which that rat belongs.

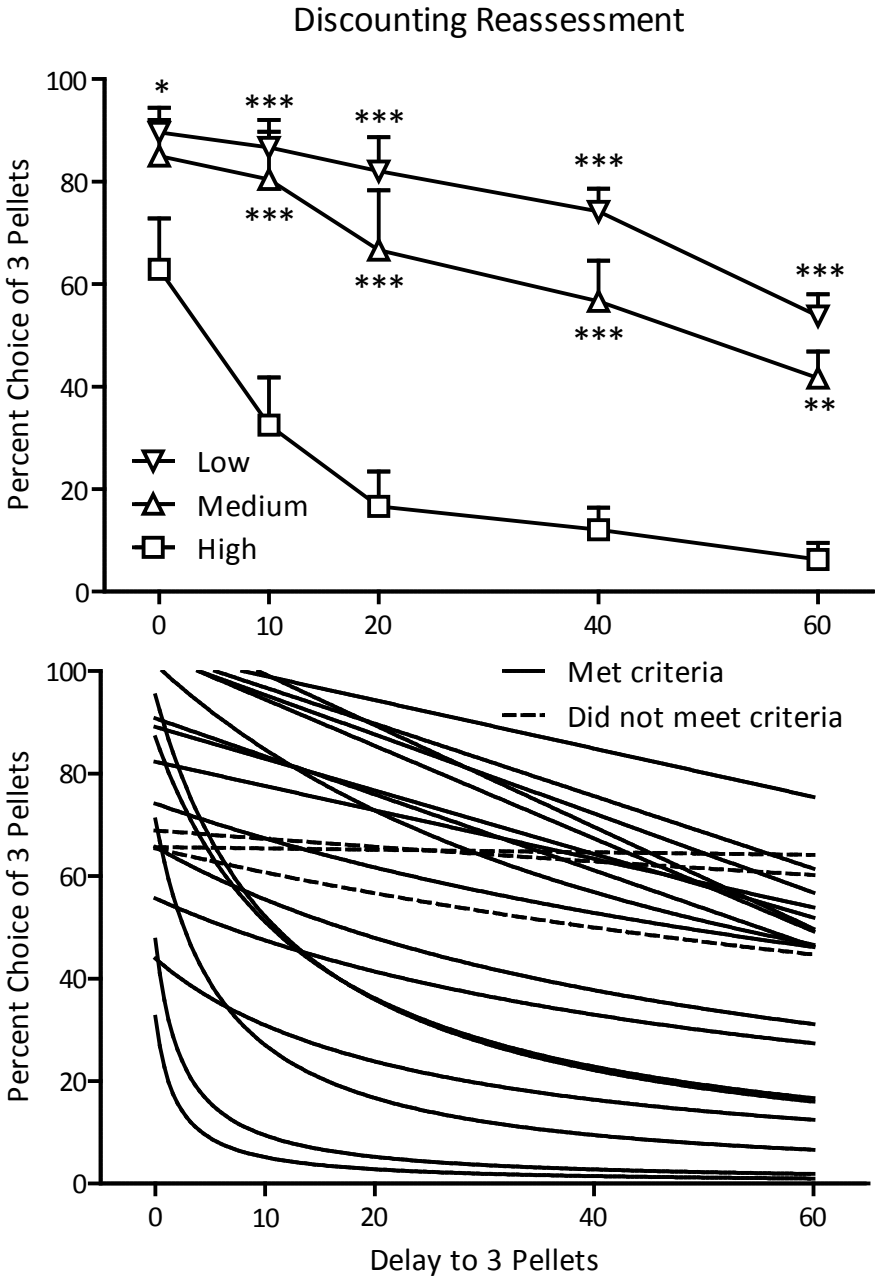

Figure 2-6. Choice data from the delay discounting reassessment. Top panel: Groups of rats divided based on the *k* parameter from Equation 2-1 fit to the individual subject data. Data are presented as percent choice of three pellets as a function of the delay to three pellets for the High (□), Medium (△), and Low (▽) groups, not necessarily comprising the same rats as in Figure 1. Symbols near points indicate that point is significantly different from the corresponding point in the High group (* $p < .05$, ** $p < .01$, *** $p < .001$), as measured by a Bonferroni-adjusted *post hoc* test. Bottom panel: The fit curves obtained by fitting Equation 2-1 to the individual subject data. Curves in solid lines represent the 18 rats for which delay significantly affected their choice behavior, as described in the Data Analysis section. Curves in broken lines represent the three rats for which delay did not significantly reduce choice behavior. These three rats are not included in the groups in the top panel.

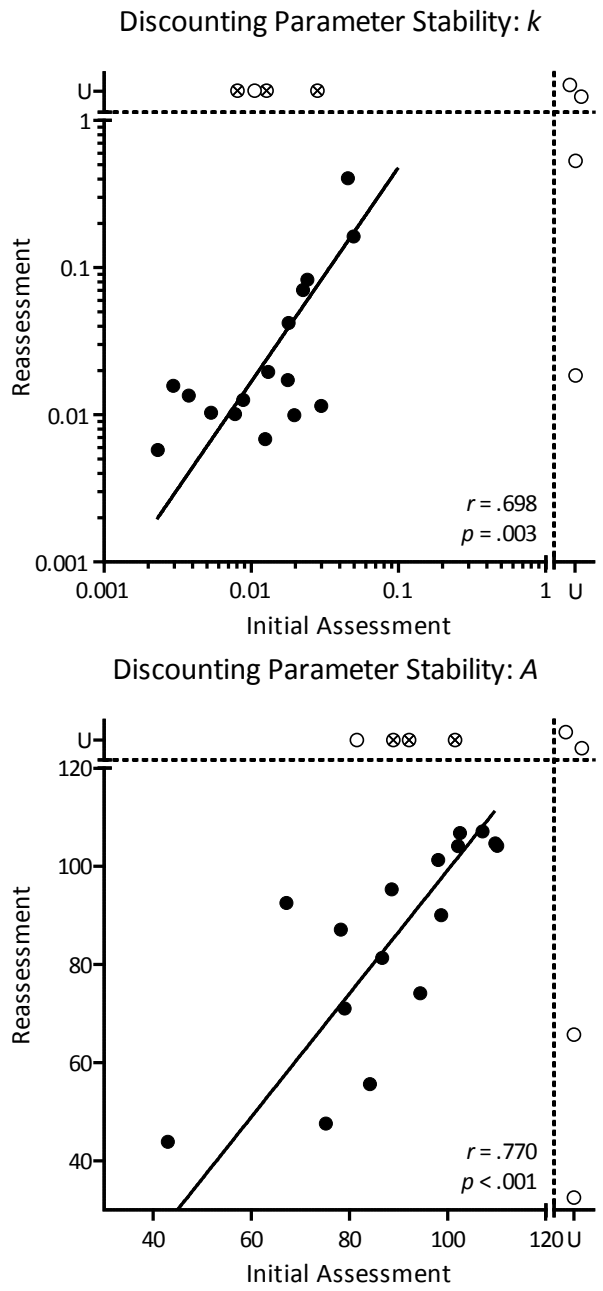

Figure 2-7. Discounting parameters collected from the initial discounting assessment compared to those collected during the discounting reassessment. Subjects for which data was available for both assessments (●) were used in statistical analyses. If a data point was unavailable (U) due to delay failing to significantly affect choices in the discounting task during one or both assessments (○) or if a subject died before one assessment (⊗), that point was placed near the right edge or top of the graph corresponding to the available. The two open symbols in the upper right portion of the graphs represent the two subjects that did not meet criteria in either assessment. Pearson product-moment correlation results are shown on the graph, and a Deming regression line has been drawn to display this correlation visually. Top panel: Comparison of the log *k* parameter from Equation 2-1 across discounting assessments. Bottom panel: Comparison of the *A* parameter from Equation 2-1 across discounting assessments.

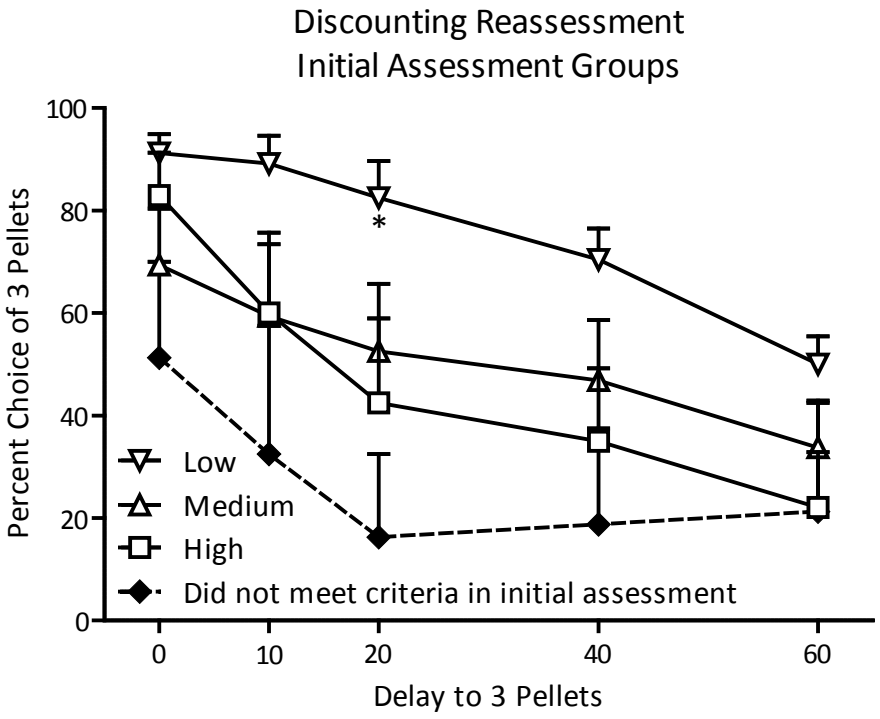

Figure 2-8. Choice from the delay discounting reassessment, grouped as a function of *k* values obtained from the initial delay discounting assessment. Symbols correspond to the original High (□), Medium (△), and Low (▽) discounting groups. Two rats that did not meet criteria in the original assessment, but did meet criteria in the reassessment, are also shown (◆). Symbols near points indicate that point is significantly different from the corresponding point in the High group (* $p < .05$), as measured by a Bonferroni-adjusted *post hoc* test.

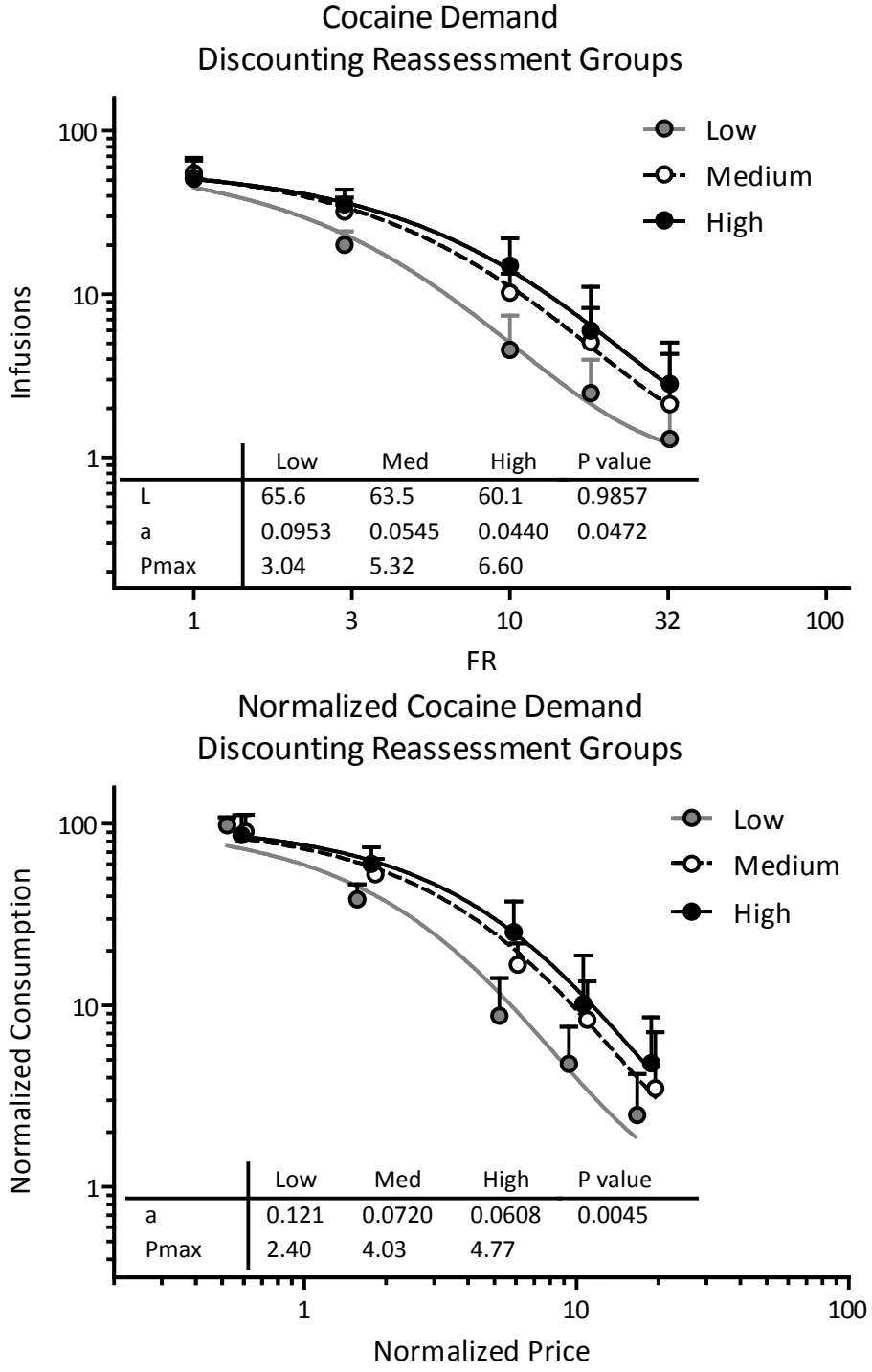

Figure 2-9. Demand for injections of 0.1 mg/kg/injection cocaine, with discounting groups determined based on the discounting reassessment. The best-fit parameters from the non-linear regression analyses are shown in the inset table for each group. The *p* value for the statistical comparison of those groups is also included for each parameter. P_{max}, derived from *a*, is also included. Top panel: Demand plotted as consumption of cocaine as a function of FR value. Bottom panel: Normalized demand plotted as normalized consumption of cocaine as a function of normalized price.

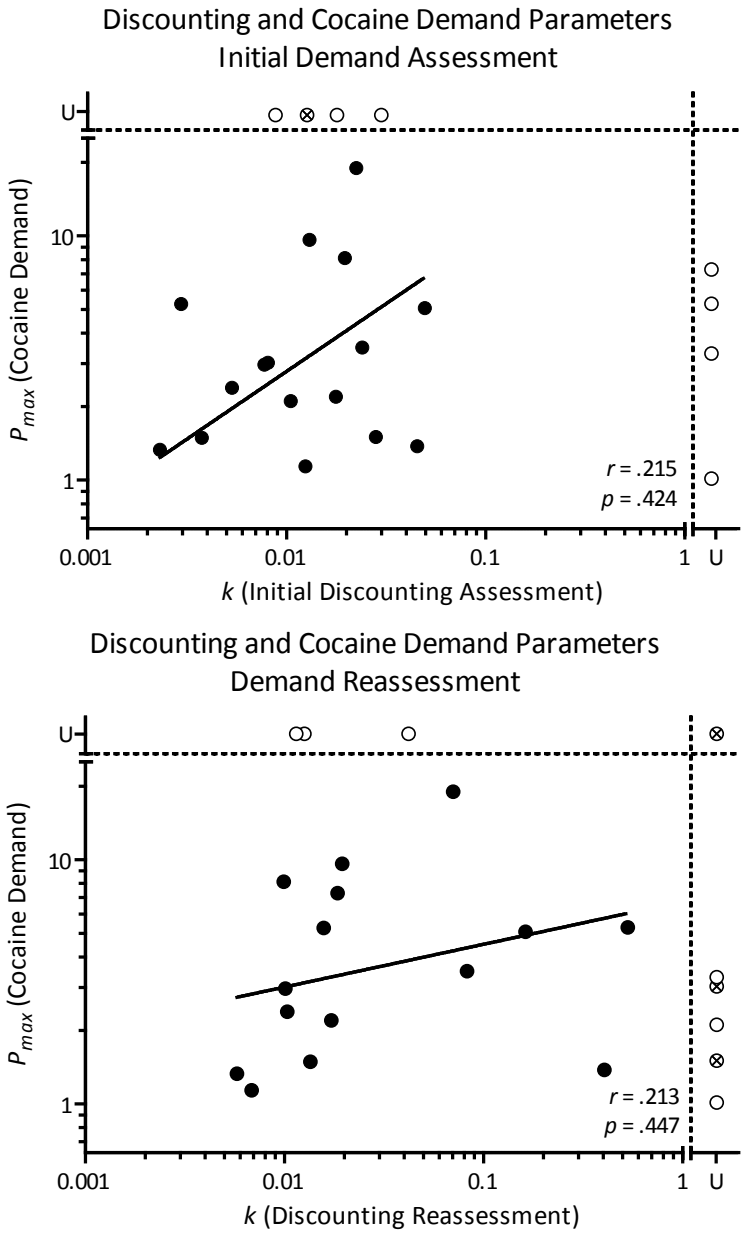

Figure 2-10. Discounting parameters compared to log P_{max} values from the individual normalized cocaine demand curves (Figure 2-5, bottom panel). Subjects for which data was available for both assessments (●) were used in statistical analyses. If a measure was unavailable (U) for one due to failure to meet inclusion criteria (○) or if a subject died before one or both assessments (⊗), that point was placed near the right edge or top of the graph corresponding to the available value. Pearson product-moment correlations were conducted to determine if a significant relationship existed between the two assessments and a Deming regression line was drawn to display this correlation visually. Top panel: Comparison of discounting and cocaine demand using the log *k* values from the initial discounting assessment as a basis. Bottom panel: Comparison of discounting and cocaine demand using the log *k* values from the discounting reassessment as a basis.

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CHAPTER 3

EFFECTS OF SELECTIVE DOPAMINERGIC COMPOUNDS ON A DELAY DISCOUNTING TASK

Impulsivity and self control are constructs used to describe what is increasingly apparent to be more than one class of behaviors. Based on operant and neurobiological experiments in humans and animals, a growing consensus largely agrees on two types of impulsive behavior: impulsive choice and what is termed impulsive action or behavioral inhibition (Dalley, Mar, Economidou, & Robbins, 2008; de Wit, 2009; Evenden, 1999; Perry & Carroll, 2008; Winstanley, Eagle, & Robbins, 2006). Impulsive choice is the tendency to be hypersensitive to delays of reward, while impulsive action refers to the inability to withhold or inhibit a prepotent response. In addition to these two, a third component of impulsivity has been proposed by some. Impulsive preparation or reflection impulsivity, acting before gathering and processing all necessary information, has been argued to encompass impulsive-like responding on a variety of cognitive tasks used in humans and an uncertain visual discrimination task in rats (Evenden, 1999).

Impulsive choice is typically measured using procedures that provide choice opportunities between a smaller amount of a reinforcer delivered after little or no delay and large amount of the same reinforcer delivered after a longer delay (Ainslie, 1975). Impulsive choice on these procedures is defined as the tendency to tolerate only small delays to the larger reinforcer before switching to choose the smaller reinforcer, while

self-control is defined as the tendency to tolerate relatively long delays to the larger reinforcer. Variants of this task are used in both humans and animals, and in humans extensive evidence links delay discounting to impulse-control disorders such as attention deficit hyperactivity disorder (ADHD) (Schweitzer & Sulzer-Azaroff, 1995; Solanto et al., 2001; Sonuga-Barke, Taylor, Sembi, & Smith, 1992; Sonuga-Barke, Williams, Hall, & Saxton, 1996) and substance abuse (Audrain-McGovern, in press; Baker, Johnson, & Bickel, 2003; Bickel, Odum, & Madden, 1999; Bobova, Finn, Rickert, & Lucas, 2009; Coffey, Gudleski, Saladin, & Brady, 2003; Dom, D'haene, Hulstijn, & Sabbe, 2006; Heyman & Gibbs, 2006; Johnson, Bickel, & Baker, 2007; Jones, Landes, Yi, & Bickel, in press; Kirby & Petry, 2004; Kirby, Petry, & Bickel, 1999; Madden, Bickel, & Jacobs, 1999; Madden, Petry, Badger, & Bickel, 1997; Mitchel, 1999; Monterosso, Ainslie, Xu, Cordova, Domier, & London, 2007; Odum, Madden, Badger, & Bickel, 2000; Odum, Madden, & Bickel, 2002; Petry, 2001; Petry & Casarella, 1999; Reynolds, 2006; Reynolds, Patak, Shroff, Penfold, Melanko, & Duhig, 2007; Vuchinich & Simpson, 1998).

Evidence for the importance of dopaminergic systems in impulsive choice comes from a variety of experimental approaches. Dopaminergic pathways from the basal ganglia to the prefrontal cortex have been identified as abnormal in people with ADHD, as well as involved in choices on the delay discounting task in animals (for recent reviews see Bickel, Miller, Yi, Kowal, Lindquist, & Pitcock, 2007; Winstanley et al., 2006). Functional magnetic resonance imaging (fMRI) scans of people choosing between delayed or immediate rewards show activation of prefrontal cortex (PFC) and the striatum, with delayed or difficult choices associated with more PFC activation (Ballard

& Knutson, 2009; Hoffman et al., 2008; McClure, Laibson, Loewenstein, & Cohen, 2004; Shamosh et al., 2008). Lesion studies in animals support the involvement of these structures, with the nucleus accumbens (NAc) core involved in valuation of reward amount in delay discounting (Acheson et al., 2006; Bezzina et al., 2007; Cardinal, Pennicott, Sugathapala, Robbins, & Everitt, 2001) and PFC involved in sensitivity to delay (Bezzina et al., 2008; Kheramin et al., 2004; Winstanley, Theobald, Cardinal, & Robbins, 2004). Given that ADHD is associated with lower PFC dopamine activity (Ernst, Zametkin, Matochik, Jons, & Cohen, 1998) and lower PFC activation during a task involving delayed reward (Rubia et al., 1999), and that methamphetamine abusers also show lower PFC activity during the delay discounting task (Monterosso et al., 2007), this neural pathway is a plausible target for treatment of impulse control disorders.

Both $D_{1\text{-like}}$ (D_1 and D_5) and $D_{2\text{-like}}$ (D_2, D_3, and D_4) dopamine receptors, as well as dopamine transporters, are known to exist in the dopaminergic pathways connecting the striatum to the PFC (Ciliax et al., 1995; Gaspar, Bloch, & Le Moine, 1995; Lévesque et al., 1992; Mrzljak, Bergson, Pappy, Huff, Levenson, & Goldman-Rakic, 1996; Muly III, Szigeti, & Goldman-Rakic, 1998; Revay, Vaughan, Grant, & Kuhar, 1996). As amphetamine and methylphenidate are the two most common pharmaceutical treatments for ADHD, it is not surprising that these have been extensively studied in experiments with rodents behaving on delay discounting tasks. Systemic methylphenidate treatment typically reduces impulsive choice (i.e., animals tolerate longer delays to the larger reinforcer) (e.g., Perry, Stairs, & Bardo, 2008; Pitts & Febbo, 2004; Pitts & McKinney, 2005; van Gaalen, van Koten, Schoffelmeer, & Vanderschuren, 2006), while treatment with *d*-amphetamine shows mixed results. In intact animals, *d*-amphetamine has been

shown to reduce impulsive choice (Floresco, Tse, & Chods-Sharifi, 2008; van den Bergh, Bloemarts, Groenink, Olivier, & Oosting, 2006; van Gaalen et al., 2006; Wade, de Wit, & Richards, 2000; Winstanley, Theobald, Dalley, & Robbins, 2005), increase impulsive choice (Evenden & Ryan, 1996; Helms, Reeves, & Mitchell, 2006), or have no significant effect (Stanis, Avila, White, & Gulley, 2008; Uslaner & Robinson, 2006). Others have explored these discrepancies further, noting that the effects of amphetamine may depend on whether there is a stimulus present during the delay to the larger reinforcer (Cardinal, Robbins, & Everitt, 2000), environmental enrichment (Perry et al., 2008), or baseline level of delay discounting (Barbelivien, Billy, Lazarus, Kelche, & Majchrzak, 2008). The nonselective dopamine antagonist flupenthixol has been shown to increase impulsive choice (Floresco et al., 2008; Wade et al., 2000). This effect may be due to $D_{1\text{-like}}$ antagonism or $D_{2\text{-like}}$ antagonism, as some reports show that the $D_{1\text{-like}}$ antagonist SCH 23390 increases impulsive choice while the $D_{2\text{-like}}$ antagonists haloperidol and eticlopride have no effect (Evenden & Ryan, 1996; van Gaalen et al., 2006), while another found an increase in impulsive choice with the $D_{2\text{-like}}$ antagonist raclopride and no effect with SCH 23390 (Wade et al., 2000). To the author's knowledge, the only direct dopamine agonist examined for effects on impulsive choice is the $D_{3\text{-preferring}}$ agonist 7-OH-DPAT, which increased impulsive choice (van den Bergh et al., 2006).

As dopaminergic systems that involve a variety of dopamine receptor subtypes are involved in impulsive choice, and the effects of systemic injections of selective dopamine receptor agonists and antagonists are largely unknown, we administered the most selective dopamine receptor agonists and antagonists readily available to male

Sprague Dawley rats responding on a slight variation of the delay discounting task described by Evenden and Ryan (1996). The drugs administered included *d*-amphetamine, the selective dopamine transporter blocker GBR 12909, the $D_{1\text{-like}}$ agonist SKF 81297, the $D_{1\text{-like}}$ antagonist SCH 23390, the $D_{2\text{-like}}$ antagonist haloperidol, the $D_{2\text{-preferring}}$ agonist sumanirole, the $D_{2\text{-preferring}}$ antagonist L-741,626, the $D_{3\text{-preferring}}$ agonist pramipexole, the $D_{3\text{-preferring}}$ antagonist PG01037, the D_4 partial agonist ABT 724, the D_4 antagonist L-745,870, and the nonselective dopamine agonist apomorphine.

Method

Subjects

Twenty-four male Sprague Dawley rats served as subjects (Harlan, Indianapolis, IN). Rats were approximately 10 weeks old at the start of the experiment. A food restriction protocol was in place to maintain the rats at approximately 325 g throughout the experiment. This weight was chosen as it is approximately 85% of the mean adult weight supplied by the manufacturer for this strain, and this weight was not changed once established. When not in session, rats were housed in accordance with institutional animal care and use guidelines in polycarbonate cages with fresh water continuously available. The lights in the housing colony were on from 7:00 AM to 7:00 PM, and sessions were conducted between 9:00 AM and 3:00 PM. These protocols were approved by the University of Michigan Committee on the Use and Care of Animals and conformed to the guidelines established by the NIH Guide for the Use of Laboratory Animals.

Apparatus

Sessions were conducted in rodent operant conditioning chambers with an area of 30.5 cm x 24.1 cm x 21.0 cm and stainless steel grid floors (ENV-008; Med-Associates Inc., St. Albans, VT). Both sides of the front panel of the chamber held a retractable lever (E23-17, Coulbourn Instruments, Whitehall, PA). Between the levers was a food tray connected to a 45 mg pellet dispenser (ENV-200R1AM and ENV-203M-45, Med-Associates, Inc.). Above both of the levers and the food tray were triple stimulus lights containing a red, green, and yellow LED (ENV-222M, Med-Associates, Inc.). A houselight was located near the top of the opposite wall to provide illumination to the chamber (ENV-215M, Med-Associates, Inc.). Chambers were connected to a computer running Med-PC IV software (Med-Associates, Inc.) to control experimental events and record data.

Procedure

Rats were trained to respond on a mixed fixed-time 60 s fixed ratio (FR) 1 schedule of reinforcement, with the active lever alternating each session between the left and right levers. This schedule arranged one sucrose pellet to be delivered every 60 s independent of behavior, with every lever press also producing a pellet. This was continued for four sessions, at which point the schedule was switched to a FR 1 with no response-independent pellet deliveries. Rats were allowed to respond on this schedule until 80 responses or more were recorded on two consecutive 20-min sessions.

The sessions were then extended to 75 min and split into five components of ten discrete-choice trials each. Total trial duration was 90 s and began with one or both levers extending into the chamber and illumination of the triple-stimulus lights above the lever(s). If a single response was made within 20 s, the levers retracted, the lights were

extinguished, and the consequence programmed for that lever was delivered. If no response was made within 20 s, that trial was recorded as an omission and the levers retracted for the remaining 70 s of that trial. The first two trials of each component were always forced-choice trials where only one lever was extended into the chamber, forcing the subject to sample the contingencies for that component. The remaining eight trials were free-choice trials where both levers were extended into the chamber, allowing the rat to respond on either. The three stimulus lights above each lever were lit whenever that lever was inserted in the chamber, and the stimulus lights above the pellet tray were lit during sucrose pellet deliveries. Initially, the consequences for both levers were immediate deliveries of either one or three 45-mg sucrose pellets, with the side associated with each amount counterbalanced across subjects. This condition was continued until rats chose the three-pellet option on at least 85% of free-choice trials. The three-pellet and one-pellet levers were then switched two times, with each new lever assignments in place until rats responded on the three-pellet option on at least 85% of trials. When this training regimen was completed, delays were introduced between responses made on the three-pellet lever and the delivery of the three pellets. The delays to the three-pellet option were 0, 10, 20, 40, or 60 s and were always presented in ascending order with one delay in effect in each of the five 10-trial components.

Drug testing began after there was an effect of delay on choices (i.e., choice of the three-pellet option decreased as a function of delay to the delivery of the three pellets), and no increasing or decreasing trend in choices was apparent over a period of five sessions. Sessions were generally conducted five days per week with vehicle injections administered on the first and fourth days of the week, drugs administered on the second

and fifth days, and no injections given on the third day. Vehicle injections always corresponded to the vehicle for the scheduled drug injection or injections for the following day in number, substance, and time relative to the experimental session. Each session was preceded by a vehicle or drug injection 5 min before the start of the session with the rat then immediately placed in the darkened experimental chamber. On some days, an antagonist or vehicle injection was administered 30 min prior to the session, with the rat placed back in his home cage for the intervening 25 min before the agonist or vehicle injection was given, as appropriate. All agonists and the corresponding vehicle injections were administered 5 min before the session. All antagonists and the corresponding vehicle injections were administered 30 min before the session start, except SCH 23390 which was administered 5 min before session start due to its relatively rapid onset and short duration of action (Hietala, Seppäla, Lappalainen, & Syvälahti, 1992). All subjects did not receive all drugs. Each drug was tested in 12 subjects, with the allocation of drugs to subjects determined semi-randomly.

Drugs

Pramipexole was generously provided by Drs. Jianyong Chen and Shaomeng Wang (University of Michigan, Ann Arbor, MI), sumanirole by Benjamin Greedy and Dr. Stephen Husbands (University of Bath, Bath, UK), GBR 12909 by Novo Industri (Bagsvaerd, Denmark), ABT-724 by Dr. Kenner Rice (Chemical Biology Research Branch, National Institute on Drug Abuse, Bethesda, MD), and PG01037 by Drs. Amy H. Newman (Medicinal Chemistry Section – National Institute on Drug Abuse, Baltimore, MD) and Peter Grundt (University of Minnesota – Duluth, Duluth, MN). Haloperidol, SKF 81297, SCH 23390, and apomorphine were obtained from Sigma-Aldrich (St. Louis,

MO), L-741,626 and L-745,870 were obtained from Tocris (Ellisville, MO), and *d*-amphetamine was obtained from the National Institute on Drug Abuse (Bethesda, MD). All drugs were dissolved in sterile saline except L-741,626, which was dissolved in 5% ethanol, and PG01037, which was dissolved in 20% β-cyclodextrin. All injections were administered subcutaneously (s.c.) in a volume of 1.0 ml/kg except 56 mg/kg PG01037 which was administered in of volume of 1.75 ml/kg due to solubility limits.

Data Analysis

If a subject responded within the limited hold period on at least four of the eight free-choice trials of any component, those data were included in data analyses. Percent choice of the three-pellet lever was compared across delays to the three-pellet option and drug dose with a two-way repeated measures analysis of variance (ANOVA) with Systat SigmaStat 3.5 (San Jose, CA). When data were excluded in some components for some subjects due to the stated inclusion criterion, SigmaStat used a Mixed Models ANOVA to assess within- and between-subjects effects on the incomplete data set. Response latency was measured from the insertion of the response lever or levers into the chamber to a response on either lever within the limited hold period. Latencies were compared across trial type (free- or forced-choice) and drug dose with a two-way repeated measures ANOVA with GraphPad Prism 5 (La Jolla, CA). If a subject did not respond on either lever during the limited hold period, that trial was recorded as an omission. Omitted free-choice trials were compared across drug doses with a one-way repeated measures ANOVA with Prism 5.

Results

A two-way ANOVA was conducted to assess the main effects of delay to three pellets, drug dose, and the interaction of the two for each drug tested. All ANOVAs revealed a highly significant main effect of delay on choices (F range = 23 to 45, all $p <$ .001), indicating that choice of the 3 pellets decreased as the delay to this option increased. Individual F values will not be reported for brevity.

Acute pretreatments of *d*-amphetamine tended to decrease choice of the three-pellet option, but only at shorter delays to the three pellets (Figure 3-1). *d*-Amphetamine dose did not significantly affect choices ($F_{4,176} = 2.3$, $p = .075$), but there was a significant dose by delay interaction ($F_{16,176} = 2.3$, $p = .005$). Bonferroni-adjusted *post hoc* tests revealed a significant reduction in choices of three pellets after 1.0 mg/kg *d*-amphetamine when the delay was 10 s ($p = .008$). Response latency was not different between forced- and free-choice trials ($F_{1,88} = 0.80$, $p = .380$) and was not affected by pretreatments of *d*-amphetamine up to doses of 1.0 mg/kg (dose main effect $F_{4,88} = 1.9$, $p = .334$; dose by trial type interaction $F_{4,88} = 0.28$, $p = .892$). *d*-Amphetamine also did not increase trials omitted (Table 3-1, $F_{4,44} = 0.84$, $p = .508$).

Pretreatments of the dopamine transporter blocker GBR 12909 up to 10 mg/kg did not significantly alter choices (dose main effect $F_{3,132} = 1.1$, $p = .344$, dose by delay interaction $F_{12,132} = 1.0$, $p = .420$, Figure 3-2). Response latency (dose main effect $F_{3,66} = 2.5$, $p = .065$, trial type main effect $F_{1,66} = 0.38$, $p = .545$, dose by trial type interaction $F_{3,66} = 0.74$, $p = .532$) and omissions (Table 3-1, $F_{3,33} = 1.3$, $p = .277$) were also not altered.

A dose of 0.32 mg/kg the $D_{3\text{-preferring}}$ agonist pramipexole decreased large-reinforcer choice across a range of delays, leading to a significant effect of pramipexole dose ($F_{3,129} = 21$, $p < .001$) and a dose by delay interaction ($F_{12,129} = 1.9$, $p = .047$; Figure 3-3). A dose of 0.32 mg/kg pramipexole reduced large-reinforcer choice as a whole ($p < .001$), and specifically at delays from 0 to 40 (all $p < .01$). Response latency (dose main effect $F_{3,66} = 4.7$, $p = .005$, trial type main effect $F_{1,66} = 0.67$, $p = .423$, dose by trial type interaction $F_{3,66} = 0.25$, $p = .860$) and omissions (Table 3-1, $F_{3,33} = 3.4$, $p = .028$) were also increased at 0.32 mg/kg pramipexole, with response latency most increased during forced-choice trials at 0.32 mg/kg ($p < .05$).

Large-reinforcer choices were not significantly altered by the $D_{2\text{-preferring}}$ agonist sumanirole up to 3.2 mg/kg (Figure 3-4, dose main effect $F_{2,83} = 1.7$, $p = .203$, dose by delay interaction $F_{8,83} = 1.8$, $p = .085$). Trials omitted (Table 3-1, $F_{2,22} = 5.9$, $p = .009$) and response latency (dose main effect $F_{2,44} = 6.5$, $p = .003$, trial type main effect $F_{1,44} = 0.42$, $p = .524$, dose by trial type interaction $F_{2,44} = 0.50$, $p = .611$) were increased at 3.2 mg/kg, however. Bonferroni-adjusted *post hoc* tests reveal an increase in free-choice trial response latency at 3.2 mg/kg sumanirole ($p < .05$).

There was no main effect of the D_4 partial agonist ABT-724 dose on large-reinforcer choice ($F_{2,88} = 0.70$, $p = .510$), but there was a significant dose by delay interaction ($F_{8,88} = 2.1$, $p = .049$, Figure 3-5). This was due to a small, but significant decrease in large-reinforcer choice after 3.2 mg/kg ABT-724 with a delay of 40 s ($p = .021$). Response latency (dose main effect $F_{2,44} = 0.53$, $p = .592$, trial type main effect $F_{1,44} = 1.2$, $p = .279$, dose by trial type interaction $F_{2,44} = 0.1.3$, $p = .291$) and omissions (Table 3-1, $F_{2,22} = 0.48$, $p = .626$) were not altered by ABT-724 at the doses tested.

The $D_{2\text{-like}}$ antagonist haloperidol reduced large-reinforcer choice at a dose that also increased response latency (Figure 3-6). There was a significant main effect of dose on choice ($F_{3,126} = 5.8$, $p = .003$), but this effect did not significantly depend on delay ($F_{12,126} = 1.7$, $p = .078$). A dose of 0.1 mg/kg haloperidol reduced large-reinforcer choice ($p = .002$), with a significant effect at delays from 0 to 20 s (all $p < .05$). At this same dose of 0.1 mg/kg, haloperidol increased response latency (dose main effect $F_{3,66} = 8.0$, $p < .001$, trial type main effect $F_{1,66} = 0.49$, $p = .491$, dose by trial type interaction $F_{3,66} = 0.43$, $p = .733$). This increase was observed during both forced- and free-choice trials (both $p < .05$). Omissions were not significantly increased at doses up to 0.1 mg/kg ($F_{3,33} = 1.9$, $p = .147$).

The $D_{3\text{-preferring}}$ antagonist PG01037 slightly decreased large-reinforcer choice at the highest dose tested (Figure 3-7). No main effect of dose was found ($F_{3,132} = 2.3$, $p = .092$), but there was a dose by delay interaction ($F_{12,132} = 1.9$, $p = .035$). The dose of 56 mg/kg PG01037 significantly reduced large-reinforcer choice at a delay of 10 s ($p = .043$). Response latency (dose main effect $F_{3,66} = 1.8$, $p = .157$, trial type main effect $F_{1,66} = 0.96$, $p = .338$, dose by trial type interaction $F_{3,6} = 0.40$, $p = .752$) and omissions (Table 3-1, $F_{3,33} = 0.65$, $p = .586$) were not affected by PG01037 at the doses tested.

The $D_{2\text{-preferring}}$ antagonist L-741,626 (Figure 3-8) dose-dependently decreased large-reinforcer choice ($F_{3,130} = 6.5$, $p = .001$) in a way that did not depend on delay (dose by delay interaction $F_{12,130} = 1.1$, $p = .394$). L-741,626 decreased large-reinforcer choice when administered at 1.0 or 3.2 mg/kg (both $p < .05$), with highly significant decreases observed in the 0 s delay condition with 3.2 mg/kg L-741,626 ($p < .001$). Response latency was increased after administration of 3.2 mg/kg L-741,626 in both forced- ($p <$

.001) and free-choice ($p < .05$) trials (dose main effect $F_{3,66} = 12$, $p < .001$, trial type main effect $F_{1,66} = 0.61$, $p = .444$, dose by trial type interaction $F_{3,66} = 0.94$, $p = .426$). Omissions were not increased at the doses tested (Table 3-1, $F_{3,33} = 1.6$, $p = .217$).

The D_4 antagonist L-745,870 had little effect on behavior at the doses tested (Figure 3-9). Large-reinforcer choice was not altered (dose main effect $F_{3,132} = 1.2$, $p = .329$, dose by delay interaction $F_{12,132} = 0.70$, $p = .751$), nor was response latency (dose main effect $F_{3,66} = 1.1$, $p = .338$, trial type main effect $F_{1,66} = 0.63$, $p = .436$, dose by trial type interaction $F_{3,66} = 0.33$, $p = .802$) or omissions (Table 3-1, $F_{3,33} = 1.0$, $p = .405$).

The $D_{1\text{-like}}$ agonist SKF 81297 dose-dependently decreased large-reinforcer choice, but this effect was limited to the shorter delays (Figure 3-10). This tendency resulted in a significant main effect of SKF 81297 dose ($F_{3,138} = 11$, $p < .001$) and a significant dose by delay interaction ($F_{12,138} = 7.6$, $p < .001$). A dose of 0.32 mg/kg SKF 81297 decreased large-reinforcer choice only at the 0 s delay condition ($p = .002$), while choice after 1.0 mg/kg hovered around 50% at all delays, significantly decreasing choice from 0 to 20 s (all $p < .001$). Omissions (Table 3-1, $F_{3,36} = 4.1$, $p = .014$) and response latency (dose main effect $F_{3,72} = 6.1$, $p < .001$, trial type main effect $F_{1,72} = 4.5$, $p = .046$, dose by trial type interaction $F_{3,72} = 0.57$, $p = .636$) were slightly increased at 1.0 mg/kg, this effect most notable during free-choice trials ($p < .01$).

Administration of the $D_{1\text{-like}}$ antagonist SCH 23390 produced a selective increase in impulsive choice, with 0.01 mg/kg decreasing choice at moderate delays without affecting choice in the 0 s delay condition (Figure 3-11). A main effect of dose was observed ($F_{4,152} = 6.7$, $p < .001$), with both 0.01 ($p < .001$) and 0.032 ($p < 0.05$) SCH 23390 decreasing large-reinforcer choice. A dose by delay interaction was also noted

($F_{16,152} = 3.1$, $p < .001$). The effects of 0.01 mg/kg were selective to the 10 and 20 s delays (both $p < .001$), while 0.032 mg/kg resulted in more indifferent choice and a significant reduction in large-reinforcer choice at the 0 and 10 s delays (both $p < .05$). This move toward indifference at 0.032 mg/kg SCH 23390 was accompanied by a large increase in trials omitted (Table 3-1, $F_{4,44} = 26$, $p < .001$) and a large increase in both forced- and free choice latency (both $p < .001$, dose main effect $F_{4,88} = 13$, $p < .001$, trial type main effect $F_{1,88} = 1.5$, $p = .230$, dose by trial type interaction $F_{4,88} = 0.06$, $p = .993$).

A range of doses of the $D_{1\text{-like}}$ agonist SKF 81297 were co-administered with 0.01 mg/kg of the $D_{1\text{-like}}$ antagonist SCH 23390 to determine if the effects seen with SCH 23390 were reversible by a $D_{1\text{-like}}$ agonist. Little systematic reversal was found with doses of SKF 81297 up to 1.0 mg/kg (Figure 3-12). There was a main effect of dose on large-reinforcer choice ($F_{4,156} = 23$, $p < .001$), with 0.01 mg/kg SCH 23390 alone decreasing choice ($p < .001$). No dose of SKF 81297 significantly reversed this effect, although there were some effects of SKF 81297 dose that depended on delay ($F_{16,156} = 5.1$, $p < .001$). A dose of 0.01 mg/kg SCH 23390 alone decreased large-reinforcer choice relative to vehicle at delays ranging from 10 s to 40 s (all $p < .05$). When co-administered with SCH 23390, compared to the effects of 0.01 mg/kg SCH 23390 alone 0.1 mg/kg SKF 81297 further decreased large-reinforcer choice at a 40 s delay ($p < .05$) and 1.0 mg/kg SKF 81297 increased large-reinforcer choice at a 20 s delay ($p < .05$), but decreased it at a 0 s ($p < .001$) and 60 s ($p < .05$) delay. Adding 1.0 mg/kg SKF 81297 to 0.01 mg/kg SCH 23390 increased the response latency over that observed with 0.01 mg/kg SCH 23390 alone in both the forced- and free-choice trials (both $p < .05$, dose main effect $F_{4,88} = 7.8$, $p < .001$, trial type main effect $F_{1,88} = 5.0$, $p = .036$, dose by trial type interaction $F_{4,88} =$

0.46, $p = .763$). No significant effect on trials omitted was observed across these dosing conditions (Table 3-1, $F_{4,44} = 1.9$, $p = .120$).

The nonselective dopamine agonist apomorphine (Figure 3-13) had little effect on large-reinforcer choice until a dose of 0.32 mg/kg, at which a sizeable decrease in choice was observed ($p < .001$, dose main effect $F_{3,128} = 43$, $p < .001$ dose by delay interaction $F_{12,128} = 6.1$, $p < .001$). That dose of 0.32 mg/kg apomorphine decreased large-reinforcer choice to below 50%, such that a majority of responses were allocated to the small-reinforcer option at all delays. This decrease was significantly different from vehicle choice data at delays ranging from 0 to 40 s (all $p < .001$). This pattern of choice was accompanied by an increase in response latency in both the forced- and free-choice trials (both $p < .01$, dose main effect $F_{3,66} = 22$, $p < .001$, trial type main effect $F_{1,66} = 1.1$, $p = .300$, dose by trial type interaction $F_{3,66} = 2.9$, $p = .039$) and in increase in omissions (Table 3-1, $F_{3,33} = 10$, $p < .001$).

Discussion

In general, doses of drugs that increased response latency or trials omitted also moved choice data toward indifference (50% choice). A decrease or increase in choice that is independent of delay is not an increase or decrease, respectively, in impulsive choice. Rather, changes in choice behavior that occurs when both consequences are not delayed are better conceptualized as an effect on sensitivity to the amount of the reinforcer or an inability to discriminate or adapt to the consequences of responding (Acheson et al., 2006; Pitts & Febbo, 2004). For the purposes of this paper, selective, potentially clinically-relevant effects were considered to be those effects on delay that did not coincide with a decrease in sensitivity to amount or a significant increase in response

latency. Those effects on delayed choice that coincided with decreases in sensitivity to amount (decrease in three-pellet choice at delay = 0 s) or increase in response latency were of less interest. The selectivity of effects on impulsive choice is indicated in the legend of each graph, with selective increases (↑) in impulsive choice or disruptions in behavior in the form of decreased sensitivity to amount or increase response latency (×) indicated. Two drugs tested did affect choice of the large reinforcer as a function of delay without altering response latency or ability to discriminate amount. These drugs are SCH 23390 and ABT-724, and are discussed in more detail below.

The $D_{1\text{-like}}$ antagonist SCH 23390 selectively increased impulsive choice at 0.01 mg/kg (Figure 3-11). This effect has been reported previously at a similar dose (van Gaalen et al., 2006), but not on an adjusting-amount procedure over the same dose range (Wade et al., 2000). The D_4 partial agonist ABT-724, which has not been previously assessed on a model of impulsive choice, also selectively increased choice of the smaller reward when the larger reward was delayed 40 s. Both D_4 and $D_{1\text{-like}}$ receptors are located in the frontal cortex. $D_{1\text{-like}}$ receptors are located both on GABAergic interneurons (Muly III et al., 1998) and on pyramidal neurons with projections back to the striatum, among other areas (Gaspar et al., 1995). D_4 receptors are located primarily on GABAergic interneurons in the monkey cortex (Mrzljak et al., 1996), but have been located on both GABAergic interneurons and pyramidal neurons in the rat cortex (Wędzony, Chocyk, Maćkowiak, Fijał, & Czyrak, 2000). As GABA is an inhibitory neurotransmitter, D_4 agonism and $D_{1\text{-like}}$ antagonism in the prefrontal cortex may functionally have the same effect depending on relative influence of binding sites on GABAergic and pyramidal sites. This complex organization of the prefrontal cortex, and the fact that the D_4

antagonist L-745,870 and the $D_{1\text{-like}}$ agonist SKF 81297 did not have the opposite result as ABT-724 and SCH 23390 in the present study, may result from the hypothesized notion that moderate stimulation of $D_{1\text{-like}}$ receptors results in optimal cell firing (Muly III et al., 1998). D_4 receptors are an intriguing target for ADHD medications. D_4 polymorphisms in humans are associated with ADHD (Faraone et al., 2005), and D_4 receptor distribution in the brain is relatively limited, but includes the prefrontal cortex (Van Tol et al., 1991). Methylphenidate has been shown to increase dopamine and norepinephrine in the prefrontal cortex to a greater extent and at lower doses than in the nucleus accumbens (dopamine) or medial septal area (norepinephrine) (Berridge et al., 2006). Added to the finding that D_4 receptors have high affinity for both dopamine and norepinephrine (Wedemeyer, Goutman, Avale, Franchini, Rubinstein, & Calvo, 2007) and dopaminergic and noradrenergic mechanisms are involved in the current commonly used ADHD treatments, the D_4 receptor is an appealing target for ADHD treatment. The effect seen with ABT-724 in the present study was small in magnitude, but this could be due to the relatively low efficacy of this compound (Brioni et al., 2004). The selective increase in impulsive choice was also in the opposite direction than would be clinically relevant, however. Further research is needed to determine if a D_4 ligand could produce a reliable, therapeutically-relevant effect.

Both the agonists (pramipexole and sumanirole) and the antagonists (haloperidol, PG01037, and L-741,626) acting through D_2 and/or D_3 receptors had similar effects. As a whole, these drugs tended to decrease amount discrimination by decreasing choice of the large reinforcer when it was not delayed. None had a selective effect on impulsive choice. In the brain, D_2 and D_3 receptors are found in large numbers in the nucleus accumbens,

but are also found in prefrontal cortex (Bouthenet, Souil, Martres, Sokoloff, Giros, & Schwartz, 1991). The core of the nucleus accumbens has been shown to be involved in accurately assessing reinforcer value on delay discounting tasks (Acheson et al., 2006; Cardinal et al., 2001). It is unknown why stimulation and blockade of D_2 or D_3 receptors would have similar effects, however.

Apomorphine had a unique profile of effects on choice, with the first active dose producing a bias toward the lever arranging the small reinforcer at all delays to the large reinforcer. Choice for the large reinforcer after administration of 0.32 mg/kg apomorphine was even below 50%, which would indicate indifference. Apomorphine has been shown to produce a robust anorectic effect at this dose (Willner, Towell, & Muscat, 1985). However, if apomorphine was causing the sucrose pellets to be unpalatable, it would seem that one pellet would not be preferred. Apomorphine has also been shown to induce perseverative responding that appears disconnected from response consequences (Robbins, Watson, Gaskin, & Ennis, 1983) or that is punished (Chapter 4), which could potentially explain these data. Why the subjects tended to perseverate on the response option producing fewer reinforcers is unknown.

Neither *d*-amphetamine nor the selective dopamine transporter blocker GBR 12909 selectively increased or decreased impulsive choice at the doses tested. At 1.0 mg/kg, *d*-amphetamine decreased sensitivity to amount. Previous research has found an increase, decrease, or lack of effect with *d*-amphetamine. The one study to previously test GBR 12909 found a decrease in impulsive choice, the same effect that was found with *d*-amphetamine in that report (van Gaalen et al., 2006). The absence of consistent effects

with these drugs is curious, although environmental conditions are known to affect the effects of *d*-amphetamine on this task (Cardinal et al., 2000; Perry et al., 2008).

In conclusion, of the five dopamine receptors $D_{1\text{-like}}$ and D_4 receptors appear to be most selectively involved in mediating impulsive choice. Both the $D_{1\text{-like}}$ antagonist SCH 23390 and the D_4 partial agonist ABT-724 increased impulsive choice, which may be explained by their differing locations within the PFC, an area known to be involved in impulsive choice. None of the selective agonists and antagonists tested reduced impulsive choice; however, so further research is needed to determine if direct dopaminergic agonists or antagonist may be therapeutically useful in the treatment of impulse control disorders.

Table 3-1. Average number of the 40 free-choice trials omitted (± SEM) for each dose of each drug tested. All doses in mg/kg.

d-Amphetamine	Dose	Veh	0.032	0.1	0.32	1.0
	Omissions	0.02 (±0.02)	0 (±0)	0 (±0)	0.17 (±0.17)	0.58 (±0.58)
GBR 12909	Dose	Veh	1.0	3.2	10	
	Omissions	0.11 (±0.08)	0 (±0)	0.08 (±0.08)	0 (±0)	
Pramipexole	Dose	Veh	0.032	0.1	0.32 *	
	Omissions	0.03 (±0.03)	1.8 (±1.6)	0.25 (±0.18)	4.5 (±1.8)	
Sumanirole	Dose	Veh	1.0	3.2 *		
	Omissions	0.08 (±0.08)	0.25 (±0.18)	8.3 (±3.4)		
ABT-724	Dose	Veh	1.0	3.2		
	Omissions	0.08 (±0.08)	0.08 (±0.08)	0 (±0)		
Haloperidol	Dose	Veh	0.01	0.032	0.1	
	Omissions	0.11 (±0.11)	0 (±0)	0.08 (±0.08)	5.1 (±3.6)	
PG01037	Dose	Veh	10	32	56	
	Omissions	0.17 (±0.09)	0 (±0)	0.17 (±0.17)	0.08 (±0.08)	
L-741,626	Dose	Veh	0.32	1.0	3.2	
	Omissions	0 (±0)	0 (±0)	0.25 (±0.18)	2.2 (±1.7)	
L-745,870	Dose	Veh	0.32	1.0	3.2	
	Omissions	0.02 (±0.02)	0 (±0)	0 (±0)	0 (±0)	
SKF 81297	Dose	Veh	0.1	0.32	1.0 *	
	Omissions	0.05 (±0.05)	0.08 (±0.08)	0.08 (±0.08)	6.3 (±3.1)	
SCH 23390	Dose	Veh	0.001	0.0032	0.01	0.032 ***
	Omissions	0.10 (±0.10)	0.08 (±0.08)	0.08 (±0.08)	1.6 (±1.0)	20.8 (±4.0)
0.01 SCH 23390	Dose	Veh	0.01 SCH	+ 0.1 SKF	+ 0.32 SKF	+ 1.0 SKF
+ SKF 81297	Omissions	0.02 (±0.02)	1.6 (±1.0)	6.6 (±3.2)	3.1 (±3.0)	5.0 (±2.3)
Apomorphine	Dose	Veh	0.032	0.1	0.32 ***	
	Omissions	0.08 (±0.04)	0 (±0)	0.08 (±0.08)	6.5 (±2.0)	

Veh: Vehicle for the drug or drugs in that condition. SCH = SCH 23390. SKF = SKF 81297.

* $p < .05$, ** $p < .01$, *** $p < .001$ compared to vehicle in Bonferroni-adjusted *post hoc* tests.

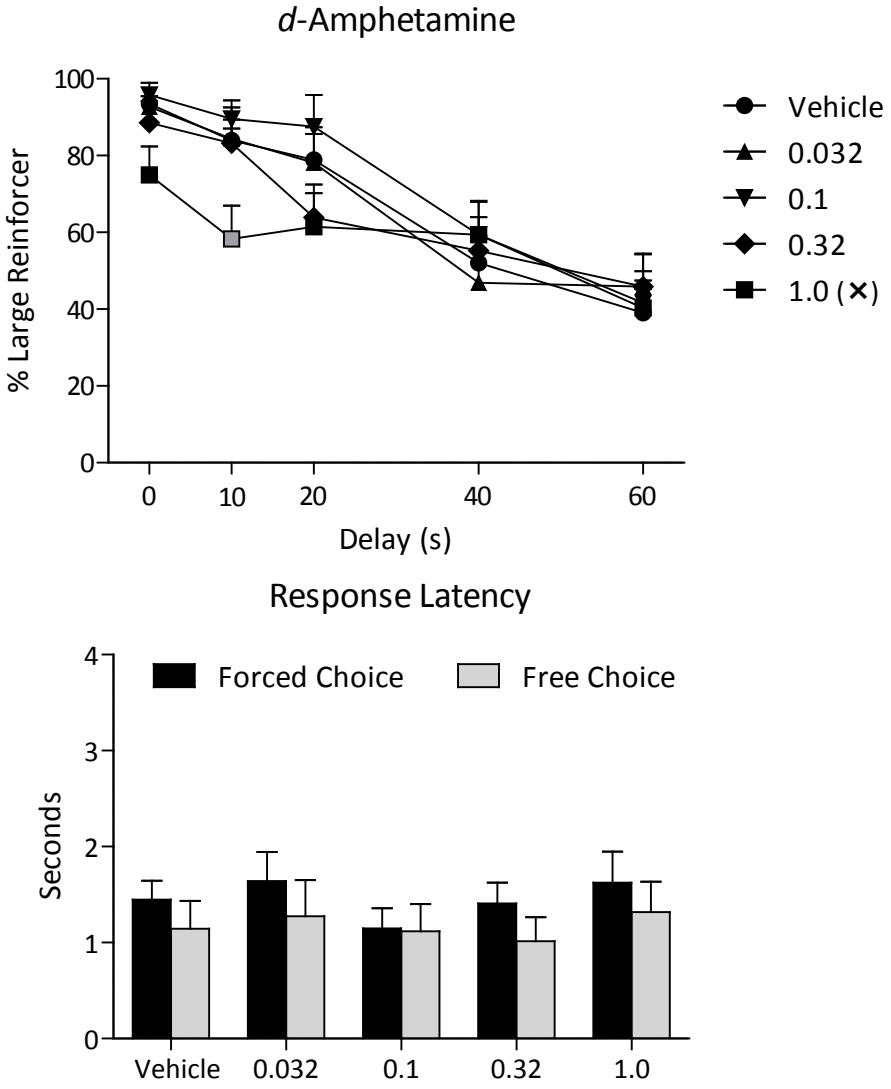

Figure 3-1. Top panel: Percent choice of the three-pellet lever (+ SEM) when that option was delayed from 0 to 60 s as a function of *d*-amphetamine pretreatment dose. Each symbol shape represents a pretreatment dose, and the symbol fill color represents statistical significance of a Bonferroni-adjusted *post hoc* test comparing that point to the corresponding Vehicle point at the same delay (black = n.s.; gray = $p < .05$; white = $p < .001$). Asterisks appearing near a dose in the legend represent a significant difference from the Vehicle condition, independent of delay (* $p < .05$; ** $p < .01$; *** $p < .001$). Selective effects on behavior corresponding to an increase (↑) or decrease (↓) in impulsive choice, or a disruption in behavior (×), is also indicated in the legend. Bottom panel: Latency to respond (+ SEM) during forced and free choice trials as a function of *d*-amphetamine pretreatment dose. Asterisks above a bar indicate statistical significance of a Bonferroni-adjusted *post hoc* test compared to the corresponding Vehicle latency, as described above.

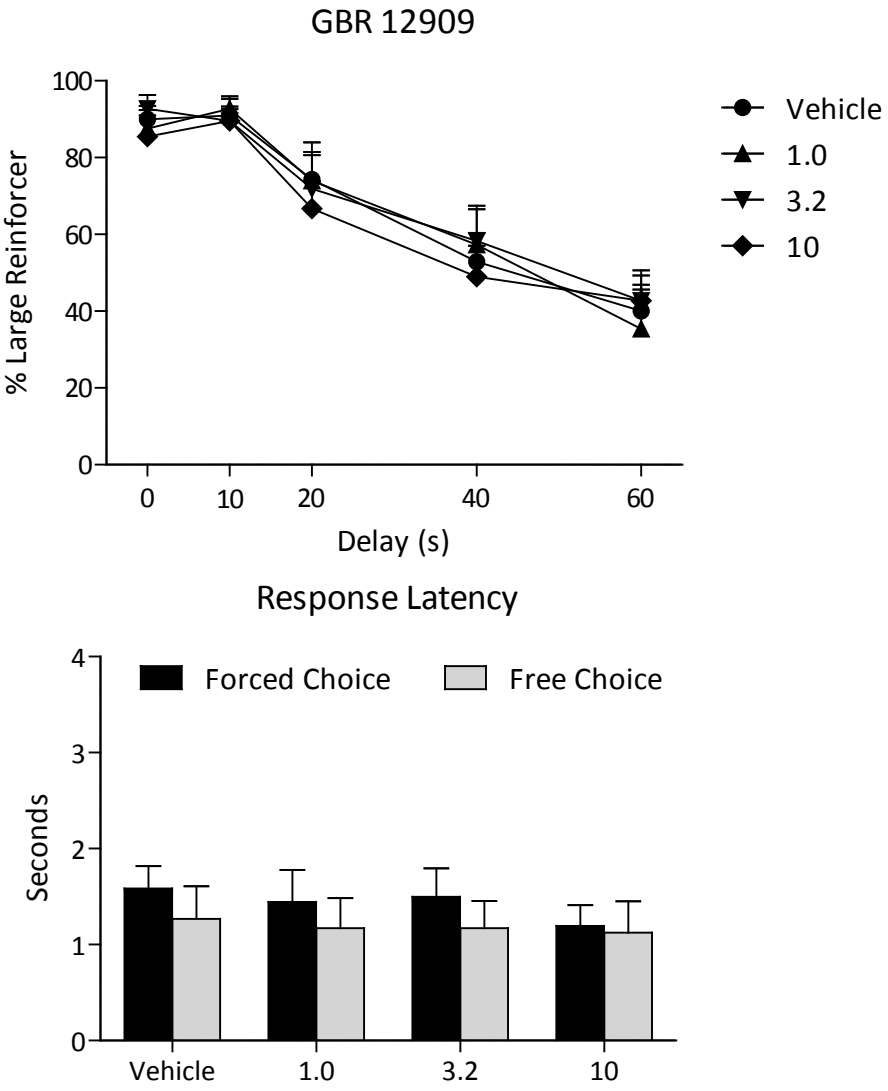

Figure 3-2. Percent choice of the three-pellet lever (top panel) and response latency (bottom panel) as a function of GBR 12909 pretreatment dose. All other details as in Figure 3-1.

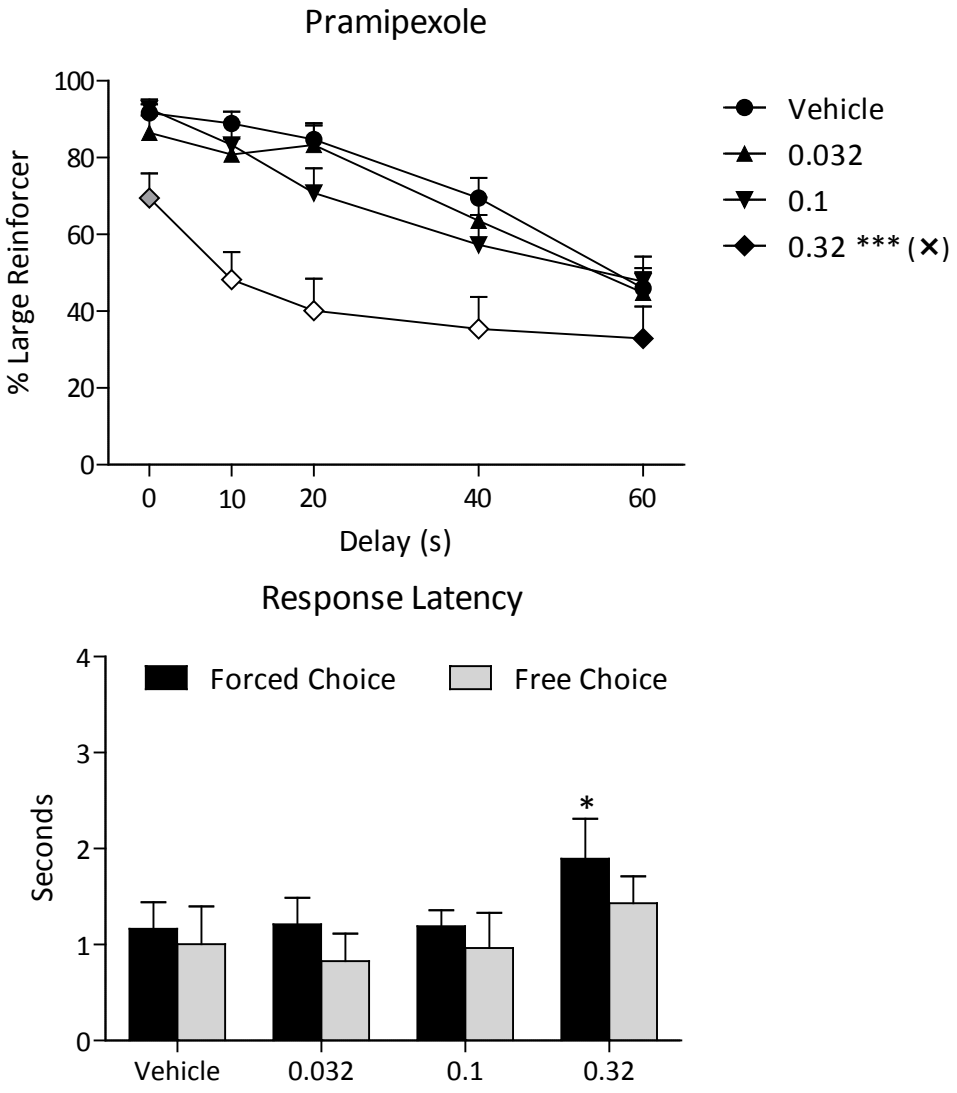

Figure 3-3. Percent choice of the three-pellet lever (top panel) and response latency (bottom panel) as a function of pramipexole pretreatment dose. All other details as in Figure 3-1.

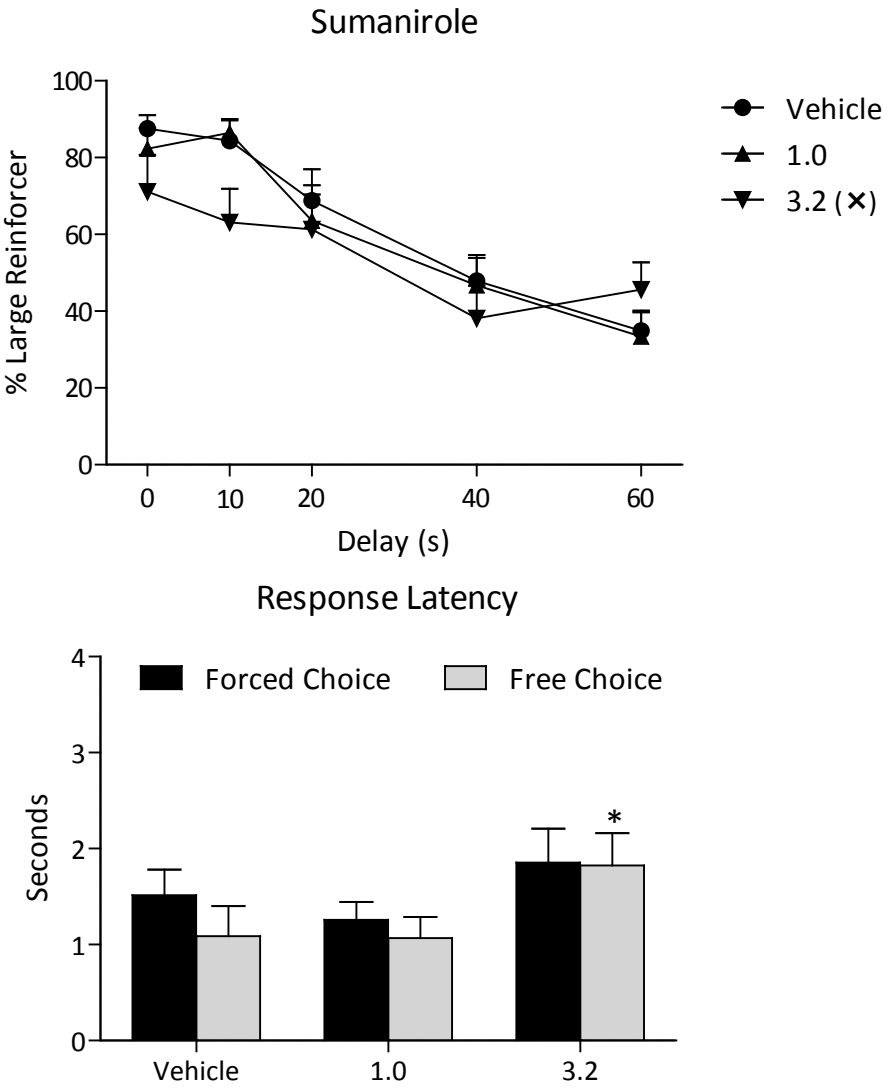

Figure 3-4. Percent choice of the three-pellet lever (top panel) and response latency (bottom panel) as a function of sumanirole pretreatment dose. All other details as in Figure 3-1.

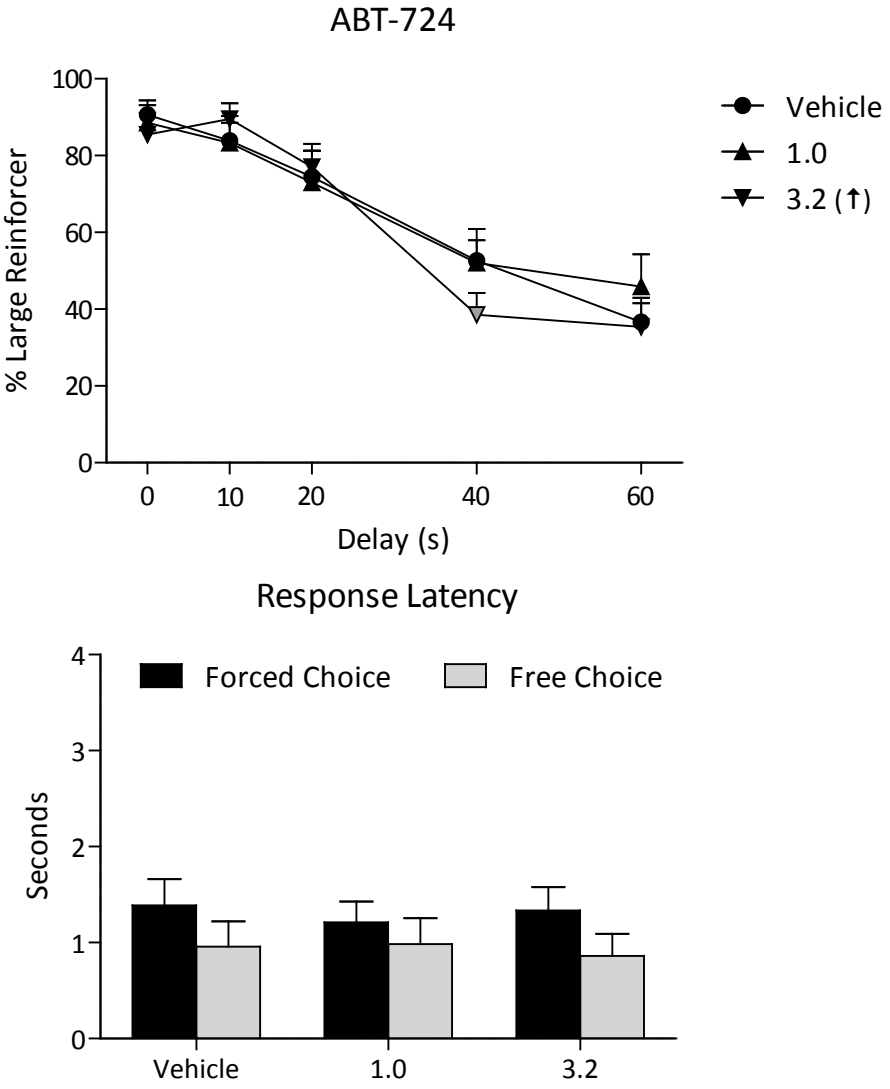

Figure 3-5. Percent choice of the three-pellet lever (top panel) and response latency (bottom panel) as a function of ABT-724 pretreatment dose. All other details as in Figure 3-1.

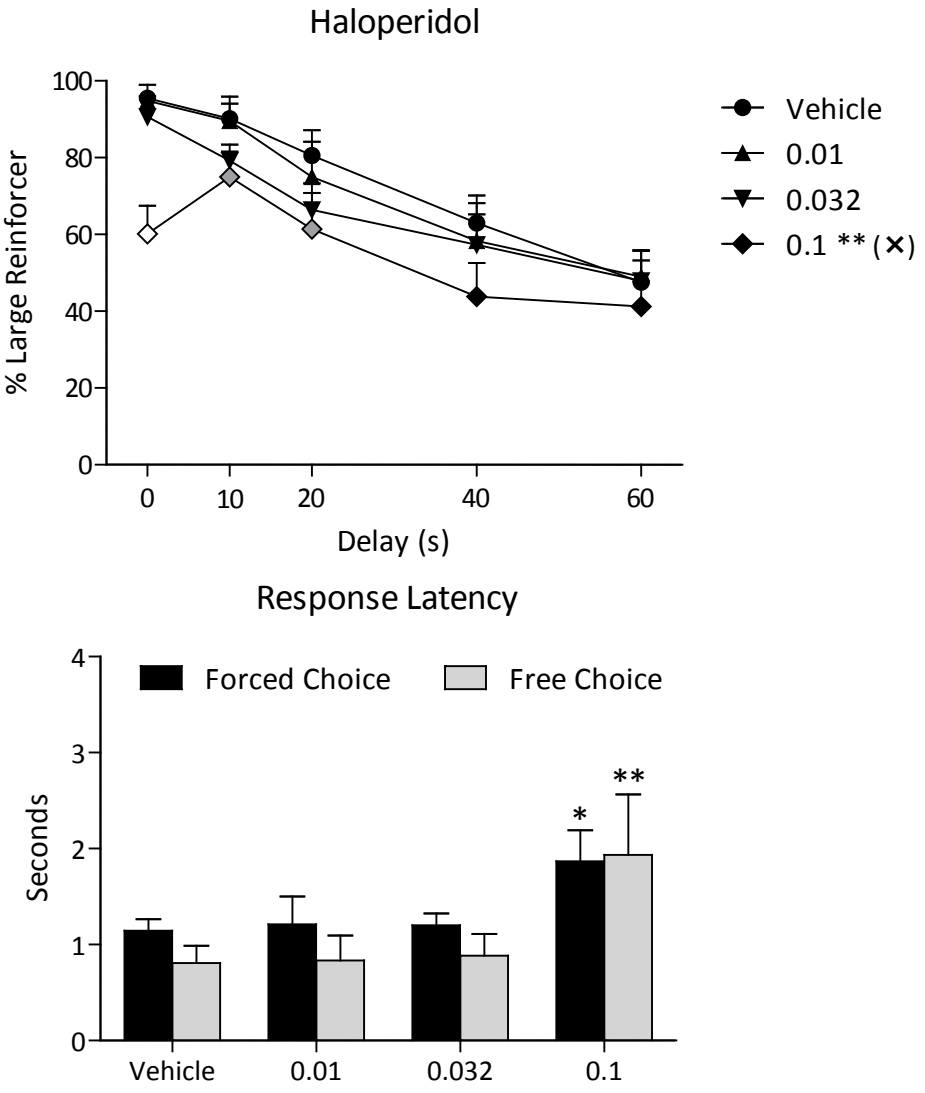

Figure 3-6. Percent choice of the three-pellet lever (top panel) and response latency (bottom panel) as a function of haloperidol pretreatment dose. All other details as in Figure 3-1.

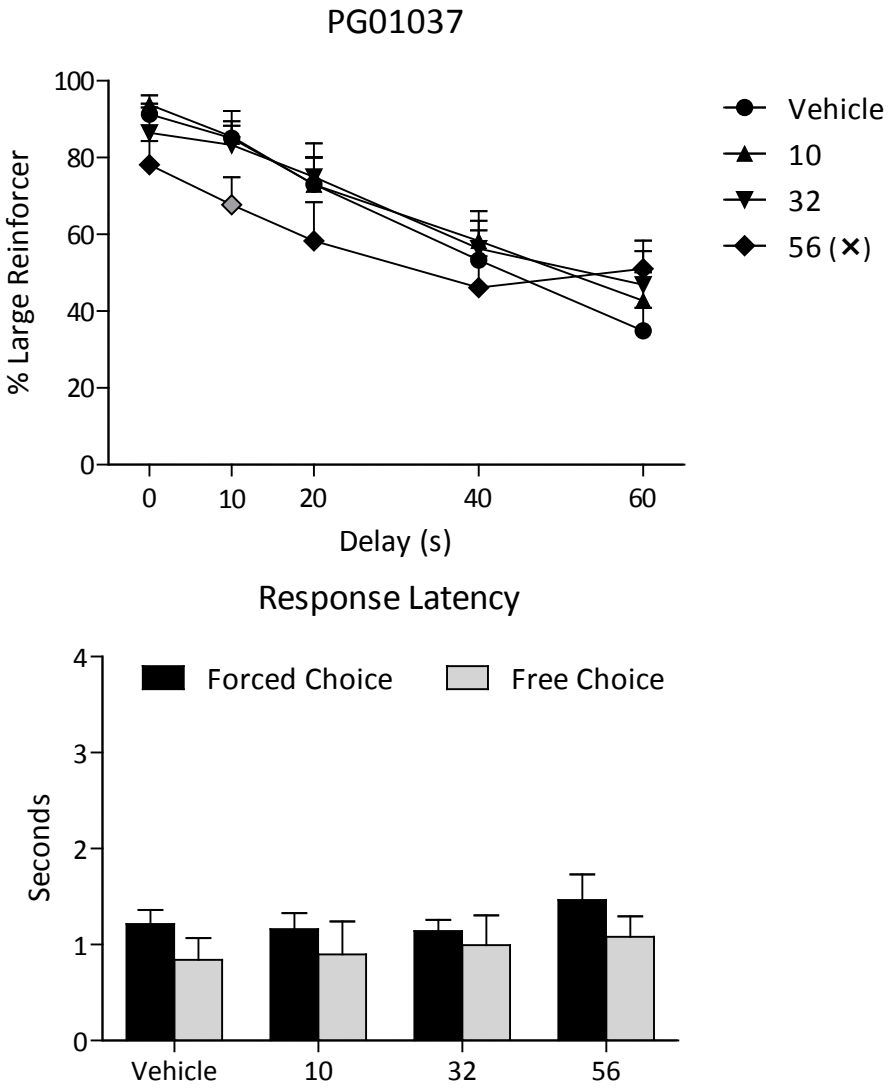

Figure 3-7. Percent choice of the three-pellet lever (top panel) and response latency (bottom panel) as a function of PG01037 pretreatment dose. All other details as in Figure 3-1.

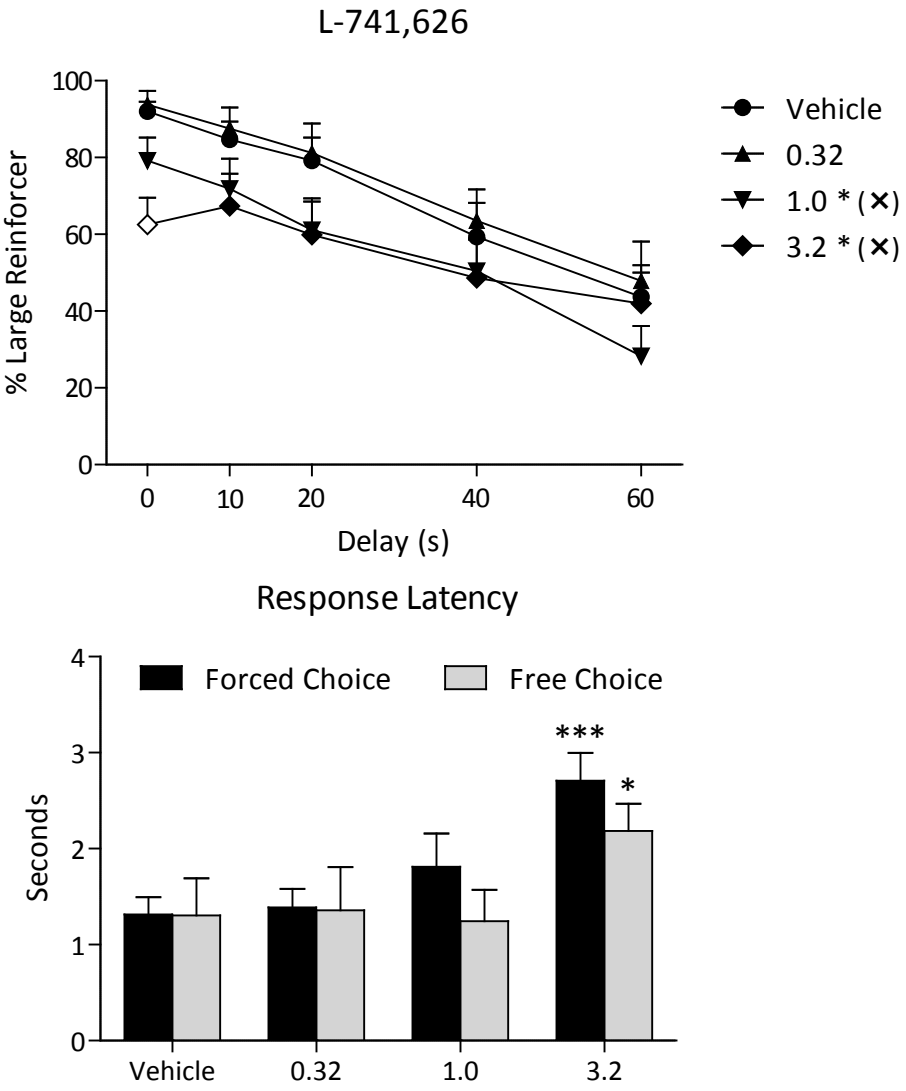

Figure 3-8. Percent choice of the three-pellet lever (top panel) and response latency (bottom panel) as a function of L-741,626 pretreatment dose. All other details as in Figure 3-1.

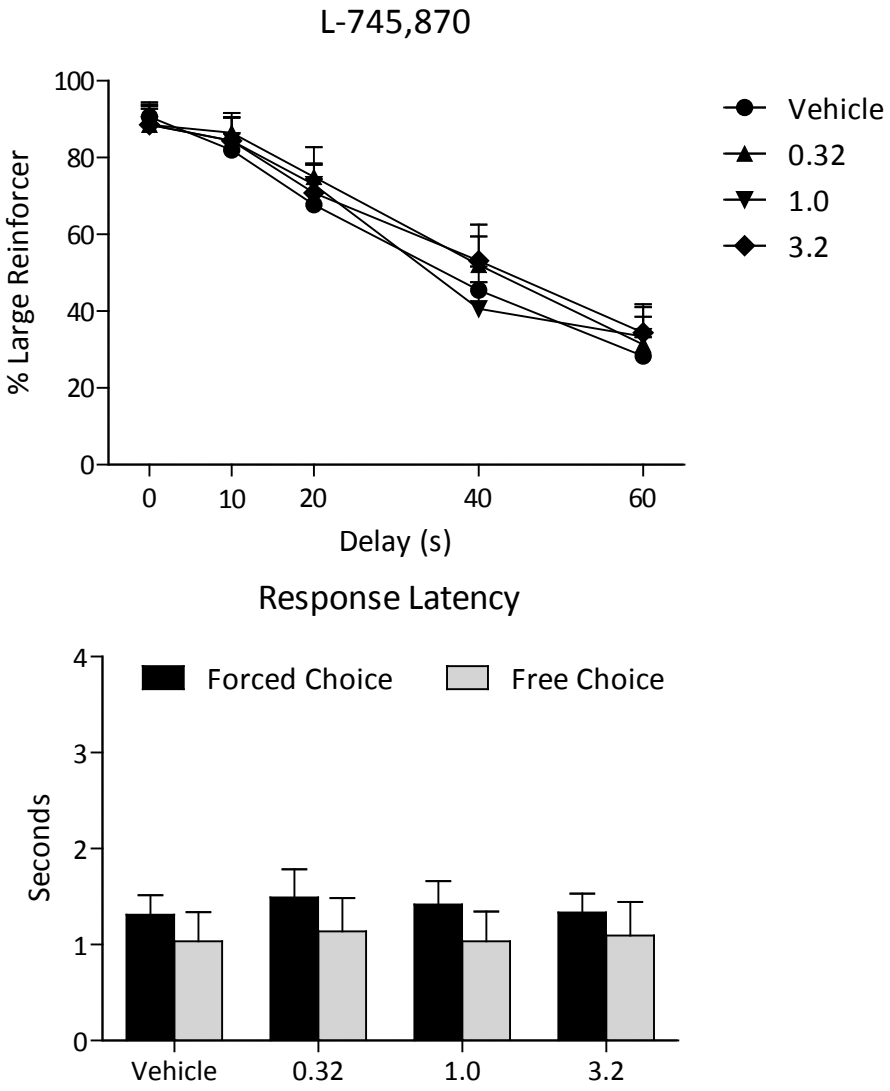

Figure 3-9. Percent choice of the three-pellet lever (top panel) and response latency (bottom panel) as a function of L-745,870 pretreatment dose. All other details as in Figure 3-1.

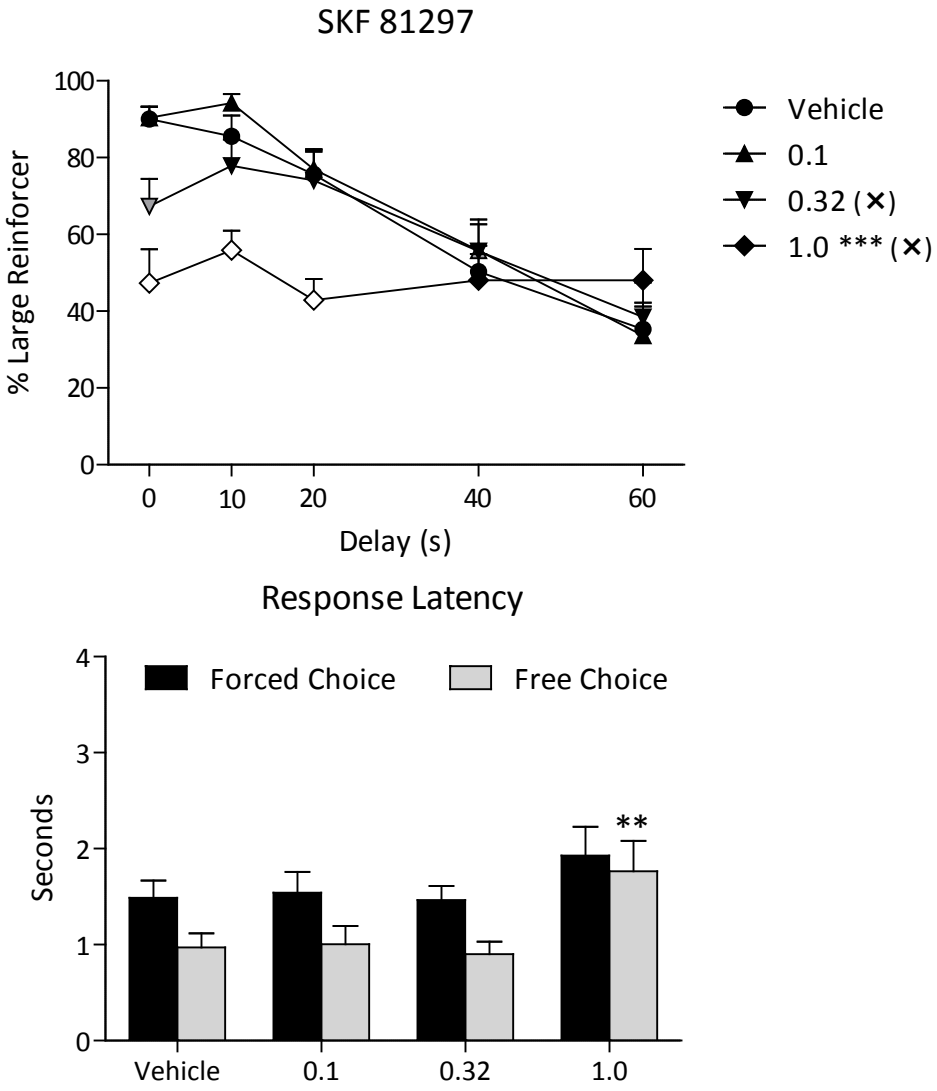

Figure 3-10. Percent choice of the three-pellet lever (top panel) and response latency (bottom panel) as a function of SKF 81297 pretreatment dose. All other details as in Figure 3-1.

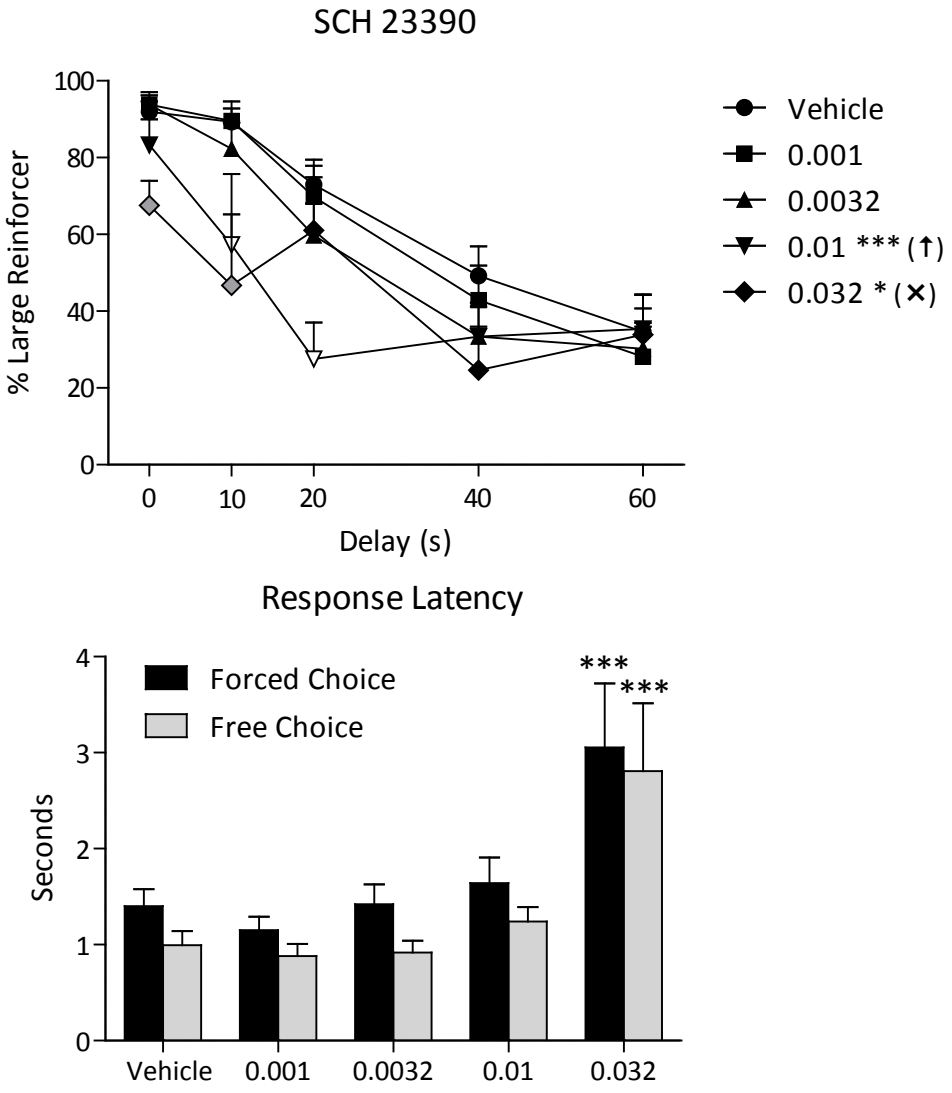

Figure 3-11. Percent choice of the three-pellet lever (top panel) and response latency (bottom panel) as a function of SCH 23390 pretreatment dose. All other details as in Figure 3-1.

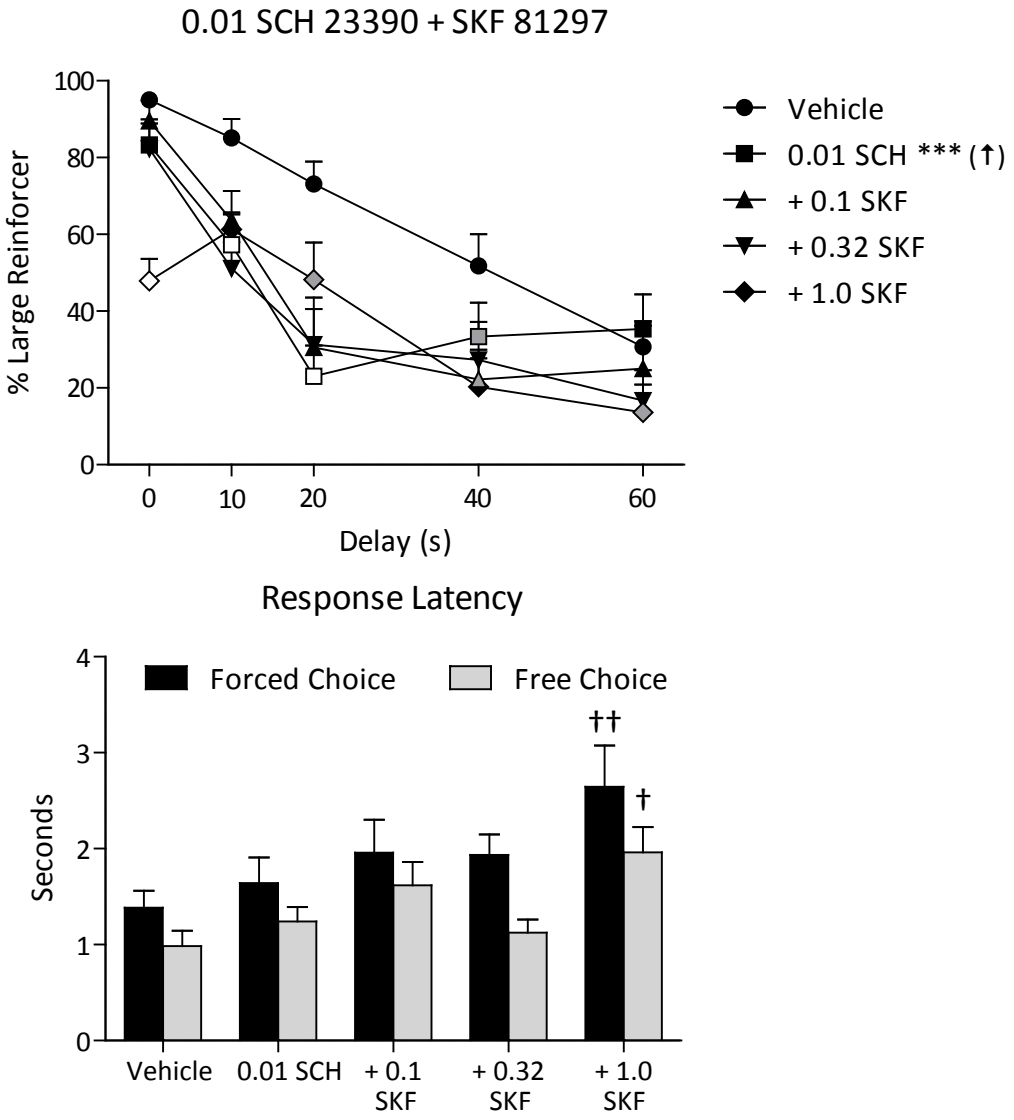

Figure 3-12. Top panel: Percent choice of the three-pellet lever (+ SEM) when that option was delayed from 0 to 60 s as a function of vehicle pretreatment, 0.01 mg/kg SCH 23390 pretreatment, or 0.01 mg/kg SCH 23390 administered with varying doses of SKF 81297. Each symbol shape represents a pretreatment condition, and the symbol fill color represents statistical significance of a Bonferroni-adjusted *post hoc* test comparing that point to the corresponding Vehicle point at the same delay (SCH 23390 alone) or to the corresponding SCH 23390 alone point at the same delay (SCH 23390 + SKF 81297 combinations) (black = $p > .05$; gray = $p < .05$; white = $p < .001$). The selective increase (↑) in impulsive choice in the SCH 23390 alone condition is also indicated in the legend. Bottom panel: Latency to respond (+ SEM) during forced and free choice trials as a function of pretreatment. Daggers above a bar indicate statistical significance of a Bonferroni-adjusted *post hoc* test compared to the corresponding agonist alone latency († $p < .05$; †† $p < .01$).

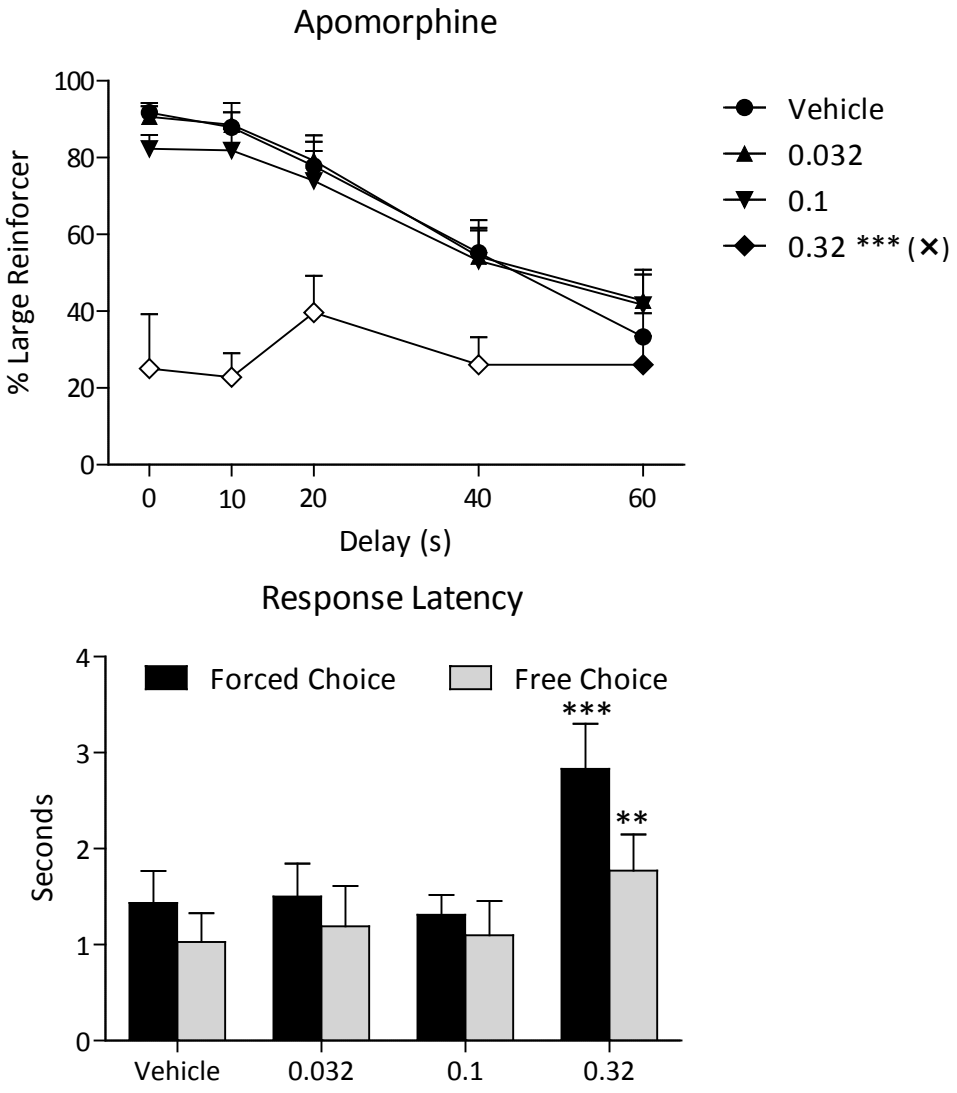

Figure 3-13. Percent choice of the three-pellet lever (top panel) and response latency (bottom panel) as a function of apomorphine pretreatment dose. All other details as in Figure 3-1.

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CHAPTER 4

EFFECTS OF SELECTIVE DOPAMINERGIC COMPOUNDS ON A PACED FIXED CONSECUTIVE NUMBER SCHEDULE

Impulsivity and self control are constructs used to describe what is increasingly apparent to be more than one class of behaviors. Based on operant and neurobiological experiments in humans and animals, a growing consensus largely agrees on two types of impulsive behavior: impulsive choice and what is termed impulsive action or behavioral inhibition (Dalley, Mar, Economidou, & Robbins, 2008; de Wit, 2009; Evenden, 1999; Perry & Carroll, 2008; Winstanley, Eagle, & Robbins, 2006). Impulsive choice is the tendency to be hypersensitive to delays to reward, while impulsive action refers to the inability to withhold or inhibit a prepotent response. In addition to these two, a third component of impulsivity has been proposed by some. Impulsive preparation or reflection impulsivity, acting before gathering and processing all necessary information, has been argued to encompass impulsive-like responding on a variety of cognitive tasks used in humans and the uncertain visual discrimination task in rats (Evenden, 1999).

Behavior maintained on a fixed consecutive number (FCN) has been purported to measure impulsive action (Evenden, 1999). To obtain a reinforcer on an FCN 8 schedule, for example, a series of at least eight responses must be emitted on a "chain" lever before a single response on a second "reinforcement lever" results in a reinforcer delivery. If fewer than 8 responses are made on the chain lever (i.e., chain length < 8), responding on

the reinforcement lever is punished with a timeout. Impulsive action on this task is defined as response chains of fewer than the requisite number before responding on the reinforcement lever. Evenden (1998b) developed a variant of this task, dubbed a paced FCN schedule, that controls for the rate-increasing or rate-decreasing effects many drugs have on schedule-maintained behavior. By withdrawing the levers after every response and reinserting them into the chamber after a specified interval, the maximum response rate can be controlled. On this procedure, spontaneously hypertensive rats, a purported rodent model of ADHD, show more impulsive action than Wistar Kyoto rats, the strain from which spontaneously hypertensive rats were selectively bred (Evenden & Myerson, 1999; for a review of spontaneously hypertensive rats, see Sagvolden, Russell, Aase, Johansen, & Fashbaf, 2005).

Dopaminergic pathways between the prefrontal cortex, anterior cingulate cortex, and basal ganglia are often implicated in attention deficit hyperactivity disorder (ADHD) and impulsive behavior (for recent reviews see Dalley et al., 2008; Winstanley et al., 2006). Imaging studies in people with ADHD reveal abnormalities in this system, with lower prefrontal activity (Ernst, Zametkin, Matochik, Jons, & Cohen, 1998; Rubia et al., 1999) and enhanced dopamine transporter availability in the striatum (Krause, Dresel, Krause, Kung, & Tatsch, 2000). Similarly, animal models of impulsive action have implicated these same pathways. Anterior cingulate cortex lesions greatly increase premature responding on the 5-choice serial reaction time (5-CSRT) task (Muir, Everitt, & Robbins, 1996), another purported measure of impulsive action (see Dalley et al., 2008). Number of premature responses emitted on the 5-CSRT task is also related to dopamine $D_{2\text{-like}}$ receptor levels in the ventral striatum (Dalley et al., 2007). While

dopamine levels in the prefrontal cortex measured during 5-CSRT task performance are elevated, the level of this elevation is not related to the amount of premature responses emitted (Dalley, Theobald, Eagle, Passetti, & Robbins, 2002), nor do prefrontal cortex lesions affect premature responding (Muir et al., 1996).

Both $D_{1\text{-like}}$ (D_1 and D_5) and $D_{2\text{-like}}$ (D_2, D_3, and D_4) dopamine receptors, as well as dopamine transporters, are known to exist in the dopaminergic pathways connecting the striatum to the prefrontal cortex (Ciliax et al., 1995; Gaspar, Bloch, & Le Moine, 1995; Lévesque et al., 1992; Mrzljak, Bergson, Pappy, Huff, Levenson, & Goldman-Rakic, 1996; Muly III, Szigeti, & Goldman-Rakic, 1998; Revay, Vaughan, Grant, & Kuhar, 1996). Amphetamine has been tested extensively on FCN and paced FCN schedules, and generally decreases chain lengths (i.e., increases impulsive action; Bardo, Cain, & Bylica, 2006; Bronson & Moerschbaecher, 1987; Evenden, 1998a, 1998b; Evenden & Myerson, 1999; Laties, 1972; Laties, Wood, & Rees, 1981; Rees, Wood, & Laties, 1985, 1987). The opposite effect has been occasionally reported with *d*-amphetamine, but only when a distinct discriminative stimulus was associated with completing the series of chain responses (Rivalan, Grégoire, & Dellu-Hagedorn, 2007, one subject in Laties, 1972). As *d*-amphetamine has been shown to increase responding associated with a stimulus paired with reinforcement (e.g., Robbins, Watson, Gaskin, & Ennis, 1983), the addition of such a stimulus may have contributed to this discrepancy. To the author's knowledge, no selective dopamine agonists or $D_{1\text{-like}}$ antagonists have been administered to rats responding on FCN schedules. On FCN schedules, the $D_{2\text{-like}}$ antagonist haloperidol has been shown to increase (Picker, 1988), decrease (Evenden, 1998a), or have no effect on chain lengths (Laties, 1972; Picker, 1989), and decreases in chain lengths are seen after

haloperidol administration on a paced FCN schedule (Evenden, 1998b; Evenden & Myerson, 1999).

As dopaminergic systems that involve a variety of dopamine receptor subtypes are involved in impulsivity, and the effects of systemic injections of selective dopamine receptor agonists and antagonists is largely unknown, we administered the most selective dopamine receptor agonists and antagonists readily available to Sprague Dawley rats responding on a paced FCN schedule as described by Evenden (1998b). The drugs administered included *d*-amphetamine, the selective dopamine transporter blocker GBR 12909, the $D_{1\text{-like}}$ agonist SKF 81297, the $D_{1\text{-like}}$ antagonist SCH 23390, the $D_{2\text{-like}}$ antagonist haloperidol, the $D_{2\text{-preferring}}$ agonist sumanirole, the $D_{2\text{-preferring}}$ antagonist L-741,626, the $D_{3\text{-preferring}}$ agonist pramipexole, the $D_{3\text{-preferring}}$ antagonist PG01037, the D_4 partial agonist ABT 724, the D_4 antagonist L-745,870, and the nonselective dopamine agonist apomorphine. The antagonists listed above were sometimes administered prior to these agonists to further elucidate the mechanisms of action of these drugs.

Method

Subjects

Eight male Sprague Dawley rats served as subjects (Harlan, Indianapolis, IN). Rats were approximately 10 weeks old at the start of the experiment. A food restriction protocol was in place to maintain the rats at approximately 325 g throughout the experiment. This weight was chosen as it is approximately 85% of the mean adult weight supplied by the manufacturer for this strain, and this weight was not changed once established. When not in session, rats were housed in accordance with institutional animal care and use guidelines in polycarbonate cages with fresh water continuously

available. The lights in the housing colony were on from 7:00 AM to 7:00 PM, and sessions were conducted between 2:30 PM and 6:30 PM. These protocols were approved by the University of Michigan Committee on the Use and Care of Animals and conformed to the guidelines established by the NIH Guide for the Use of Laboratory Animals.

Apparatus

Sessions were conducted in rodent operant conditioning chambers with an area of 30.5 cm x 24.1 cm x 21.0 cm and stainless steel grid floors (ENV-008; Med-Associates Inc., St. Albans, VT). Both sides of the front panel of the chamber held a retractable lever (E23-17, Coulbourn Instruments, Whitehall, PA). Between the levers was a food tray connected to a 45-mg pellet dispenser (ENV-200R1AM and ENV-203M-45, Med-Associates, Inc.). Above both of the levers and the food tray were triple stimulus lights containing a red, green, and yellow LED (ENV-222M, Med-Associates, Inc.). A houselight was located near the top of the opposite wall to provide illumination to the chamber (ENV-215M, Med-Associates, Inc.). Chambers were connected to a computer running Med-PC IV software (Med-Associates, Inc.) to control experimental events and record data.

Procedure

Rats were trained to respond on a mixed fixed-time 60 s FR 1 schedule of reinforcement, with the active lever alternating each session between the left and right levers. This schedule arranged one sucrose pellet to be delivered every 60 s independent of behavior, with every lever press also producing a pellet. This was continued for four sessions, at which point the schedule was switched to a FR 1 with no response-

independent pellet deliveries. Rats were allowed to respond on this schedule until 80 responses or more were recorded on two consecutive 20-min sessions.

Paced FCN schedule training then began with the subjects placed in the operant chambers and both levers extended. Left and right levers were randomly assigned to each subject as either the "chain lever" or the "sucrose lever", and these assignments did not change over the course of the experiment. The FCN contingency reinforced responding on the chain lever a number of times equal to or greater than the FCN schedule value followed by a single response on the sucrose lever. Training started with an FCN 1 schedule, where one or more responses on the chain lever followed by one response on the sucrose lever resulted in a 45-mg sucrose pellet delivery and both levers being retracted for 5 s. After each response, both levers were retracted and reinserted such that the maximum response rate was controlled, but with no minimum response rate, as described in detail by Evenden (1998b). Sessions were also split into five components, separated by 1-min blocks with the houselight off and the levers retracted. Components 1, 3, and 5 were 10 min in duration with a pacing interval of 2.5 s, and components 2 and 4 were 20 min in duration with a pacing interval of 5.0 s. The total session duration during all paced FCN sessions with the five components and four intervening blackout periods was 74 min. The FCN schedule value was then gradually increased over a number of sessions to FCN 8, where eight or more responses on the chain lever were required before one response on the sucrose lever was reinforced with a food pellet. At each paced FCN schedule value, chain lengths greater than required were reinforced with a sucrose pellet, but fewer responses than required led to both levers being retracted for 5 s and no sucrose pellet delivery.

Drug testing began after there was no apparent increasing or decreasing trend in mean chain length in each component over a period of five sessions. Sessions were generally conducted five days per week with vehicle injections administered on the first and fourth days of the week, drugs administered on the second and fifth days, and no injections given on the third day. Vehicle injections always corresponded to the vehicle for the scheduled drug injection or injections for the following day in number, substance, and time relative to the experimental session. Each session was preceded by a vehicle or drug injection 5 min before the start of the session with the rat then immediately placed in the darkened experimental chamber. On some days, an antagonist or vehicle injection was administered 30 min prior to the session, with the rat placed back in his home cage for the intervening 25 min before the agonist or vehicle injection was given, as appropriate. All agonists and the corresponding vehicle injections were administered 5 min before the session. All antagonists and the corresponding vehicle injections were administered 30 min before the session start, except SCH 23390 which was administered 5 min before session start due to its relatively rapid onset and short duration of action (Hietala, Seppäla, Lappalainen, & Syvälahti, 1992).

Drugs

Pramipexole was generously provided by Drs. Jianyong Chen and Shaomeng Wang (University of Michigan, Ann Arbor, MI), sumanirole by Benjamin Greedy and Dr. Stephen Husbands (University of Bath, Bath, UK), GBR 12909 by Novo Industri (Bagsvaerd, Denmark), ABT-724 by Dr. Kenner Rice (Chemical Biology Research Branch, National Institute on Drug Abuse, Bethesda, MD), and PG01037 by Drs. Amy H. Newman (Medicinal Chemistry Section – National Institute on Drug Abuse, Baltimore,

MD) and Peter Grundt (University of Minnesota – Duluth, Duluth, MN). Haloperidol, SKF 81297, SCH 23390, and apomorphine were obtained from Sigma-Aldrich (St. Louis, MO), L-741,626 and L-745,870 were obtained from Tocris (Ellisville, MO), and *d*-amphetamine was obtained from the National Institute on Drug Abuse (Bethesda, MD). All drugs were dissolved in sterile saline except L-741,626, which was dissolved in 5% ethanol, and PG01037, which was dissolved in 20% β-cyclodextrin. All injections were administered subcutaneously (s.c.) in a volume of 1.0 ml/kg except 56 mg/kg PG01037 which was administered in of volume of 1.75 ml/kg due to solubility limits.

Data Analysis

Chain length was defined as the number of consecutive responses on the chain lever before a response was recorded on the sucrose lever, and a decrease in chain length was interpreted as an increase in impulsive action. Chain length data were analyzed and plotted as survival plots, or the percent of chains of at least *X* responses as a function of drug dose. Summarized in this manner, data were well-approximated by the sigmoidal equation

$$Y = \frac{100}{1+10^{(C_{50}-X)*S}} \quad (4\text{-}1)$$

where *Y* is the percent chains meeting *X* or more responses and C_{50} and *S* are derived parameters, C_{50} indicating the chain length that 50% of chains met or exceeded, and *S* indicating the slope of the curve at point C_{50}. Data were fit to Equation 4-1 and curves were compared with GraphPad Prism 5 (La Jolla, CA) to determine if drug dose significantly altered the C_{50} parameter. Specific doses were considered to be significantly different from each other if the 95% confidence intervals around the C_{50} parameter did not overlap for those doses. Specific chain lengths were also compared between doses

with Bonferroni-adjusted *post hoc* tests following a significant main effect of dose or a dose by chain length interaction of a two-way Analysis of Variance (ANOVA) in Prism 5. Chain lengths were computed separately for the short (2.5 s) pacing-interval components and the long (5.0 s) pacing-interval components. Chain-length data for the short or long components of any session for any subject were excluded if less than five chains were completed for that session. Data for any dose were excluded if less than two rats met this chains-completed criterion.

Perseverative responses were defined as sucrose-lever responses that were not preceded by at least one chain-lever response (i.e., consecutive sucrose-lever responses), and were expressed as a percent of total sucrose-lever responses. These were compared across dose with a one-way repeated measures ANOVA in Systat SigmaStat 3.5 (San Jose, CA), with Bonferroni-adjusted *post hoc* tests following significant main effects of dose. Perseverative-response data for any session were only included in analyses if ten or more trials were recorded for that subject. If data were excluded, SigmaStat uses a Mixed Models ANOVA to assess within- and between-subjects effects on an incomplete data set. Total trials were defined as the total number of sucrose-lever responses (including perseverative responses), each of which was followed by a timeout. Trials were recorded separately for short and long components, and compared with a two-way repeated measures ANOVA with Prism 5. Relevant Bonferroni-adjusted *post hoc* tests were conducted if a significant main effect of dose or a dose by pacing interval interaction was found.

Results

The dopaminergic drugs assessed in the current paper had varied effects on behavior, but of most interest were "selective" increases or decreases in impulsive action that did not coincide with overall disruptions in responding. Significant increases or decreases in chain length in either component after a given dose of a drug were considered selective unless those effects coincided with a significant reduction in trials completed. Defined in this way, increases in impulsive action (↑), decreases in impulsive action (↓), and disruptions in behavior (×) are indicated on each graph in the legend.

d-Amphetamine dose-dependently decreased chain lengths during both the short and long components (Figure 4-1, Table 4-1). In the short components, the derived chain length met 50% of the time (C_{50} in Equation 4-1; roughly equal to the median chain length) was significantly decreased at 0.32 and 1.0 mg/kg, with 1.0 mg/kg being the only dose with significant *post hoc* tests for specific points. In the long components, each dose of *d*-amphetamine tested from 0.1 to 1.0 mg/kg decreased the C_{50} parameter, while *post hoc* tests revealed significant reductions at specific chain lengths at 0.32 and 1.0 mg/kg. Total trials completed (Table 4-2) and perseverative responses (Table 4-3) were both dose-dependently increased by *d*-amphetamine. Larger increases in number of trials completed were seen in the long-pacing components, leading to a significant main effect of dose ($F_{3,20} = 4.6$, $p = .014$) and a dose by pacing interval interaction ($F_{3,20} = 4.8$, $p = .012$) with no main effect on pacing interval ($F_{1,20} = 0.19$, $p = .666$). Perseverative responses were also increased at 1.0 mg/kg (main effect, $F_{3,15} = 13$, $p < .001$).

The dopamine transporter blocker GBR 12909 significantly affected chain lengths in both the short and long components, but these shifts were not dose-dependent or

sizeable (Figure 4-2, Table 4-1). Significant increases in chain lengths were seen with 1.0 mg/kg in both the short and long components and at 10.0 mg/kg in the short components only. The 3.2 mg/kg dose had no significant effect on chain lengths in either component. Across this same dose range, GBR 12909 did not alter total trials completed (pacing interval main effect $F_{1,28} = 195$, $p < .001$, dose main effect $F_{3,28} = 1.3$, $p = .305$, dose by pacing interval interaction $F_{3,28} = 1.1$, $p = .351$; Table 4-2) or perseverative responses ($F_{3,21} = 1.8$, $p = .187$; Table 4-3).

The $D_{3\text{-preferring}}$ agonist pramipexole dose-dependently decreased chain lengths in both the short and long pacing interval components (Figure 4-3, Table 4-1). In the short components, doses from 0.032 to 0.32 mg/kg decreased chain lengths, while doses from 0.01 to 0.1 mg/kg decreased chain lengths in the long components. These decreases with low doses of pramipexole up to 0.032 mg/kg did not significantly decrease trials completed (Table 4-2), but higher doses did decrease trials completed (pacing interval main effect $F_{1,30} = 102$, $p < .001$, dose main effect $F_{4,30} = 23$, $p < .001$, pacing interval by dose interaction $F_{4,30} = 2.5$, $p = .067$). The percent of sucrose lever responses that were perseverative ($F_{4,20} = 18$, $p < .001$) were also dose-dependently increased, but only at doses that also decreased responding (Table 4-3).

The effects of the $D_{2\text{-preferring}}$ agonist sumanirole on chain length depended on dose and pacing interval (Figure 4-4, Table 4-1). In the short components, 0.32 mg/kg sumanirole slightly increased chain lengths, while the same dose had no effect in the long components. The 0.56 mg/kg dose had no effect in either component, while 1.0 mg/kg decreased chain length in both components. Sumanirole dose-dependently decreased trials completed (pacing interval main effect $F_{1,24} = 71$, $p < .001$, dose main effect $F_{3,24} =$

5.7, $p = .004$, pacing interval by dose interaction $F_{3,24} = 4.1$, $p = .017$; Table 4-2), while perseverative responses increased over the same dose range ($F_{3,18} = 5.7$, $p = .007$, Table 4-3).

The D_4-partial agonist ABT-724 significantly altered chain lengths in the short components, but these shifts were small and not dose-dependent (Figure 4-5, Table 4-1). The doses of 0.32 and 3.2 mg/kg both decreased chain lengths, while 1.0 mg/kg had no effect. This same range of doses did not alter chain lengths in the long components, and Bonferroni-adjusted *post hoc* tests did not reveal a significant increase or decrease in chain length distributions at any number of responses in either component. ABT-724 had no effect on trials completed (pacing interval main effect $F_{1,28} = 147$, $p < .001$, dose main effect $F_{3,28} = 0.37$, $p = .773$, pacing interval by dose interaction $F_{3,28} = 0.46$, $p = .714$) or perseverative responses ($F_{3,21} = 2.4$, $p = .096$) over the range of doses tested (Table 4-2, Table 4-3).

The $D_{2\text{-like}}$ antagonist haloperidol significantly shifted chain lengths in the short and long components, the direction of which depended on both pacing interval and dose (Figure 4-6, Table 4-1). The smallest dose of haloperidol tested, 0.01 mg/kg, significantly shifted chain lengths to the right in the short components only, while higher doses shifted chain lengths to the left in both components. At the highest dose tested, 0.1 mg/kg, trials completed were significantly reduced in both components (Table 4-2; pacing interval main effect $F_{1,24} = 69$, $p < .001$, dose main effect $F_{3,24} = 13$, $p < .001$, pacing interval by dose interaction $F_{3,24} = 1.9$, $p = .015$). Perseverative responses were also dose-dependently increased, but only significantly so at a dose that also reduced trials completed (Table 4-3; $F_{3,15} = 12$, $p < .001$).

The $D_{3\text{-preferring}}$ antagonist PG01037 increased chain lengths in both the short and long components (Figure 4-7, Table 4-1). In the short components chain lengths were increased at the two highest doses tested, while 10 mg/kg had no significant effect. In the long components, 10 mg/kg and 32 mg/kg significantly increased chain lengths, albeit only slightly, while 56 mg/kg decreased chain lengths. Across this dose range, trials completed were not altered (Table 4-2; pacing interval main effect $F_{1,24} = 30$, $p < .001$, dose main effect $F_{3,24} = 0.32$, $p = .809$, pacing interval by dose interaction $F_{3,24} = 2.7$, $p = .070$), and perseverative responses were increased at 56 mg/kg (Table 4-3; dose main effect $F_{3,18} = 5.0$, $p = .011$).

The $D_{2\text{-preferring}}$ antagonist L-741,626 significantly decreased chain lengths in both components (Figure 4-8, Table 4-1). In the short components, L-741,626 had no effect except when a dose of 3.2 mg/kg was administered, a dose that drastically reduced responding. In the long components, 1.0 mg/kg L-741,626 reduced chain lengths slightly. Trials completed were substantially reduced at 3.2 mg/kg (Table 4-2; pacing interval main effect $F_{1,28} = 118$, $p < .001$, dose main effect $F_{3,28} = 107$, $p < .001$, pacing interval by dose interaction $F_{3,28} = 6.9$, $p = .001$), while percent perseverative responses were increased at this same dose (Table 4-3; $F_{3,17} = 31$, $p < .001$).

The D_4 antagonist L-745,870 only slightly altered behavior, although some shifts in chain lengths did reach statistical significance (Figure 4-9, Table 4-1). Chain lengths were slightly increased by 0.32 mg/kg in the short components, and decreased by 3.2 mg/kg in the long components. Specific chain lengths were not altered in either component, as measured by Bonferroni-adjusted *post hoc* tests. Across this range of doses, total trials completed (pacing interval main effect $F_{1,28} = 147$, $p < .001$, dose main

effect $F_{3,28} = 0.55$, $p = .652$, pacing interval by dose interaction $F_{3,28} = 0.76$, $p = .529$) or perseverative responses (main effect $F_{3,21} = 0.85$, $p = .485$) were not altered (Table 4-2, Table 4-3).

To determine which receptors mediated the effects seen with pramipexole, antagonists at various receptors were administered as pretreatments to pramipexole. Haloperidol at 0.01 mg/kg was able to partially reverse the decreases in chain lengths caused by 0.1 mg/kg pramipexole in both components (Figure 4-10, Table 4-1). Haloperidol at 0.32 mg/kg partially reversed the effects of 0.1 mg/kg pramipexole in the long components, but potentiated this effect in the short components. Haloperidol at 0.032 mg/kg also significantly reversed the decrease in total trials completed cause by 0.1 mg/kg pramipexole, while 0.01 mg/kg haloperidol had no significant effect (Table 4-2; pacing interval main effect $F_{1,24} = 87$, $p < .001$, dose main effect $F_{3,24} = 14$, $p < .001$, pacing interval by dose interaction $F_{3,24} = 0.71$, $p = .557$). Perseverative responses were significantly altered across the conditions tested ($F_{3,18} = 4.9$, $p = .012$), but no specific comparisons of interest were statistically significant (Table 4-3).

In the short component, 10 mg/kg of the $D_{3\text{-preferring}}$ antagonist PG01037 administered prior to 0.1 mg/kg pramipexole completely reversed the decrease in chain lengths seen with this dose (Figure 4-11; Table 4-1). In the long component, effects of PG01037 pretreatments were difficult to interpret. Pramipexole at 0.1 mg/kg decreased chain lengths alone, and chain lengths were shortened further by 32 mg/kg PG01037 but increased by 56 mg/kg. This lack of dose-dependency may have been due to the low number of total trials completed on which these chain length distributions were based. PG01037 did not reverse the decrease in trials completed caused by 0.1 mg/kg

pramipexole, and in the short component further decreased trials completed at 10 and 56 mg/kg (Table 4-2; pacing interval main effect $F_{1,35} = 167$, $p < .001$, dose main effect $F_{4,35} = 35$, $p < .001$, pacing interval by dose interaction $F_{4,35} = 1.8$, $p = .157$). PG01037 also did not reverse the increase in perseverative responses caused by 0.1 mg/kg pramipexole (Table 4-3; main effect $F_{4,27} = 3.8$, $p = .014$).

The $D_{2\text{-preferring}}$ antagonist L-741,626 at 0.32 mg/kg significantly reversed the decrease in chain lengths caused by 0.1 mg/kg pramipexole in both the short and long components (Figure 4-12, Table 4-1). Administered as a pretreatment to 0.1 mg/kg pramipexole, 1.0 mg/kg L-741,626 decreased chain lengths compared with pramipexole alone in the short component and had no effect in the long component. L-741,626 did not reverse the decrease in trials completed caused by 0.1 mg/kg pramipexole, instead further decreasing trials completed (Table 4-2; pacing interval main effect $F_{1,28} = 94$, $p < .001$, dose main effect $F_{3,28} = 37$, $p < .001$, pacing interval by dose interaction $F_{3,28} = 1.1$, $p = .348$). L-741,626 also did not reverse the increase in perseverative responses caused by 0.1 mg/kg pramipexole (Table 4-3; dose main effect $F_{3,20} = 3.7$, $p = .028$).

The $D_{1\text{-like}}$ agonist SKF 81297 slightly, but significantly, increased chain lengths in the short component at 0.1 and 0.32 mg/kg, but these same doses had no effect in the long component (Figure 4-13, Table 4-1). SKF 81297 at 1.0 mg/kg decreased chain lengths in both components. At the doses tested, SKF 81297 did not alter trials completed (Table 4-2; pacing interval main effect $F_{1,28} = 24$, $p < .001$, dose main effect $F_{3,28} = 0.19$, $p = .904$, pacing interval by dose interaction $F_{3,28} = 1.2$, $p = .342$), but did dose-dependently increase perseverative responses (Table 4-3; dose main effect $F_{3,21} = 7.4$, $p = .002$).

The $D_{1\text{-like}}$ antagonist SCH 23390 had no significant effect on behavior at doses that did not also significantly alter trials completed (Figure 4-14, Table 4-1). A dose of 0.032 mg/kg in the short component and 0.01 mg/kg in the long component both reduced chain lengths, and not enough responses were made to compute chain lengths in the long component following the administration of 0.032 mg/kg. Trials completed were dose-dependently decreased by SCH 23390 (Table 4-2; pacing interval main effect $F_{1,28} = 255$, $p < .001$, dose main effect $F_{3,28} = 255$, $p < .001$, pacing interval by dose interaction $F_{3,28} = 15$, $p < .001$). Perseverative responses were increased, but only at a dose that decreased responding overall (Table 4-3; dose main effect $F_{2,14} = 6.6$, $p = .010$).

The $D_{1\text{-like}}$ antagonist SCH 23390 was administered along with 1.0 mg/kg of the $D_{1\text{-like}}$ agonist SKF 81297 to determine whether the behavioral effects of this dose were reversible. SCH 23390 from 0.001 to 0.01 mg/kg did not reverse the decrease in chain lengths caused by 1.0 mg/kg SKF 81297, and actually decreased chain lengths further at each dose (Figure 4-15; Table 4-1). SKF 81297 at 1.0 mg/kg alone did not alter trials completed, and the addition of SCH 23390 did not significantly affect this measure either, although there was a trend toward a decrease in trials completed at higher doses of SCH 23390 (Table 4-2; pacing interval main effect $F_{1,35} = 6.1$, $p = .019$, dose main effect $F_{4,35} = 2.5$, $p = .059$, pacing interval by dose interaction $F_{4,35} = 2.2$, $p = .085$). SCH 23390 also did not affect the increase in perseverative responses caused by 1.0 mg/kg SKF 81297 (dose main effect $F_{4,27} = 8.2$, $p < .001$; Table 4-3).

The nonselective dopamine agonist apomorphine had effects on chain lengths that depended on pacing-interval and dose (Figure 4-16, Table 4-1). Significant effects that were small in absolute magnitude were noted with 0.032 mg/kg in both components and

0.1 mg/kg in the long component, but sizeable increases were caused by 0.32 mg/kg in the short component. This same dose decreased chain lengths in the long component, and decreased total trials completed (Table 4-2; pacing interval main effect $F_{1,28} = 64$, $p < .001$, dose main effect $F_{3,28} = 16$, $p < .001$, pacing interval by dose interaction $F_{3,28} = 2.4$, $p = .089$). Perseverative responses were also dose-dependently increased with apomorphine (Table 4-3; main effect $F_{3,20} = 5.5$, $p = .007$).

The $D_{1\text{-like}}$ antagonist SCH 23390 and the $D_{2\text{-like}}$ antagonist haloperidol were administered with 0.32 apomorphine to determine if the effects of this dose could be reversed. A dose of 0.01 mg/kg SCH 23390 reversed the increase in chain lengths in the short component caused by 0.32 mg/kg apomorphine, but no dose of SCH 23390 tested reversed the decrease in chain lengths caused by 0.32 mg/kg apomorphine in the long component (Figure 4-17, Table 4-1). SCH 23390 also did not reverse the decrease in trials completed cause by 0.32 mg/kg apomorphine, and further decreased trials completed at 0.01 mg/kg (Table 4-2; pacing interval main effect $F_{1,28} = 29$, $p < .001$, dose main effect $F_{3,28} = 14$, $p < .001$, pacing interval by dose interaction $F_{3,28} = 2.1$, $p = .126$). SCH 23390 also appeared to further increase the increase in perseverative responses noted with 0.32 mg/kg apomorphine, although these effects were not significant due to a large amount of subject variability (Table 4-3; main effect $F_{3,16} = 2.5$, $p = .094$).

The $D_{2\text{-like}}$ antagonist haloperidol, when given as a pretreatment to 0.32 mg/kg apomorphine, did not reverse the effects on chain lengths seen with this dose (Figure 4-18, Table 4-1). A dose of 0.01 mg/kg haloperidol had no effect in either pacing-interval component, while 0.032 mg/kg decreased chain lengths in both components. A dose of 0.032 mg/kg haloperidol also decreased trials completed beyond the decrease seen with

0.32 apomorphine alone (Table 4-2; pacing interval main effect $F_{1,28} = 38$, $p < .001$, dose main effect $F_{3,28} = 22$, $p < .001$, pacing interval by dose interaction $F_{3,28} = 4.7$, $p = .009$. Haloperidol at the doses tested did not significantly alter the increase in perseverative responses seen with 0.32 mg/kg apomorphine (Table 4-3; main effect $F_{3,13} = 5.6$, $p = .011$).

Discussion

Responding on a paced FCN 8 schedule was learned by all subjects and performance remained relatively stable over the course of the experiment. Chain lengths on this schedule were very sensitive to the effects of the dopaminergic drugs administered. Chain lengths were altered after administration of most of the compounds tested, but selective increases and decreases that did not coincide with significant decreases in trials completed were more limited.

d-Amphetamine dose-dependently decreased chain lengths over a range of doses that also dose-dependently increased trials completed. Similar effects have been reported before on FCN schedules (Bardo et al., 2006; Bronson & Moerschbaecher, 1987; Evenden, 1998a, 1998b; Evenden & Myerson, 1999; Laties, 1972; Laties et al., 1981; Rees et al., 1985, 1987). The changes in chain length induced by the dopamine transporter-selective ligand GBR 12909 were small in magnitude, suggesting that the effects of *d*-amphetamine were likely mediated through serotonergic or noradrenergic mechanisms.

The selective drugs with affinity for D_2 and D_3 receptors had effects that seemed to depend on receptor subtype selectivity and efficacy at that receptor. The $D_{3\text{-preferring}}$ agonist pramipexole and the $D_{2\text{-preferring}}$ antagonist L-741,626 both selectively reduced

chain lengths, while the $D_{2\text{-preferring}}$ agonist sumanirole and the $D_{3\text{-preferring}}$ antagonist PG01037 selectively increased chain lengths in at least one case. A model of impulsive action have been shown to be related to $D_{2\text{-like}}$ receptors in the ventral striatum (Dalley et al., 2007), but this apparent opposing action of D_2 and D_3 receptors has not previously been demonstrated on models of impulsivity. D_2 and D_3 receptors have been shown to have opposing effects in other behavioral systems, however. D_3 receptor activation induces yawning and penile erections while D_2 receptor activation inhibits those same behaviors (Collins et al., 2007), and the discriminative stimulus properties of these same drugs share an analogous pattern of results. In rats trained to discriminate the subjective effects of pramipexole from saline, L-741,626 substituted for the pramipexole stimulus; and in rats trained to discriminate the subjective effects of sumanirole from saline, PG01037 substituted for the sumanirole stimulus (Koffarnus, Greedy, Husbands, Grundt, Newman, & Woods, 2009). It is not known for certain what pathways of the brain are important for paced FCN responding, but given that D_3 and D_2 receptors are more often located on presynaptic and postsynaptic sites, respectively (Bouthenet, Souil, Martres, Sokoloff, Giros, & Schwartz, 1991), the opposing effects in the current study of agonist and antagonists that act through these receptors may be a consequence of this relationship.

The decreasing effect of 0.1 mg/kg pramipexole on chain lengths was antagonized in at least one component by at least one dose of haloperidol, PG01037, and L-741,626. A dose of 0.01 mg/kg haloperidol reversed the decrease in chain lengths caused by 0.1 mg/kg pramipexole in both the short and long components, although this dose increased chain lengths in the short component when administered alone. A dose of 10 mg/kg

PG01037, which did not alter chain lengths in the short component when administered alone, reversed the decrease caused by pramipexole in the short component, while the effects of PG01037 in the long component were not dose-dependent and difficult to interpret. A dose of 0.32 mg/kg L-741,626, a dose that had no effect when administered alone, at least partially reversed the decrease caused by 0.1 mg/kg pramipexole in both components. These data suggest the decrease in chain lengths caused by 0.1 mg/kg pramipexole may be partially mediated through agonism at both D_2 and D_3 receptors. L-741,626 is only about 15-fold selective for D_2 over D_3 receptors, however (Grundt, Husbands, Luedtke, Taylor, & Newman, 2007), leaving open the possibility that all three antagonists are acting through D_3 receptors.

The $D_{1\text{-like}}$ agonist SKF 81297 significantly increased chain lengths at 0.1 and 0.32 mg/kg in the short component, although these increases were very small in magnitude, while 1.0 mg/kg SKF 81297 decreased chain lengths in both components. SCH 23390 had no significant effect on chain lengths up to doses that drastically reduced trials completed. In addition, SCH 23390, when administered as a pretreatment to 1.0 mg/kg SKF 81297, only potentiated the decrease in chain lengths caused by SKF 81297 at every dose tested. This remained true for doses of SCH 23390 that had no significant effect when administered alone, and the very low dose of 0.001 mg/kg which was not tested in isolation.

In the short components, 0.32 mg/kg apomorphine produced the largest increase in chain length in absolute size of any dose of any drug administered. Since apomorphine is an agonist at all five dopamine receptor subtypes, SCH 23390 and haloperidol were administered as pretreatments to this dose of apomorphine to assess the involvement of

$D_{1\text{-like}}$ or $D_{2\text{-like}}$ receptors. A dose of 0.01 mg/kg SCH 23390, which had no significant effect when administered alone, reversed the increase in chain lengths in the short component caused by 0.32 mg/kg apomorphine. A dose of 0.032 mg/kg haloperidol also reversed this apomorphine-induced increase. This dose of haloperidol lowered chain lengths when administered alone, however, so it is not clear that this effect was due to an antagonism of apomorphine. Apomorphine is known to produce perseverative responding that seems disconnected from the consequences that result (Robbins et al., 1983), which may have contributed to these effects. Perseverating on the chain lever would likely manifest as an increase in chain lengths, although a similar increase was not observed in the long component. Perseverative responding on the reinforcement lever was also significantly increased with 0.32 mg/kg apomorphine (Table 4-3).

While no drug administered significantly decreased perseverative responding on the sucrose lever, increases in perseverative responses were also caused by a number of the drugs in the current experiment. The pattern of these increases appeared to be of two types. One might conceptualize perseverative responses as chain lengths of zero, as each is a response on the sucrose lever with no preceding responses on the chain lever. In the current study, all of the drugs that produced large decreases in chain lengths also produced significant increases in perseverative responses at similar doses. As a drug tended to increase the proportion of lower-length chains, the proportion of the lowest-length chain possible (0 responses) was also increased. This tendency has been described quantitatively on an individual-subject basis, with a strong negative correlation between drug effects on chain lengths and perseverative responses on the paced FCN (Chapter 6). This pattern was observed seemingly independent of drug mechanism, and was found

in the current experiment with administration of relatively high doses of *d*-amphetamine, pramipexole, sumanirole, haloperidol, PG01037, L-741,626, SKF 81297, and SCH 23390. A pattern of effects that differed from the one described above was noted for two drugs, however. Doses of 56 mg/kg PG01037 and 0.32 mg/kg apomorphine both increased perseverative responses with a mixed effect on chain length. These drugs both increased chain lengths in the short component, but decreased chain lengths in the long component. Upon further analysis, however, most of the increase in perseverative responses occurred in the long component along with the decrease in chain lengths. Additional two-way repeated measures ANOVAs (assessing pacing interval, drug dose, and the interaction between these factors; analysis not shown) revealed a significant increase in perseverative responses only in the long component with these drugs, with smaller non-significant increases with both drugs in the short component. Therefore, the pattern of the increase in perseverative responses with all drugs assessed in the current study is similar, with increases uniformly coinciding with decreases in chain length. Also of note regarding perseverative responses was the lack of any antagonism observed with any of the increases observed. Antagonists administered prior to 0.1 mg/kg pramipexole (antagonists tested: haloperidol, PG01037, and L-741,626), 1.0 mg/kg SKF 81297 (antagonist tested: SCH 23390), or 0.32 mg/kg apomorphine (antagonists tested: haloperidol and SCH 23390) did not reverse the increase in perseverative responses seen with the respective agonist. This is true even though some of the antagonists were effective at reversing the change in chain lengths observed with the respective agonist (e.g., 0.01 mg/kg haloperidol + 0.1 mg/kg pramipexole). The strong relationship between chain lengths and perseverative responses noted with agonists and antagonists

administered alone did not seem to hold when these same compounds were co-administered.

In conclusion, dopaminergic modulation of paced FCN responding is apparent, with most compounds tested influencing chain lengths, often at low doses that did not disturb total responding. An interesting opposing action was observed with D_2 and D_3 receptor agonists and antagonists, suggesting differential mediation of chain lengths by these receptors. The $D_{2\text{-preferring}}$ agonist sumanirole and the $D_{3\text{-preferring}}$ antagonist PG01037 had similar effects, both increasing chain lengths and therefore decreasing impulsive action as defined by this task. These increases were observed at relatively low doses that did not adversely affect total responding on this or other operant schedules (e.g., Koffarnus et al., 2009). Involvement of $D_{2\text{-like}}$ receptors and brain areas rich in $D_{2\text{-like}}$ receptors in impulsive action has been proposed previously (Dalley et al., 2007). The opposing mechanism of D_2 and D_3 receptors in the current paper has not been described previously, and has implications for potentially therapeutically-relevant specific dopaminergic compounds in the treatment of impulse control disorders.

Table 4-1. The derived value of C_{50} (± SEM) from Equation 4-1, or the number of responses that was met by 50% of the chains for each dose of each drug tested. C_{50} values are reported separately for the long- and short-pacing components.

d-Amphetamine	Dose	Vehicle	0.1	0.32	1.0	
(*n* = 6)	Short	10.55(0.10)	10.30(0.11)	9.67(0.10) **	7.41(0.10) **	
	Long	8.67(0.11)	8.23(0.09) *	7.05(0.12) **	3.94(0.12) **	
GBR 12909	Dose	Vehicle	1.0	3.2	10	
(*n* = 8)	Short	9.16(0.03)	9.45(0.05) **	9.18(0.04)	9.55(0.03) **	
	Long	8.76(0.05)	9.17(0.05) **	8.93(0.06)	8.78(0.05)	
Pramipexole	Dose	Vehicle	0.01	0.032	0.1	0.32
(*n* = 7)	Short	10.50(0.08)	10.67(0.11)	9.35(0.08) **	9.10(0.07) **	6.93(0.21) **
	Long	8.93(0.20)	8.41(0.06) *	7.91(0.14) **	5.21(0.20) **	n.d.
Sumanirole	Dose	Vehicle	0.32	0.56	1.0	
(*n* = 7)	Short	9.66(0.08)	10.04(0.09) *	9.52(0.09)	8.58(0.06) **	
	Long	8.25(0.07)	8.35(0.08)	8.46(0.14)	6.06(0.19) **	
ABT-724	Dose	Vehicle	0.32	1.0	3.2	
(*n* = 8)	Short	9.98(0.07)	9.36(0.06) **	9.99(0.12)	9.50(0.09) **	
	Long	9.18(0.08)	8.92(0.07)	8.95(0.10)	9.47(0.13)	
Haloperidol	Dose	Vehicle	0.01	0.032	0.1	
(*n* = 7)	Short	10.26(0.09)	11.08(0.12) **	7.45(0.10) **	5.83(0.15) **	
	Long	8.89(0.09)	9.05(0.09)	5.83(0.15) **	n.d.	
PG01037	Dose	Vehicle	10	32	56	
(*n* = 7)	Short	9.57(0.07)	9.36(0.06)	10.24(0.10) **	10.40(0.12) **	
	Long	8.60(0.04)	8.91(0.08) *	8.97(0.06) **	7.93(0.12) **	
L-741,626	Dose	Vehicle	0.32	1.0	3.2	
(*n* = 8)	Short	8.92(0.05)	9.02(0.06)	8.85(0.06)	4.46(0.15) **	
	Long	8.37(0.03)	8.43(0.07)	7.99(0.09) **	n.d.	
L-745,870	Dose	Vehicle	0.32	1.0	3.2	
(*n* = 8)	Short	9.43(0.04)	9.63(0.06) *	9.27(0.06)	9.41(0.07)	
	Long	8.82(0.04)	8.86(0.05)	8.84(0.06)	8.64(0.05) *	
Haloperidol +	Dose	Vehicle	0.1 Pram	+ 0.01 Hal	+ 0.032 Hal	
0.1 Pramipexole	Short	10.23(0.09)	9.10(0.07) **	9.84(0.09) ††	8.19(0.17) ††	
(*n* = 7)	Long	9.10(0.09)	5.21(0.20) **	7.27(0.15) ††	6.47(0.15) ††	

PG01037 +	Dose	Vehicle	0.1 Pram	+ 10 PG	+ 32 PG	+ 56 PG
0.1 Pramipexole	Short	9.62(0.06)	8.85(0.11) **	10.13(0.15) ††	8.61(0.25)	8.85(0.25)
(*n* = 8)	Long	8.59(0.05)	5.76(0.20) **	6.67(0.05)	4.64(0.26) †	7.98(0.22) ††
L-741,626 +	Dose	Vehicle	0.1 Pram	+ 0.32 L-741	+ 1.0 L-741	
0.1 Pramipexole	Short	9.52(0.05)	8.85(0.11) **	9.79(0.13) ††	7.87(0.24) ††	
(*n* = 8)	Long	8.72(0.06)	5.76(0.20) **	7.23(0.41) †	6.44(0.18)	
SKF 81297 (*n* = 8)	Dose	Vehicle	0.1	0.32	1.0	
	Short	9.30(0.04)	9.58(0.09) *	9.74(0.03) **	8.52(0.12) **	
	Long	8.73(0.05)	8.97(0.08)	8.90(0.08)	6.37(0.14) **	
SCH 23390 (*n* = 8)	Dose	Vehicle	0.0032	0.01	0.032	
	Short	9.43(0.04)	9.57(0.06)	9.32(0.07)	8.02(0.18) **	
	Long	9.28(0.08)	8.96(0.09)	7.25(0.14) **	n.d.	
SCH 23390 +	Dose	Vehicle	1.0 SKF	+ 0.001 SCH	+ 0.0032 SCH	+ 0.01 SCH
1.0 SKF 81297	Short	9.37(0.04)	8.53(0.12) **	7.33(0.37) †	5.41(0.44) ††	6.04(0.21) ††
(*n* = 8)	Long	8.77(0.05)	6.37(0.14) **	4.71(0.27) ††	3.90(0.32) ††	4.90(0.22) ††
Apomorphine (*n* = 8)	Dose	Vehicle	0.032	0.1	0.32	
	Short	9.38(0.04)	9.64(0.05) **	9.51(0.06)	10.50(0.13) **	
	Long	8.70(0.04)	8.94(0.03) **	8.48(0.05) **	8.32(0.15) *	
SCH 23390 +	Dose	Vehicle	0.32 Apo	+ 0.0032 SCH	+ 0.01 SCH	
0.32 Apomorphine	Short	9.43(0.04)	10.50(0.13) **	10.44(0.14)	9.57(0.16) ††	
(*n* = 8)	Long	8.76(0.03)	8.32(0.15) *	7.22(0.40) †	n.d.	
Haloperidol +	Dose	Vehicle	0.32 Apo	+ 0.01 Hal	+ 0.032 Hal	
0.32 Apomorphine	Short	9.37(0.03)	10.50(0.13) **	10.49(0.16)	7.29(0.27) ††	
(*n* = 8)	Long	8.80(0.04)	8.32(0.15) *	8.64(0.13)	6.92(0.26) ††	

n.d.: Not enough data to compute value. Apo = apomorphine. Hal = haloperidol. L741 = L-741,626. PG = PG01037. Pram = pramipexole. SCH = SCH 23390. SKF = SKF 81297.
* $p < .05$, ** $p < 0.01$, *** $p < .001$ compared to vehicle in Bonferroni-adjusted *post hoc* tests.
† $p < .05$, †† $p < 0.01$, ††† $p < .001$ compared to agonist alone in Bonferroni-adjusted *post hoc* tests.

Table 4-2. Total trials completed (± SEM) for each dose of each drug tested. As each trial ends with a sucrose-lever response, this figure is also equal to total sucrose-lever responses. Values are reported separately for the long- and short-pacing components.

	Dose	Vehicle	0.1	0.32	1.0	
d-Amphetamine	Short	54.9(3.4)	54.5(4.9)	60.7(4.6)	82.8(12.8)	
	Long	44.9(3.6)	43.0(3.0)	55.7(5.81	103.3(24.1) ***	
	Dose	Vehicle	1.0	3.2	10	
GBR 12909	Short	60.9(2.2)	60.3(1.8)	60.3(1.6)	55.0(2.9)	
	Long	44.9(1.0)	43.3(1.4)	44.6(1.8)	43.3(1.4)	
	Dose	Vehicle	0.01	0.032	0.1	0.32
Pramipexole	Short	52.8(2.9)	48.4(4.8)	41.6(4.0)	23.3(0.9) ***	11.6(3.4) ***
	Long	36.5(3.4)	40.7(5.9)	21.4(6.5) *	8.0(2.2) ***	0.9(0.6) ***
	Dose	Vehicle	0.32	0.56	1.0	
Sumanirole	Short	60.3(3.2)	56.1(4.0)	51.0(6.7)	38.4(7.0) *	
	Long	48.9(3.7)	50.1(3.6)	30.3(5.4) *	19.1(7.3) ***	
	Dose	Vehicle	0.32	1.0	3.2	
ABT-724	Short	58.0(3.3)	63.4(2.3)	58.6(4.1)	59.3(4.0)	
	Long	43.8(2.2)	46.0(2.4)	44.9(3.6)	43.0(2.6)	
	Dose	Vehicle	0.01	0.032	0.1	
Haloperidol	Short	53.5(4.4)	49.9(4.1)	48.0(8.4)	12.4(3.8) ***	
	Long	42.3(4.3)	36.9(4.4)	28.3(8.0)	2.9(1.8) ***	
	Dose	Vehicle	10	32	56	
PG01037	Short	60.4(3.0)	60.6(3.5)	58.4(2.3)	58.0(4.6)	
	Long	47.0(1.9)	50.4(2.1)	48.4(0.9)	56.7(6.8)	
	Dose	Vehicle	0.32	1.0	3.2	
L-741,626	Short	62.3(2.7)	65.6(2.7)	61.1(3.7)	10.6(2.1) ***	
	Long	46.2(2.1)	46.8(3.3)	53.6(3.2)	1.4(0.5) ***	
	Dose	Vehicle	0.32	1.0	3.2	
L-745,870	Short	56.2(3.1)	55.4(3.5)	58.5(2.7)	58.9(3.4)	
	Long	41.6(2.7)	44.1(2.0)	47.5(1.9)	45.0(2.4)	
	Dose	Vehicle	0.1 Pram	+ 0.01 Hal	+ 0.032 Hal	
Haloperidol + 0.1 Pramipexole	Short	56.5(2.8)	23.3(0.9) ***	28.4(4.7)	43.1(8.6) ††	
	Long	43.9(1.7)	8.0(2.2) ***	13.0(2.8)	23.7(6.4) †	

PG01037 + 0.1 Pramipexole	Dose	Vehicle	0.1 Pram	+ 10 PG	+ 32 PG	+ 56 PG
	Short	58.8(2.4)	33.4(4.6) ***	19.3(3.4) ††	25.9(3.2)	21.4(2.4) †
	Long	41.8(3.0)	10.8(3.8) ***	5.8(3.1)	5.6(1.9)	7.6(1.1)
L-741,626 + 0.1 Pramipexole	Dose	Vehicle	0.1 Pram	+ 0.32 L-741	+ 1.0 L-741	
	Short	60.5(1.9)	33.4(4.6) ***	20.3(4.0) †	22.0(4.5)	
	Long	44.6(3.2)	10.8(3.8) ***	6.4(3.2)	5.9(1.6)	
SKF 81297	Dose	Vehicle	0.1	0.32	1.0	
	Short	61.2(2.2)	61.6(2.9)	54.9(3.7)	58.4(11.7)	
	Long	43.8(3.1)	46.1(3.8)	42.4(5.0)	53.6(15.8)	
SCH 23390	Dose	Vehicle	0.0032	0.01	0.032	
	Short	58.9(2.1)	60.5(1.9)	29.0(2.1) ***	5.1(0.5) ***	
	Long	42.6(2.4)	40.0(1.9)	6.9(2.1) ***	0.1(0.1) ***	
SCH 23390 + 1.0 SKF 81297	Dose	Vehicle	1.0 SKF	+ 0.001 SCH	+ 0.0032 SCH	+ 0.01 SCH
	Short	60.2(2.2)	58.4(11.7)	30.1(11.6)	27.3(10.5)	23.6(6.4)
	Long	43.6(2.9)	53.6(15.8)	22.3(8.6)	28.5(12.7)	24.5(9.1)
Apomorphine	Dose	Vehicle	0.032	0.1	0.32	
	Short	59.1(2.9)	58.8(2.1)	51.6(4.0)	24.5(4.6) ***	
	Long	46.8(2.1)	47.4(2.0)	37.4(4.2)	19.8(6.7) ***	
SCH 23390 + 0.32 Apomorphine	Dose	Vehicle	0.32 Apo	+ 0.0032 SCH	+ 0.01 SCH	
	Short	58.4(2.9)	24.5(4.6) ***	27.6(8.0)	13.8(3.0)	
	Long	44.7(2.4)	19.8(6.7) **	22.5(7.4)	0.9(0.5) †	
Haloperidol + 0.32 Apomorphine	Dose	Vehicle	0.32 Apo	+ 0.01 Hal	+ 0.032 Hal	
	Short	61.8(1.2)	24.5(4.6) ***	17.0(6.3)	12.5(4.1)	
	Long	44.3(1.0)	19.8(6.7) ***	12.5(4.7)	4.8(2.6) †	

Apo = apomorphine. Hal = haloperidol. L741 = L-741,626. PG = PG01037. Pram = pramipexole. SCH = SCH 23390. SKF = SKF 81297.
* $p < .05$, ** $p < 0.01$, *** $p < .001$ compared to vehicle in Bonferroni-adjusted *post hoc* tests.
† $p < .05$, †† $p < 0.01$, ††† $p < .001$ compared to agonist alone in Bonferroni-adjusted *post hoc* tests.

Table 4-3. Perseverative responses, or sucrose-lever responses not preceded by any chain responses, as a percent of total sucrose-lever responses.

d-Amphetamine	Vehicle	0.1	0.32	1.0	
	7.95(3.35)	6.49(2.48)	8.75(4.51)	33.90(6.33) ***	
GBR 12909	Vehicle	1.0	3.2	10	
	3.64(0.83)	3.21(0.96)	3.71(1.09)	1.76(0.39)	
Pramipexole	Vehicle	0.01	0.032	0.1	0.32
	10.24(2.50)	10.66(3.33)	13.87(3.66)	22.25(3.08) *	54.59(4.87) ***
Sumanirole	Vehicle	0.32	0.56	1.0	
	9.66(2.42)	6.50(1.70)	16.95(6.11)	28.42(5.48) *	
ABT-724	Vehicle	0.32	1.0	3.2	
	7.71(2.37)	4.34(1.30)	5.98(1.63)	7.67(1.85)	
Haloperidol	Vehicle	0.01	0.032	0.1	
	7.06(2.19)	8.73(2.44)	23.78(7.31)	60.82(11.10) ***	
PG01037	Vehicle	10	32	56	
	6.11(1.64)	4.57(1.42)	5.98(1.17)	12.66(2.44) *	
L-741,626	Vehicle	0.32	1.0	3.2	
	5.26(1.21)	4.91(0.87)	9.03(2.16)	46.35(10.13) ***	
L-745,870	Vehicle	0.32	1.0	3.2	
	3.13(0.50)	4.21(0.62)	4.10(1.08)	3.70(0.72)	
Haloperidol +	Vehicle	0.1 Pram	+ 0.01 Hal	+ 0.032 Hal	
0.1 Pramipexole	10.08(3.25)	22.25(3.08)	18.94(4.12)	32.96(8.99)	
PG01037 +	Vehicle	0.1 Pram	+ 10 PG	+ 32 PG	+ 56 PG
0.1 Pramipexole	5.49(1.46)	27.09(5.32) *	23.22(5.77)	30.65(9.30)	24.80(10.24)
L-741,626 +	Vehicle	0.1 Pram	+ 0.32 L-741	+ 1.0 L-741	
0.1 Pramipexole	5.10(1.21)	27.09(5.32) *	24.79(5.46)	27.12(10.29)	
SKF 81297	Vehicle	0.1	0.32	1.0	
	5.38(1.50)	11.00(2.50)	7.35(3.17)	32.96(9.40) **	

SCH 23390	Vehicle	0.0032	0.01	0.032	
	3.91(0.82)	3.51(0.78)	14.12(4.21) *	n.d.	
SCH 23390 +	Vehicle	1.0 SKF	+ 0.001 SCH	+ 0.0032 SCH	+ 0.01 SCH
1.0 SKF 81297	4.23(1.19)	32.96(9.40) **	40.02(9.09)	39.11(8.96)	31.30(7.99)
Apomorphine	Vehicle	0.032	0.1	0.32	
	5.81(1.17)	4.99(1.52)	7.17(2.15)	17.75(6.04) **	
SCH 23390 +	Vehicle	0.32 Apo	+ 0.0032 SCH	+ 0.01 SCH	
0.32 Apomorphine	4.99(1.17)	17.75(6.04)	28.70(11.49)	38.53(13.26)	
Haloperidol +	Vehicle	0.32 Apo	+ 0.01 Hal	+ 0.032 Hal	
0.32 Apomorphine	4.22(0.79)	17.75(6.04) *	12.85(5.57)	22.48(6.41)	

n.d.: Not enough data to compute value. Apo = apomorphine. Hal = haloperidol. L741 = L-741,626. PG = PG01037. Pram = pramipexole. SCH = SCH 23390. SKF = SKF 81297.
* $p < .05$, ** $p < 0.01$, *** $p < .001$ compared to vehicle in Bonferroni-adjusted *post hoc* tests.
† $p < .05$, †† $p < 0.01$, ††† $p < .001$ compared to agonist alone in Bonferroni-adjusted *post hoc* tests.

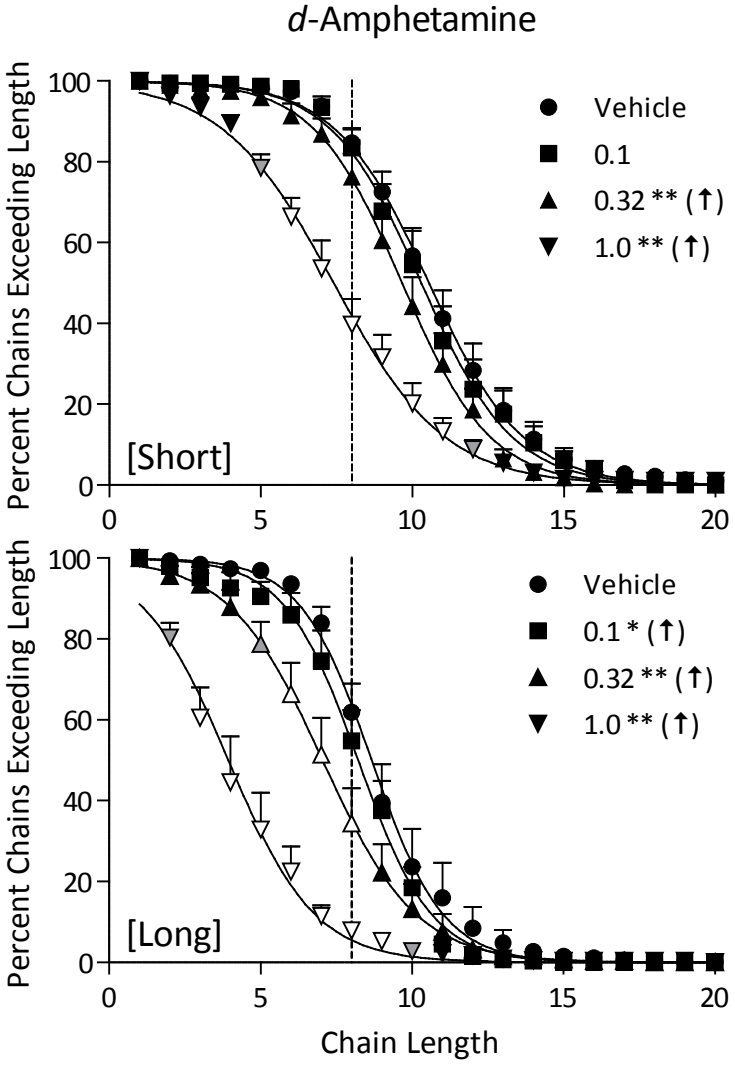

Figure 4-1. Effects of *d*-amphetamine pretreatments on chain length distributions in the short (top panel) and long (bottom panel) pacing components. Chain lengths are displayed as a percent of chains meeting or exceeding *x* responses as function of dose. All chains meeting or exceeding eight responses (dashed vertical line) were reinforced with a sucrose pellet. Asterisks appearing in the legend indicate, following a significant *F* test, that the 95% (*) or 99% (**) confidence intervals around the C_{50} parameter of the function fit to the data for the indicated dose and the corresponding vehicle point did not overlap. Shading of individual points indicates a significant difference from the corresponding vehicle point (black, n.s.; gray, $p < .05$; white, $p < .001$). Selective effects on behavior corresponding to an increase (↑) or decrease (↓) in impulsive action, or a disruption in behavior (✕), is also indicated in the legend.

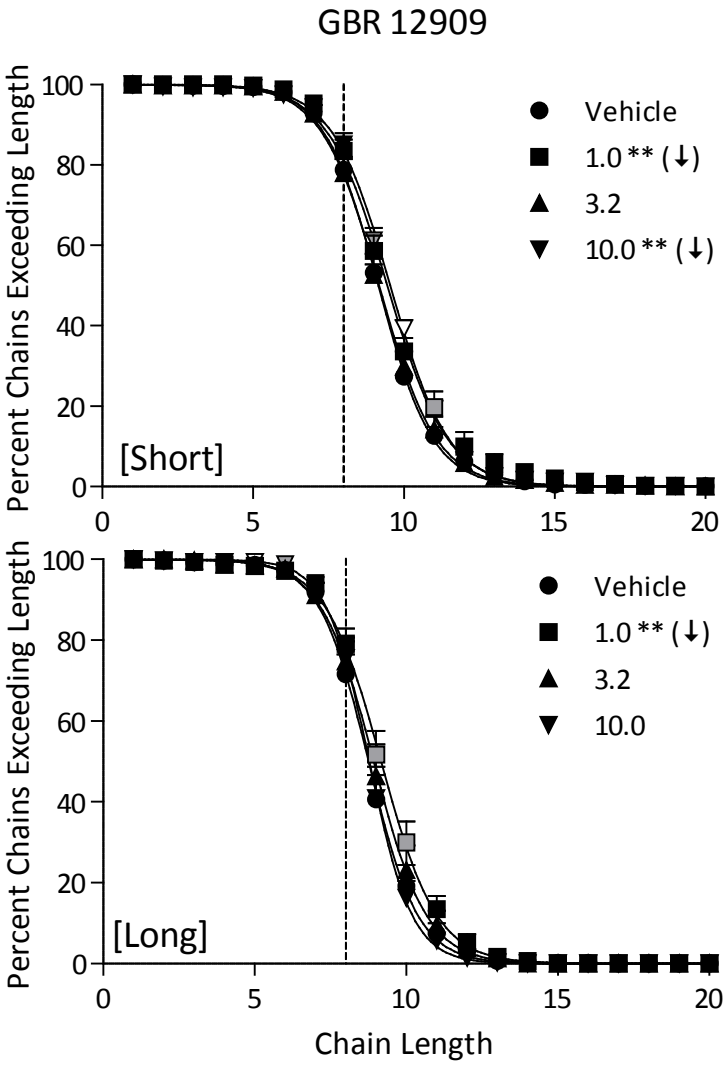

Figure 4-2, Effects of GBR 12909 pretreatments on chain length distributions in the short (top panel) and long (bottom panel) pacing components. All other details as in Figure 4-1.

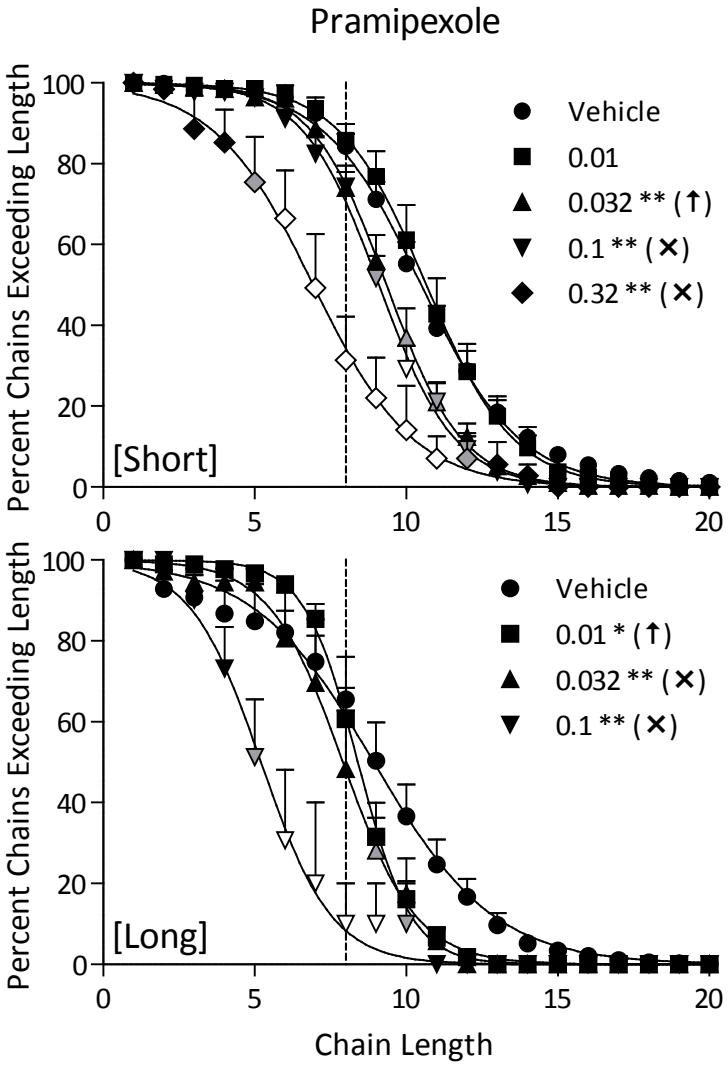

Figure 4-3. Effects of pramipexole pretreatments on chain length distributions in the short (top panel) and long (bottom panel) pacing components. All other details as in Figure 4-1.

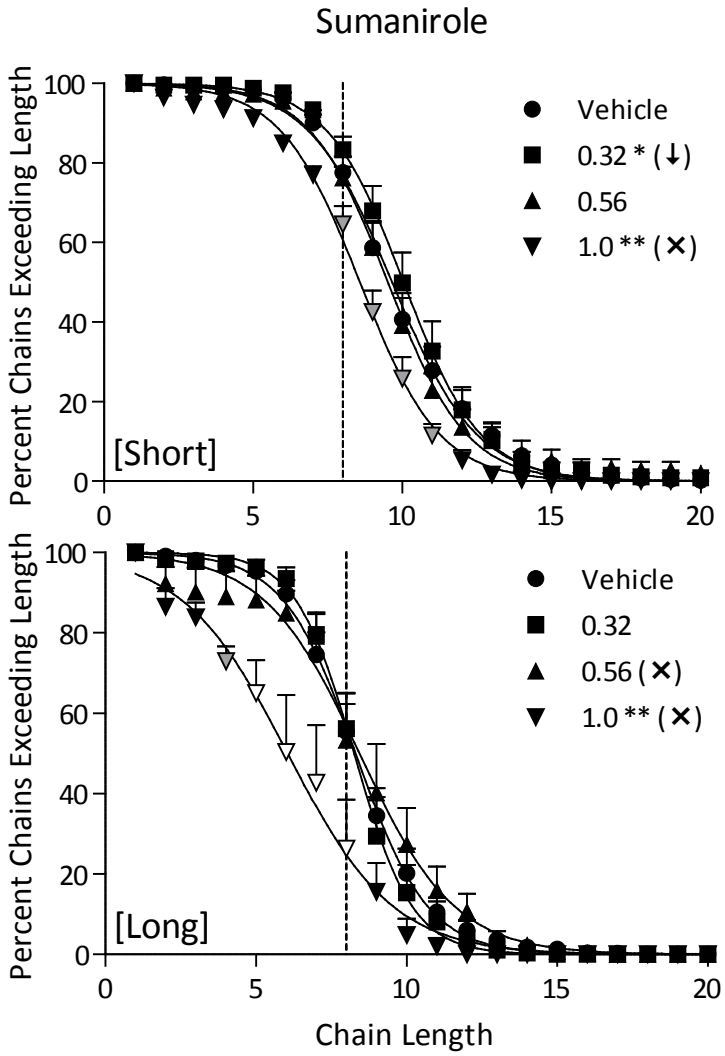

Figure 4-4. Effects of sumanirole pretreatments on chain length distributions in the short (top panel) and long (bottom panel) pacing components. All other details as in Figure 4-1.

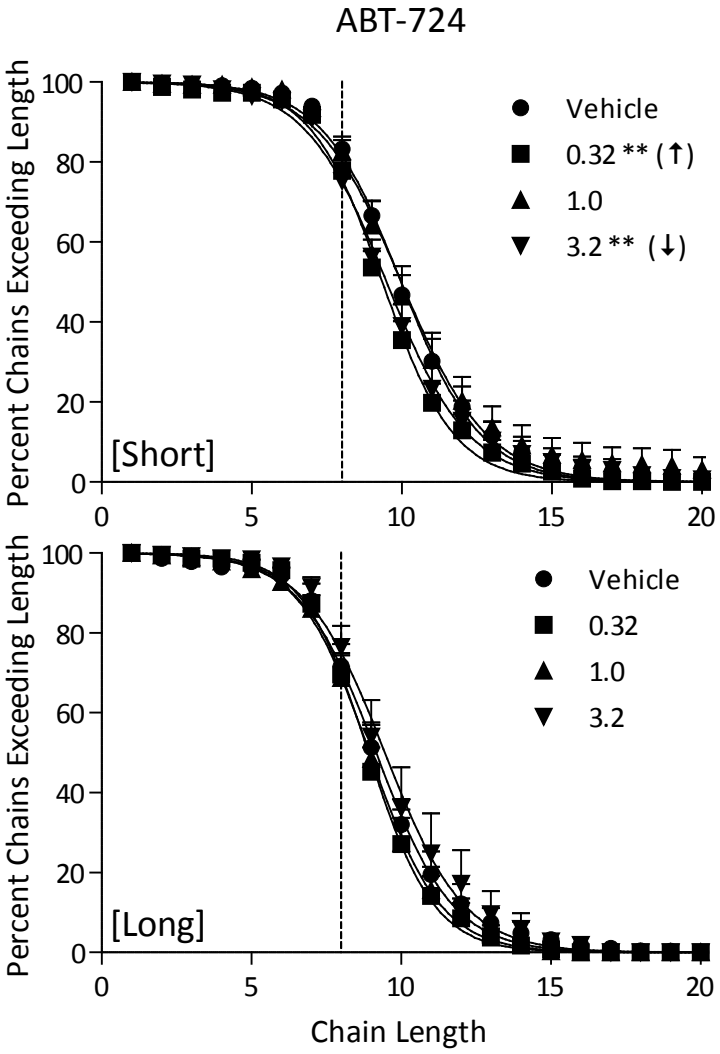

Figure 4-5. Effects of ABT-724 pretreatments on chain length distributions in the short (top panel) and long (bottom panel) pacing components. All other details as in Figure 4-1.

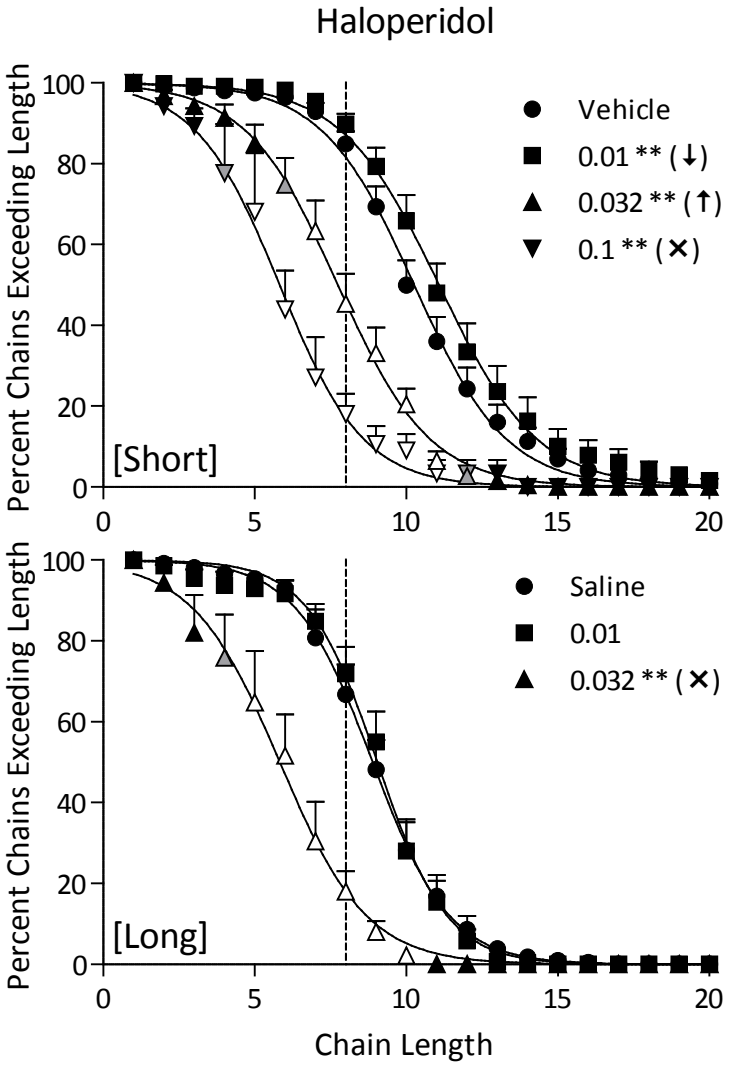

Figure 4-6. Effects of haloperidol pretreatments on chain length distributions in the short (top panel) and long (bottom panel) pacing components. All other details as in Figure 4-1.

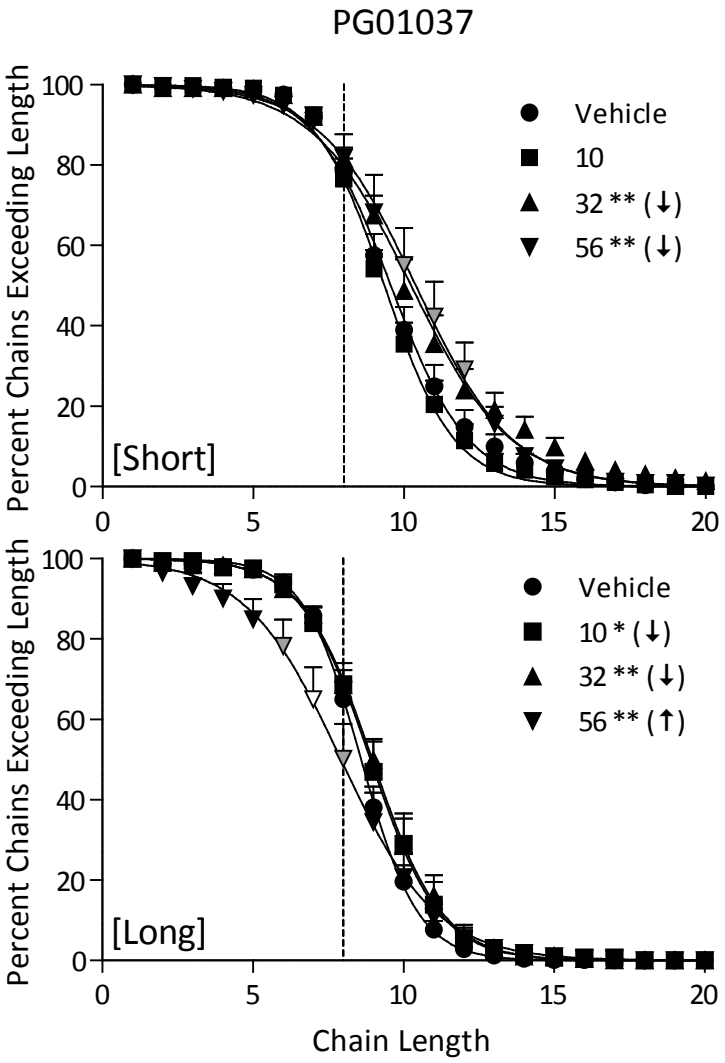

Figure 4-7. Effects of PG01037 pretreatments on chain length distributions in the short (top panel) and long (bottom panel) pacing components. All other details as in Figure 4-1.

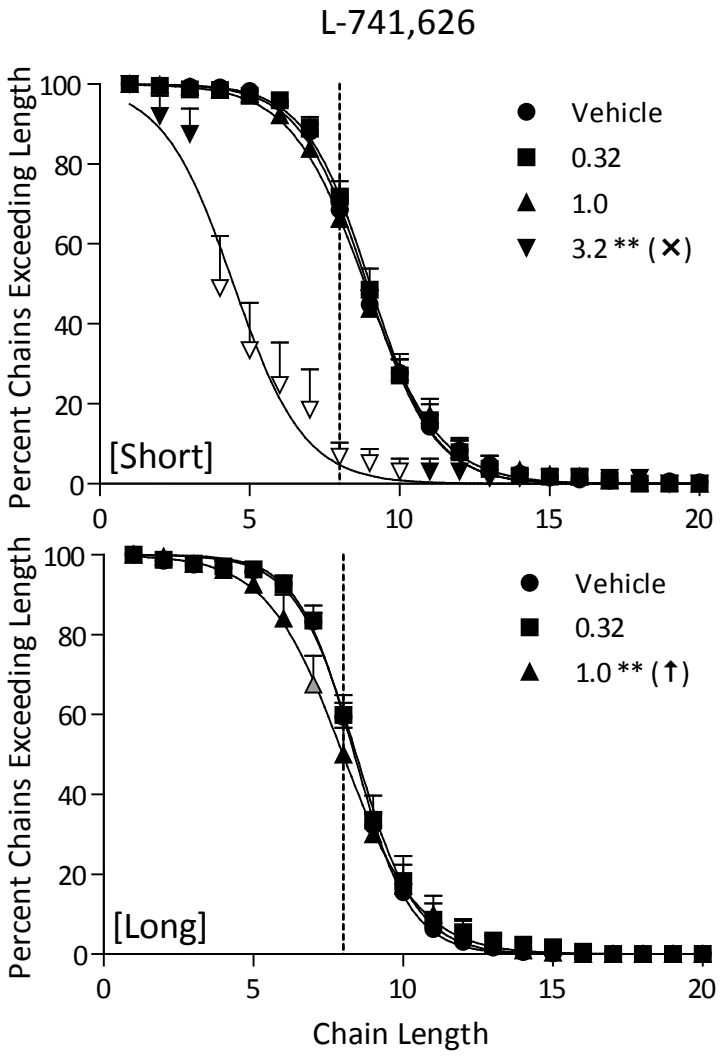

Figure 4-8. Effects of L-741,626 pretreatments on chain length distributions in the short (top panel) and long (bottom panel) pacing components. All other details as in Figure 4-1.

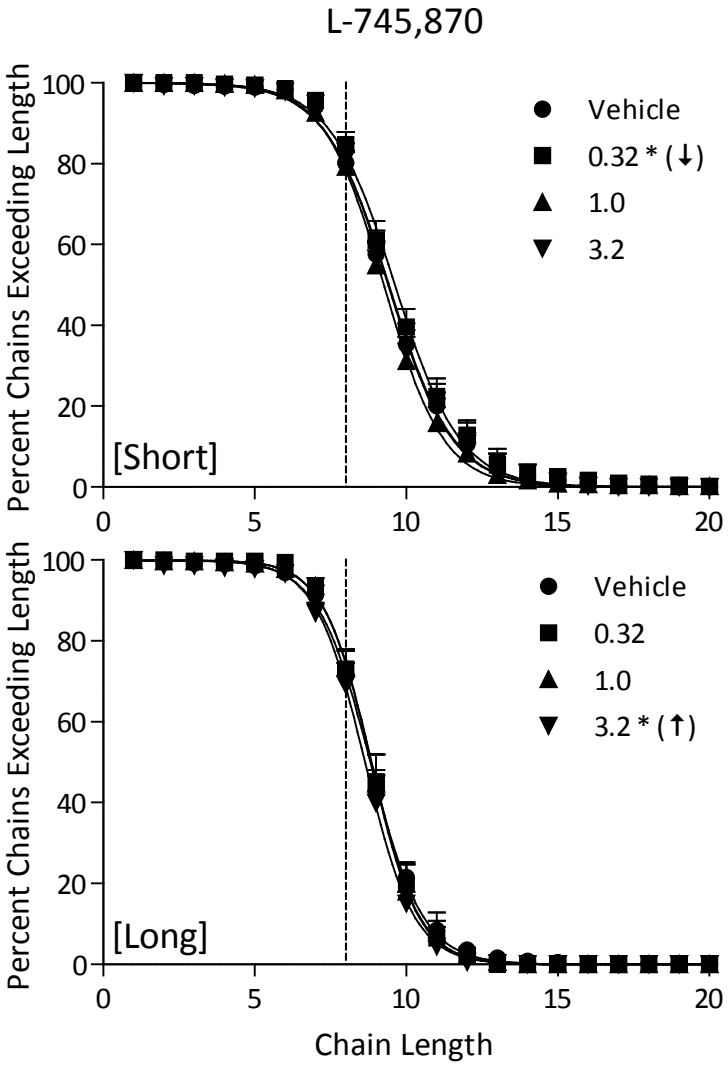

Figure 4-9. Effects of L-745,870 pretreatments on chain length distributions in the short (top panel) and long (bottom panel) pacing components. All other details as in Figure 4-1.

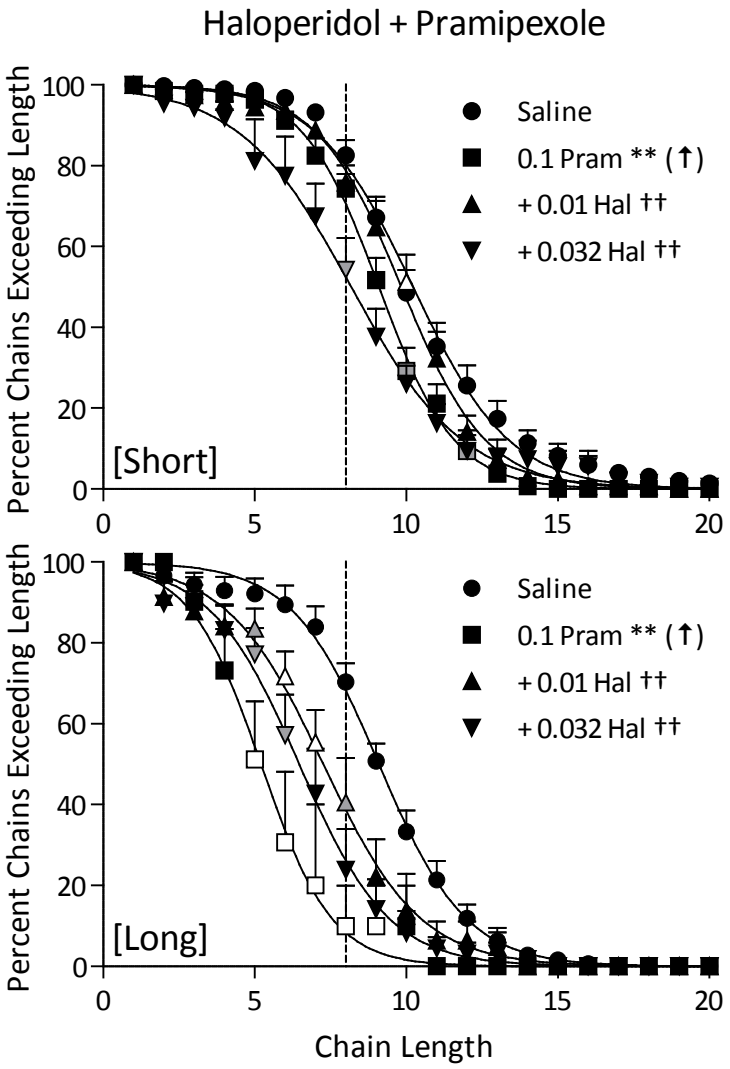

Figure 4-10. Effects of haloperidol pretreatments on the effects of 0.1 mg/kg pramipexole on chain length distributions in the short (top panel) and long (bottom panel) pacing components. Chain lengths are displayed as a percent of chains meeting or exceeding *x* responses as function of dose. All chains meeting or exceeding eight responses (dashed vertical line) were reinforced with a sucrose pellet. Asterisks appearing in the legend indicate, following a significant *F* test, that the 95% (*) or 99% (**) confidence intervals around the C_{50} parameter of the function fit to the data for the indicated dose and the corresponding vehicle point did not overlap. Daggers indicate that the 95% (†) or 99% (††) confidence intervals of the agonist plus antagonist and agonist alone lines do not overlap. Shading of individual points in the agonist alone curve indicates a significant difference from the corresponding vehicle point, while shading of the antagonist plus agonist points indicates a significant difference from the corresponding agonist alone point (black, n.s.; gray, $p < .05$; white, $p < .001$). Selective effects on behavior corresponding to an increase (↑) or decrease (↓) in impulsive action, or a disruption in behavior (✕), is also indicated in the legend for the agonist alone condition.

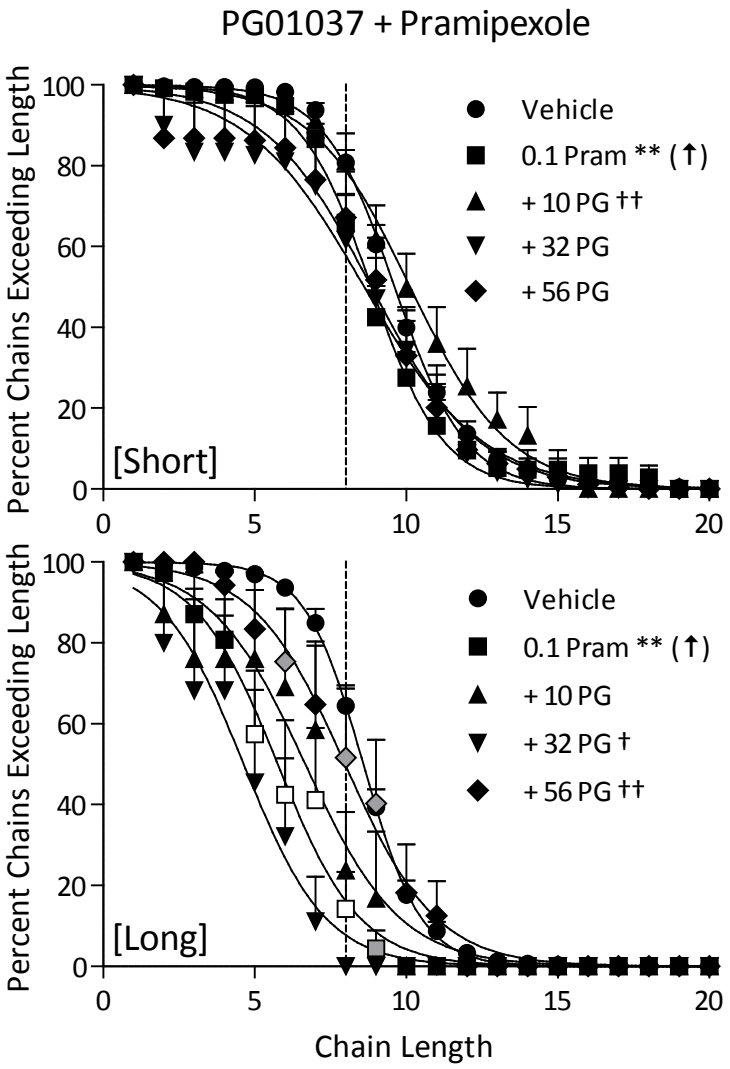

Figure 4-11. Effects of PG01037 pretreatments on the effects of 0.1 mg/kg pramipexole on chain length distributions in the short (top panel) and long (bottom panel) pacing components. All other details as in Figure 4-10.

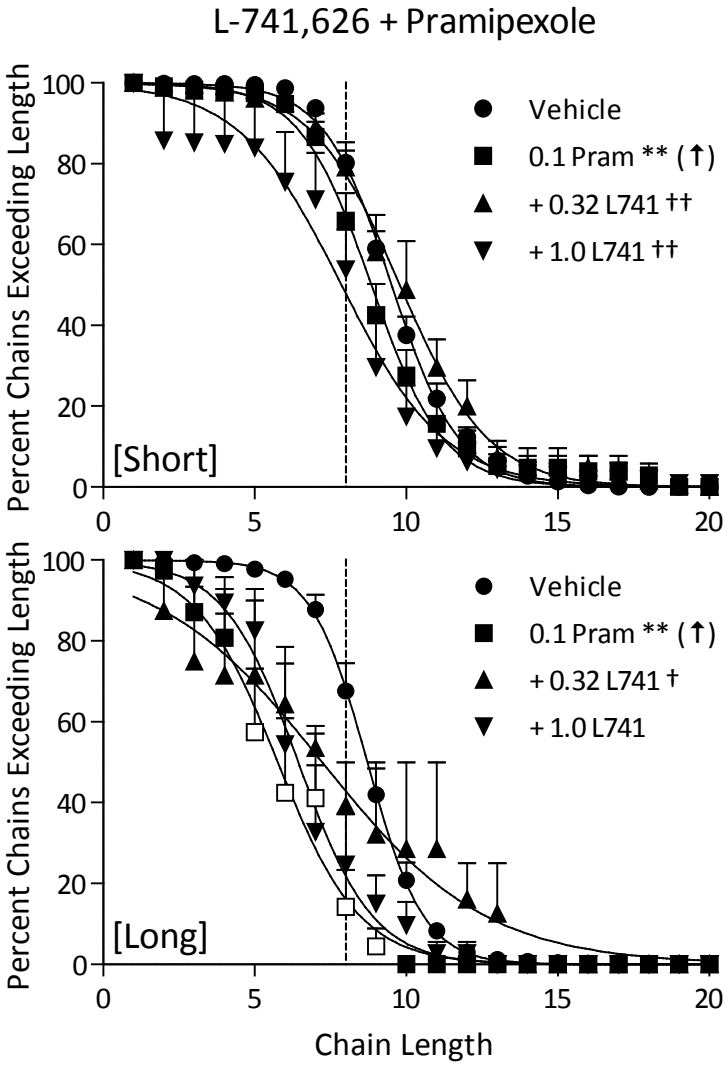

Figure 4-12. Effects of L-741,626 pretreatments on the effects of 0.1 mg/kg pramipexole on chain length distributions in the short (top panel) and long (bottom panel) pacing components. All other details as in Figure 4-10.

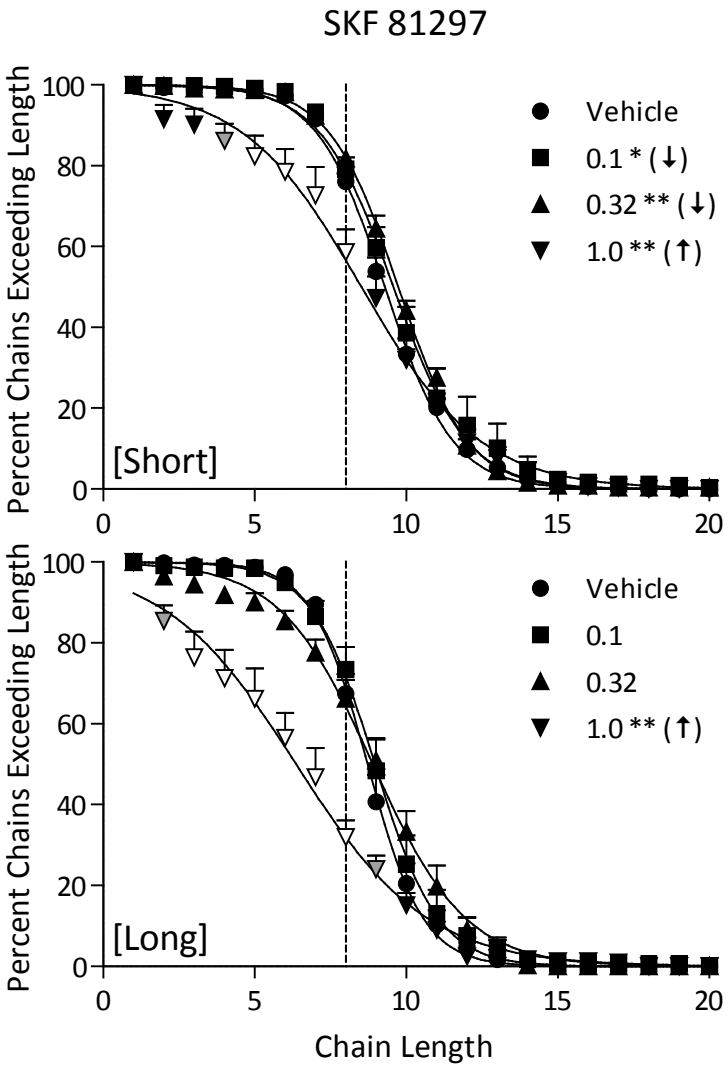

Figure 4-13. Effects of SKF 81297 pretreatments on chain length distributions in the short (top panel) and long (bottom panel) pacing components. All other details as in Figure 4-1.

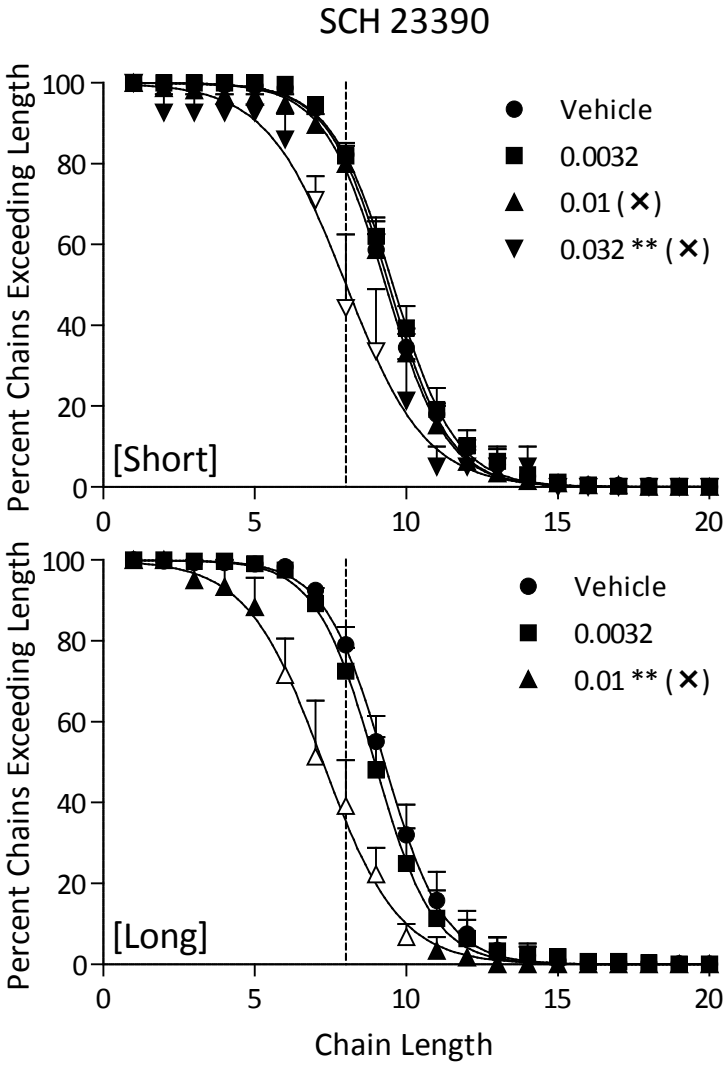

Figure 4-14. Effects of SCH 23390 pretreatments on chain length distributions in the short (top panel) and long (bottom panel) pacing components. All other details as in Figure 4-1.

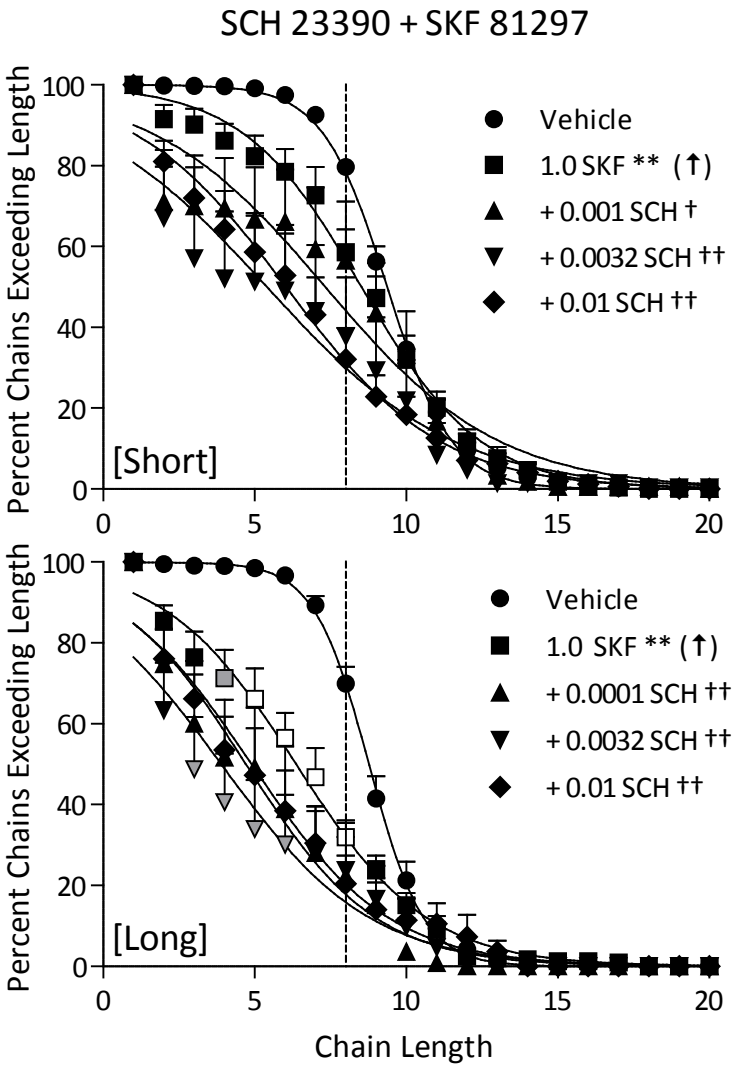

Figure 4-15. Effects of SCH 23390 pretreatments on the effects of 1.0 mg/kg SKF 81297 on chain length distributions in the short (top panel) and long (bottom panel) pacing components. All other details as in Figure 4-10.

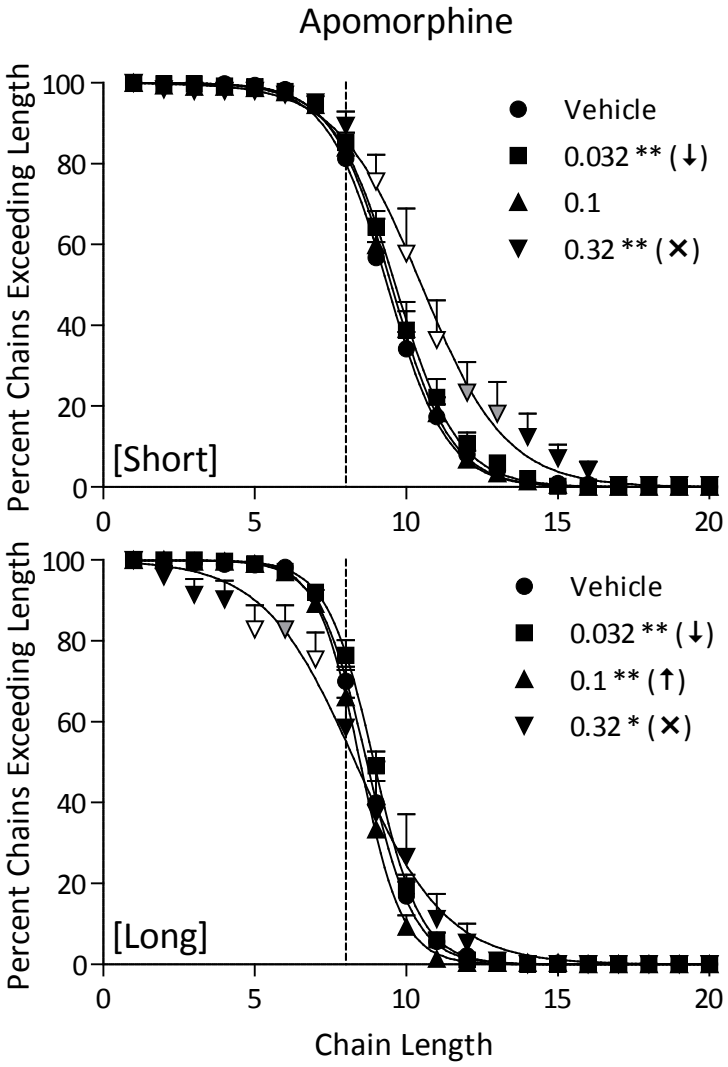

Figure 4-16. Effects of apomorphine pretreatments on chain length distributions in the short (top panel) and long (bottom panel) pacing components. All other details as in Figure 4-1.

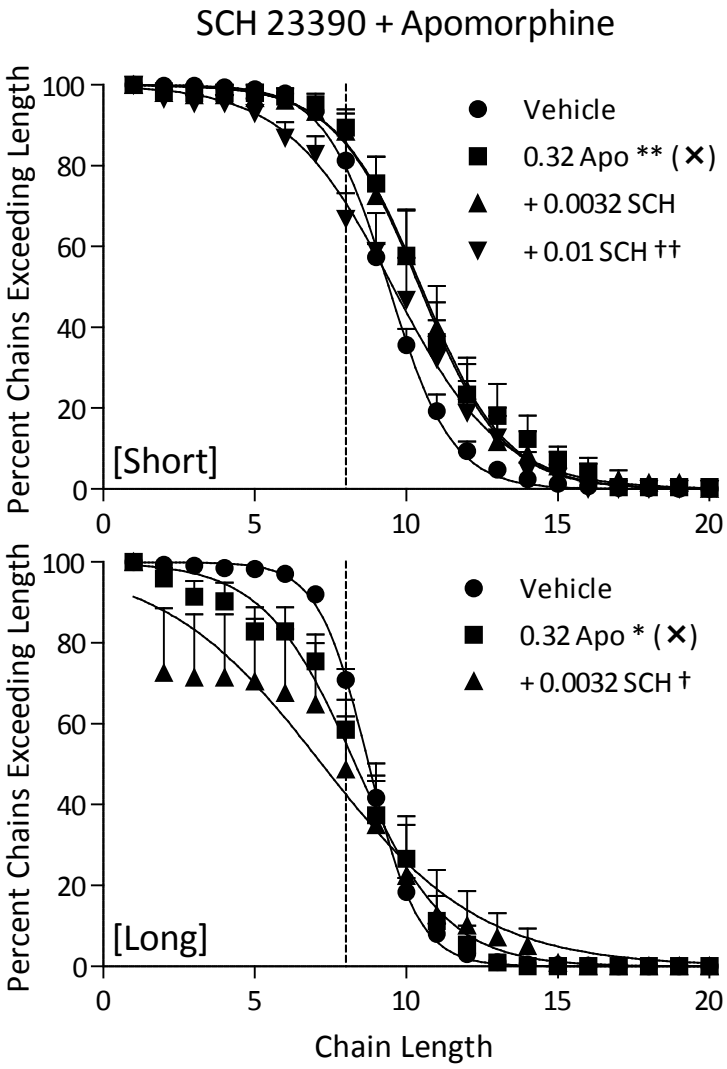

Figure 4-17. Effects of SCH 23390 pretreatments on the effects of 0.32 mg/kg apomorphine on chain length distributions in the short (top panel) and long (bottom panel) pacing components. All other details as in Figure 4-10.

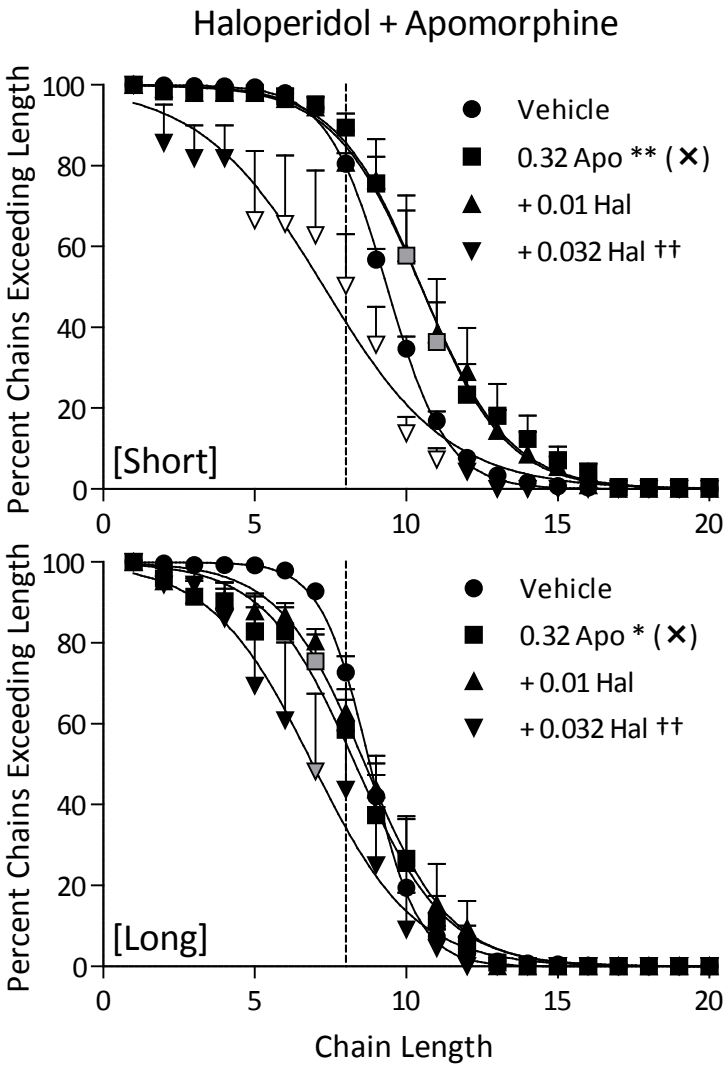

Figure 4-18. Effects of haloperidol pretreatments on the effects of 0.32 mg/kg apomorphine on chain length distributions in the short (top panel) and long (bottom panel) pacing components. All other details as in Figure 4-10.

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CHAPTER 5

EFFECTS OF SELECTIVE DOPAMINERGIC COMPOUNDS ON AN UNCERTAIN VISUAL DISCRIMINATION TASK

Impulsivity and self control are constructs used to describe what is increasingly apparent to be more than one class of behaviors. Based on operant and neurobiological experiments in humans and animals, a growing consensus largely agrees on two types of impulsive behavior: impulsive choice and what is termed impulsive action or behavioral inhibition (Dalley, Mar, Economidou, & Robbins, 2008; de Wit, 2009; Evenden, 1999a; Perry & Carroll, 2008; Winstanley, Eagle, & Robbins, 2006). Impulsive choice is the tendency to be hypersensitive to delays to reward, while impulsive action refers to the inability to withhold or inhibit a prepotent response. In addition to these two, a third component of impulsivity has been proposed by some. Impulsive preparation or reflection impulsivity, acting before gathering and processing all necessary information, has been argued to encompass impulsive-like responding on a variety of cognitive tasks used in humans and the uncertain visual discrimination (UVD) task in rats (Evenden, 1999a).

The UVD task is an interesting model of impulsivity in rats, as behavior on this task may include components of impulsive action and impulsive preparation (Dalley et al., 2008; Evenden, 1999a). In a two-lever operant chamber, responses on one lever are reinforced while responses on the other lever are punished with a timeout. The reinforced

lever is determined randomly at the beginning of each trial, and visual stimuli that probabilistically correlate with the correct lever are illuminated above the levers. The probability that the stimuli are correct increases as the trial progresses, such that withholding a response for a few seconds greatly increases the ability to discriminate the correct response location. This behavior pattern is hypothesized to model cognitive tasks such as the Matching Familiar Figures Test and the Tower of London, which have been used to study impulsivity in humans (Evenden, 1999a). Responses made prior to the illumination of the uncertain stimuli, or premature responses, on this task are also punished with a timeout. Premature responses on the 5-CSRT task, originally developed as a model of sustained attention (Robbins, 2002), are typically thought of as a model of impulsive action. Therefore, the UVD task provides two distinct measures of impulsivity within a single session.

Dopaminergic pathways between the prefrontal cortex, anterior cingulate cortex, and basal ganglia are often implicated in attention-deficit/hyperactivity disorder (ADHD) and impulsive behavior (for recent reviews see Dalley et al., 2008; Winstanley et al., 2006). Imaging studies in people with ADHD reveal abnormalities in this system, with lower prefrontal activity (Ernst, Zametkin, Matochik, Jons, & Cohen, 1998; Rubia et al., 1999) and enhanced dopamine transporter availability in the striatum (Krause, Dresel, Krause, Kung, & Tatsch, 2000). Similarly, animal models of impulsive action have implicated these same pathways. Anterior cingulate cortex lesions greatly increase premature responding on the 5-CSRT task (Muir, Everitt, & Robbins, 1996), and number of premature responses emitted is related to dopamine $D_{2\text{-like}}$ receptor levels in the ventral striatum (Dalley et al., 2007). While dopamine levels in the prefrontal cortex measured

during 5-CSRT task performance are elevated, the level of this elevation is not related to the amount of premature responses emitted (Dalley, Theobald, Eagle, Passetti, & Robbins, 2002), nor do prefrontal cortex lesions affect premature responding (Muir et al., 1996). Brain circuitry has not been explicitly associated with levels of impulsive responding in models of impulsive preparation, but prefrontal cortical areas are critical for responding on these tasks (Crews & Boettiger, 2009).

Both $D_{1\text{-like}}$ (D_1 and D_5) and $D_{2\text{-like}}$ (D_2, D_3, and D_4) dopamine receptors, as well as dopamine transporters, are known to exist in the dopaminergic pathways connecting the striatum to the prefrontal cortex (Ciliax et al., 1995; Gaspar, Bloch, & Le Moine, 1995; Lévesque et al., 1992; Mrzljak, Bergson, Pappy, Huff, Levenson, & Goldman-Rakic, 1996; Muly III, Szigeti, & Goldman-Rakic, 1998; Revay, Vaughan, Grant, & Kuhar, 1996). The only dopaminergic compounds to be tested on the uncertain visual discrimination task are haloperidol, which increased response latency (decreased impulsive preparation), and amphetamine which had no effect on latency, but increased premature responses (Evenden, 1999b). Amphetamine also increased premature responses on the 5-choice serial reaction time task (Cole & Robbins, 1987; van Gaalen, Brueggeman, Bronius, Schoffelmeer, & Vanderschuren, 2006), but not if these responses were not punished with a timeout (Bizzarro, Patel, Murtagh, & Stolerman, 2004; Bizarro & Stolerman, 2003). Cocaine and the selective dopamine transporter blocker GBR 12909 also increasd premature responses (van Gaalen et al., 2006), but methylphenidate has this effect only under limited conditions or not at all (Navarra et al., 2008; Paine, Tomasiewicz, Zhang, & Carlezon, 2007). The dopamine $D_{1\text{-like}}$ antagonist SCH 23390 and the $D_{2\text{-like}}$ antagonist raclopride tended to decrease premature responses, but the $D_{2\text{-like}}$

antagonist eticlopride did not (Koskinen & Sirviö, 2006; van Gaalen, 2006). SCH 23390 and the $D_{2\text{-like}}$ antagonist sulpiride administered directly into the nucleus accumbens did not alter premature responses, while the $D_{1\text{-like}}$ partial agonist SKF 38393 increased premature responses (Pezze, Dalley, & Robbins, 2007).

As dopaminergic systems that include a variety of dopamine receptor subtypes are involved in impulsivity, and the effects of systemic injections of selective dopamine receptor agonists and antagonists is largely unknown, we administered the most selective dopamine receptor agonists and antagonists readily available to male Sprague Dawley rats responding on the uncertain visual discrimination task first described by Evenden (1999b). The drugs administered included *d*-amphetamine, the selective dopamine transporter blocker GBR 12909, the $D_{1\text{-like}}$ agonist SKF 81297, the $D_{1\text{-like}}$ antagonist SCH 23390, the $D_{2\text{-like}}$ antagonist haloperidol, the $D_{2\text{-preferring}}$ agonist sumanirole, the $D_{2\text{-preferring}}$ antagonist L-741,626, the $D_{3\text{-preferring}}$ agonist pramipexole, the $D_{3\text{-preferring}}$ antagonist PG01037, the D_4 partial agonist ABT 724, the D_4 antagonist L-745,870, and the nonselective dopamine agonist apomorphine. The antagonists listed above were sometimes administered prior to these agonists to further elucidate the mechanism of effects these drugs have on this task.

Method

Subjects

Twelve male Sprague Dawley rats served as subjects (Harlan, Indianapolis, IN). Rats were approximately 10 weeks old at the start of the experiment. A food restriction protocol was in place to maintain the rats at approximately 325 g throughout the experiment. This weight was chosen as it is approximately 85% of the mean adult weight

supplied by the manufacturer for this strain, and this weight was not changed once established. When not in session, rats were housed in accordance with institutional animal care and use guidelines in polycarbonate cages with fresh water continuously available. The lights in the housing colony were on from 7:00 AM to 7:00 PM, and sessions were conducted between 12:00 PM and 4:00 PM. These protocols were approved by the University of Michigan Committee on the Use and Care of Animals and conformed to the guidelines established by the NIH Guide for the Use of Laboratory Animals.

Apparatus

Sessions were conducted in rodent operant conditioning chambers with an area of 30.5 cm x 24.1 cm x 21.0 cm and stainless steel grid floors (ENV-008; Med-Associates Inc., St. Albans, VT). Both sides of the front panel of the chamber held a retractable lever (E23-17, Coulbourn Instruments, Whitehall, PA). Between the levers was a food tray connected to a 45 mg pellet dispenser (ENV-200R1AM and ENV-203M-45, Med-Associates, Inc.). Above both of the levers and the food tray were triple stimulus lights containing a red, green, and yellow LED (ENV-222M, Med-Associates, Inc.). The three colors of each of the three stimulus lights were always illuminated or extinguished in tandem, and each trio is referred to as a single light throughout the paper. A houselight was located near the top of the opposite wall to provide illumination to the chamber, and remained on throughout all sessions (ENV-215M, Med-Associates, Inc.). Chambers were connected to a computer running Med-PC IV software (Med-Associates, Inc.) to control experimental events and record data.

Procedure

Rats were trained to respond on a mixed fixed-time 60 s FR 1 schedule of reinforcement, with the active lever alternating each session between the left and right levers. This schedule arranged one sucrose pellet to be delivered every 60 s independent of behavior, with every lever press also producing a pellet. This was continued for four sessions, at which point the schedule was switched to a FR 1 with no response-independent pellet deliveries. Rats were allowed to respond on this schedule until 80 responses or more were recorded on two consecutive 20-min sessions.

Rats were then trained to discriminate visual stimuli presented above the levers. In a series of discrete trials, the stimulus light above one of the levers was lit and both levers were extended into the chamber. The location of the light was determined randomly at the start of each trial. A response to the lever below the illuminated stimulus light was recorded as a correct response and led to both levers retracting, a 45-mg sucrose pellet delivery, and a 5-s timeout period with no stimulus lights illuminated. Responses to the lever with no stimulus light was recorded as an incorrect response and resulted in lever retraction and the timeout only. If no response occurred within a limited hold of 30 s, an omission was recorded, the levers were retracted, and a 5-s timeout occurred. After four sessions, a pre-stimulus lever insertion duration was added such that the levers were inserted into the chamber 1 s before the randomly-determined stimulus light was illuminated. Responses made before the stimulus presentation, regardless of lever, led to the levers retracting and a 5-s timeout. Over a number of sessions, the duration that the levers were inserted into the chamber before a stimulus was lit was extended to 8 s. Rats were allowed to respond with these contingencies until at least 85% of responses made after stimulus illumination were on the lever under the lit stimulus light.

The test procedure was similar to the final training procedure, with the exception that the stimuli did not predict the correct lever with a probability of 1.0. Once each trial began, 8 s after the levers were inserted into the chamber, a series of 0.2-s cycles began with the stimulus location during each cycle determined on a probabilistic basis. During the first cycle, any of the three stimulus lights ("correct," the light above the lever with the active FR 1 schedule; "incorrect," the light above the other lever; or "irrelevant," the light above the food cup that did not differentially signal food availability) had an equal probability of being illuminated. With each subsequent cycle (n), the probability that the "correct" light was illuminated increased such that the correct probability (p_c) was

$$p_c = \frac{2+n}{8+n} \tag{5-1}$$

and the probability that the incorrect or irrelevant stimulus was illuminated (p_i) was

$$p_i = \frac{1-\frac{2+n}{8+n}}{2}. \tag{5-2}$$

When $n = 1$, both Equation 5-1 and Equation 5-2 equal $.\overline{3}$ and the probability that each of the three stimuli being lit was the same. The probability that the lit stimulus was above the correct lever increased to approximately .8 after 4 s elapsed ($n = 21$). A response on the correct lever at any point after stimuli were lit was reinforced with a food pellet, while a response on the other lever led to the 5-s timeout period. Sessions ended after 60 min or 144 trials, whichever occurred first.

Drug testing began after no increasing or decreasing trend in response latency was apparent over a period of five sessions. Sessions were generally conducted five days per week with vehicle injections administered on the first and fourth days of the week, test compounds or conditions were assessed on the second and fifth days, and no injections given on the third day. Vehicle injections always corresponded to the vehicle for the

scheduled drug injection or injections for the following day in number, substance, and time relative to the experimental session. Each session was preceded by a vehicle or drug injection 5 min before the start of the session with the rat then immediately placed in the darkened experimental chamber. On some days, an antagonist or vehicle injection was administered 30 min prior to the session, with the rat placed back in his home cage for the intervening 25 min before the agonist or vehicle injection was given, as appropriate. All agonists and the corresponding vehicle injections were administered 5 min before the session. All antagonists and the corresponding vehicle injections were administered 30 min before the session start, except SCH 23390 which was administered 5 min before session start due to its relatively rapid onset and short duration of action (Hietala, Seppäla, Lappalainen, & Syvälahti, 1992).

To assess the influence on behavior of the 8-s pre-stimulus lever insertion duration and uncertain properties of the stimuli, probe trials were conducted with these parameters altered. Near to the end of drug testing and in the absence of any drug treatment, the pre-stimulus lever insertion duration was increased to either 10 or 12 s on separate sessions. In addition, a "certain" probe session was conducted with each subject wherein the stimuli presented were correlated with the correct lever with a probability of 1.0 throughout the trial instead of the uncertain, increasing probability described by Equation 5-1. These "certain" trials approximated the training conditions before the uncertain stimuli were introduced.

Drugs

Pramipexole was generously provided by Drs. Jianyong Chen and Shaomeng Wang (University of Michigan, Ann Arbor, MI), sumanirole by Benjamin Greedy and

Dr. Stephen Husbands (University of Bath, Bath, UK), GBR 12909 by Novo Industri (Bagsvaerd, Denmark), ABT-724 by Dr. Kenner Rice (Chemical Biology Research Branch, National Institute on Drug Abuse, Bethesda, MD), and PG01037 by Drs. Amy H. Newman (Medicinal Chemistry Section – National Institute on Drug Abuse, Baltimore, MD) and Peter Grundt (University of Minnesota – Duluth, Duluth, MN). Haloperidol, SKF 81297, SCH 23390, and apomorphine were obtained from Sigma-Aldrich (St. Louis, MO), L-741,626 and L-745,870 were obtained from Tocris (Ellisville, MO), and *d*-amphetamine was obtained from the National Institute on Drug Abuse (Bethesda, MD). All drugs were dissolved in sterile saline except L-741,626, which was dissolved in 5% ethanol, and PG01037, which was dissolved in 20% β-cyclodextrin. All injections were administered subcutaneously (s.c.) in a volume of 1.0 ml/kg except 56 mg/kg PG01037 which was administered in of volume of 1.75 ml/kg due to solubility limits.

Data Analysis

Latency was defined as the time to a response on either lever, regardless of accuracy, measured from the onset of the stimulus presentations. Latencies were analyzed and plotted as survival plots, or the percent of latencies of at least *X* seconds as a function of drug dose or treatment condition. Summarized in this manner, data were well-approximated by the exponential equation

$$Y = 100^{-K*X} \tag{5-3}$$

where *Y* is the percent of latencies of *X* or more s in duration and *K* is a derived parameter indicating the steepness of the exponential curve. A higher proportion of long latencies leads to an increased *K*. Latencies distributions were compared across doses with a two-way repeated measures Analysis of Variance (ANOVA) in Systat SigmaStat 3.5 (San

Jose, CA) with Bonferroni-adjusted *post hoc* tests conducted to compare relevant conditions.

Accuracy was defined as the percent of responses made to the lever on which sucrose reinforcement was programmed after the stimulus lights were illuminated and before the limited hold expired. Accuracy was analyzed as a function of response latency and was split into five bins: $0 \leq x < 1$ s, $1 \leq x < 2$ s, $2 \leq x < 3$ s, $3 \leq x < 4$ s, and $4 \leq x$ s. Accuracy data for an individual bin for each session was only included for analysis if five or more responses were made in that bin. Accuracy was compared across doses as a function of response latency with a two-way repeated measures ANOVA in SigmaStat 3.5 with Bonferroni-adjusted *post hoc* tests conducted to compare relevant conditions. When data were excluded for some latency bins for some subjects, SigmaStat used a Mixed Models ANOVA to assess within- and between-subjects effects on an incomplete data set.

Omissions were defined as a failure to respond on either lever during the limited hold. Premature responses were defined as a response made to either lever before the illumination of stimuli above the levers. Omissions and premature responses were each compared across drug dose or experimental condition using a one-way repeated measures ANOVA or paired *t*-test, as appropriate, in SigmaStat 3.5 with Bonferroni-adjusted *post hoc* tests conducted to compare relevant conditions.

Response bias was defined as the proportion of responses made on the lever on which the majority of responses were emitted for that session. Therefore, the possible range of bias values was 50% (equal responding on both levers) to 100% (exclusive responding on one lever). Response bias was compared across drug doses or conditions

using a one-way repeated measures ANOVA or paired *t*-test, as appropriate, in GraphPad Prism 5 (La Jolla, CA). In some rats, an extreme bias (defined as >90%) was noted. Response latency, response accuracy, omission, and premature response data were not included in analyses for any drug condition if that subject exhibited an extreme bias during the corresponding vehicle or control sessions for that condition.

Results

Distribution of response latencies was presented in survival plots for all conditions. Therefore, proportion of response latencies $\geq X$ seconds decreased as X increased in all conditions, and F values for ANOVAs conducted assessing this main effect ranged from 37 to 316 (all $p < .001$). These individual values are not reported for brevity. Significant effects on response latency or premature responses were considered "selective" if they did not coincide with a significant increase in trials omitted. Selective effects on impulsive preparation or impulsive action, as defined, are indicated by upward (↑) or downward (↓) deflecting arrows in the legend of each graph indicating increases or decreases, respectively, in impulsive behavior. Disruptions in behavior are also indicated (×).

For all drug tests, the duration that the levers were inserted into the chamber before illumination of visual stimuli was 8 s. When that duration was increased during probe trials to 10 or 12 s, the distribution of response latencies was altered (Figure 5-1, top panel; insertion duration main effect $F_{2,140} = 6.0$, $p = .013$, insertion duration by response latency interaction $F_{20,140} = 5.2$, $p < .001$). Response latencies in the 12 s condition tended to be shorter in duration. Pre-stimulus lever insertion duration manipulations did not affect accuracy, however (Figure 5-1, middle panel). Accuracy

increased as a function of response latency, but this pattern did not depend on pre-stimulus lever insertion duration (insertion duration main effect $F_{2,72} = 1.4$, $p = .264$, response latency main effect $F_{4,72} = 21$, $p < .001$, insertion duration by response latency interaction $F_{8,72} = 0.35$, $p = .945$). Premature responses increased as the lever insertion duration increased, reaching significant at a 12 s duration (Figure 5-1, bottom panel; lever insertion main effect $F_{2,14} = 14$, $p < .001$). Lever biases (Table 5-1; $F_{2,20} = 0.58$, $p = .567$) and trials omitted (Table 5-2) were not affected by increasing the lever insertion duration.

For all the drug tests, the visual stimuli were presented in a probabilistic manner described by Equation 5-1 and Equation 5-2. The results of the "certain" probe sessions with the visual stimuli perfectly correlated with the correct response option are shown in Figure 5-2. Removing the probabilistic properties of the stimuli had no effect on distribution of response latencies (Figure 5-2, top panel; stimulus certainty main effect $F_{1,70} = 0.36$, $p = .568$, stimulus certainty by response latency interaction $F_{10,70} = 0.08$, $p > 0.999$). Stimulus certainty did have a significant effect on response accuracy (Figure 5-2, middle panel; stimulus certainty main effect $F_{1,44} = 11$, $p = .002$, response latency main effect $F_{4,44} = 3.7$, $p = .011$, stimulus certainty by response latency interaction $F_{4,44} = 1.7$, $p = .157$). In the uncertain stimulus condition, response accuracy increased as a function of response latency, following the increase in the accuracy of the stimuli dictated by Equations 1 and 2 (programmed stimulus probabilities shown in Figure 5-2, middle panel, dashed line). When the probabilistic nature of the visual stimuli was removed, however, response accuracy was high at all response latencies, and was not a function of response latency. Stimulus certainty did not affect premature responses (Figure 5-2, bottom panel; $t_7 = 1.5$, $p = .167$) or trials omitted (Table 5-2; $t_7 = 1.0$, $p = .351$). Lever

bias was significantly lower in the certain stimulus condition, however (Table 5-1, t_{10} = 2.7, p = .022).

d-Amphetamine pretreatments significantly increased response latencies, with a significant increase at 1.0 mg/kg (Figure 5-3, top panel; dose main effect $F_{3,210}$ = 4.4, p = .015, dose by response latency interaction $F_{30,210}$ = 1.9, p = .005). Accuracy increased as a function of response latency, and there was a trend toward increased accuracy with *d*-amphetamine pretreatments, but this effect was statistically significant (Figure 5-3, middle panel; dose main effect $F_{3,96}$ = 2.6, p = .060, response latency main effect $F_{4,96}$ = 38, p < .001, dose by response latency interaction $F_{12,96}$ = 1.2, p = .302). Premature responses were dose-dependently increased by *d*-amphetamine pretreatments, with a significant increase seen at 1.0 mg/kg (Figure 5-3, bottom panel; dose main effect $F_{3,21}$ = 1.7, p = .010). Lever bias (Table 5-1; dose main effect $F_{3,27}$ = 0.37, p = .778) and trials omitted (Table 5-2; dose main effect $F_{3,21}$ = 0.85, p = .183) were not altered by *d*-amphetamine at the doses tested.

At the doses tested, the dopamine transporter blocker GBR 12909 had little effect on response latencies, although the higher dose of 10 mg/kg tended to increase the proportion of response latencies exceeding 1, 2, and 3 s (Figure 5-4, top panel; dose main effect $F_{3,210}$ = 1.4, p = .275, dose by response time interaction $F_{30,210}$ = 1.7, p = .016). Response accuracy increased as a function of response latency, but this was not altered by GBR 12909 (Figure 5-4, middle panel; dose main effect $F_{3,92}$ = 0.65, p = .587, response latency main effect $F_{4,92}$ = 36, p < .001, dose by response latency interaction $F_{12,92}$ = 0.94, p = .516). Premature responses (Figure 5-4, bottom panel; dose main effect

$F_{3,21} = 0.62$, $p = .610$), lever bias (Table 5-1; dose main effect $F_{3,27} = 1.0$, $p = .397$), and trials omitted (Table 5-2) were not affected by GBR 12909 at the doses tested.

The $D_{3\text{-preferring}}$ agonist pramipexole dose-dependently increased response latency (Figure 5-5, top panel; dose main effect $F_{3,240} = 25$, $p < .001$, dose by response time interaction $F_{30,240} = 6.7$, $p < .001$). A dose of 0.32 mg/kg increased the proportion of response latencies exceeding 1, 2, and 3 s, while 0.1 and 0.32 mg/kg pramipexole increased the proportion of response latencies across a wide range of response times. Response accuracy was not affected by pramipexole, however, with accuracy at each dose increasing as a function of response latency (Figure 5-5, middle panel; dose main effect $F_{3,139} = 0.53$, $p = .665$, response latency main effect $F_{4,139} = 39$, $p < .001$, dose by response latency interaction $F_{12,139} = 0.55$, $p = .875$). Premature responses (Figure 5-5, bottom panel; dose main effect $F_{3,24} = 4.2$, $p = .083$) and lever bias (Table 5-1; dose main effect $F_{3,27} = 0.96$, $p = .425$) were not significantly altered. Trials omitted were dose-dependently increased after pramipexole administration, with a large proportion of trials omitted at 0.32 mg/kg pramipexole (Table 5-2; dose main effect $F_{3,24} = 59$, $p < .001$). The 0.1 mg/kg pramipexole dose was administered to some rats multiple times to redetermine the effects of this dose prior to antagonist treatment, and the effects of 0.1 mg/kg pramipexole differed during some tests in some subsets of rats (see the results for L-741,626 plus 0.1 mg/kg pramipexole, reported below). To describe more fully the effects of this dose, premature response data from all administrations that met bias criteria (see Method section) were averaged for each subject and compared with the corresponding mean vehicle data for these administrations. Analyzed this way, premature responses after administration of 0.1 mg/kg pramipexole in the 11 rats that received this dose (M =

17.4, *SD* = 10.2) were not significantly greater than after vehicle administration (*M* = 15.0, *SD* = 16.1; paired $t_{10} = 0.70$, $p = .501$).

Like pramipexole, the $D_{2\text{-preferring}}$ agonist sumanirole dose-dependently increased response latencies (Figure 5-6, top panel; dose main effect $F_{3,210} = 13$, $p < .001$, dose by response time interaction $F_{30,210} = 3.9$, $p < .001$) without altering the response-latency-dependent increases in response accuracy (Figure 5-6, middle panel; dose main effect $F_{3,114} = 0.44$, $p = .728$, response latency main effect $F_{4,114} = 25$, $p < .001$, dose by response latency interaction $F_{12,114} = 1.5$, $p = .143$). Premature responses were not altered (Figure 5-6, bottom panel; $F_{3,21} = 2.2$, $p = .122$). A dose of 3.2 mg/kg sumanirole both decreased lever bias (Table 5-1; dose main effect $F_{3,24} = 5.2$, $p = .007$) and increased trials omitted (Table 5-2; dose main effect $F_{3,21} = 15$, $p < .001$).

Across doses ranging from 0.1 mg/kg to 3.2 mg/kg, the D_4 partial agonist ABT-724 had no significant effect on any dependent measure. Response latency (Figure 5-7, top panel; dose main effect $F_{4,280} = 2.0$, $p = .120$, dose by response time interaction $F_{40,280} = 0.78$, $p = .822$), response accuracy (Figure 5-7, middle panel; dose main effect $F_{4,115} = 1.8$, $p = .138$, response latency main effect $F_{4,115} = 20$, $p < .001$, dose by response latency interaction $F_{16,115} = 1.2$, $p = .293$), premature response (Figure 5-7, bottom panel; dose main effect $F_{4,28} = 0.91$, $p = .470$), lever bias (Table 5-1; $F_{4,44} = 1.7$, $p = .174$), and trials omitted (Table 5-2) were all unaffected.

The $D_{2\text{-like}}$ antagonist haloperidol had little effect on behavior at 0.032 mg/kg, but drastically reduced responding and increased response latencies at 0.1 mg/kg (Figure 5-8, top panel; dose main effect $F_{2,140} = 16$, $p < .001$, dose by response time interaction $F_{20,140} = 3.1$, $p < .001$). Response accuracy was not altered by haloperidol at these doses,

however (Figure 5-8, middle panel; dose main effect $F_{3,91} = 0.36$, $p = .779$, response latency main effect $F_{4,91} = 24$, $p < .001$, dose by response latency interaction could not be computed due to pattern of missing data). Haloperidol did not affect premature responses (Figure 5-8, bottom panel; dose main effect $F_{2,14} = 1.0$, $p = .383$) or lever bias (Table 5-1; dose main effect $F_{2,18} = 2.0$, $p = .165$), but did increase omissions at 0.1 mg/kg (Table 5-2; dose main effect $F_{2,14} = 948$, $p < .001$).

The $D_{3\text{-preferring}}$ antagonist PG01037 dose-dependently increased response latency with 56 mg/kg significantly increasing latency compared to vehicle (Figure 5-9, top panel; dose main effect $F_{3,210} = 3.0$, $p = .054$, dose by response time interaction $F_{30,210} = 1.6$, $p = .027$). Accuracy was not affected over the dose range tested (Figure 5-9, middle panel; dose main effect $F_{3,106} = 0.15$, $p = .931$, response latency main effect $F_{4,106} = 22$, $p < .001$, dose by response latency interaction $F_{12,106} = 0.68$, $p = .768$). PG01037 did not significantly alter any of the other dependent measures, including premature responses (Figure 5-9, bottom panel; $F_{3,21} = 0.17$, $p = .914$), lever bias (Table 5-1; $F_{3,30} = 0.27$, $p = .846$), and trials omitted (Table 5-2; $F_{3,21} = 2.3$, $p = .107$).

The $D_{2\text{-preferring}}$ antagonist L-741,626 dose-dependently increased response latencies (Figure 5-10, top panel; dose main effect $F_{3,286} = 45$, $p < .001$, dose by response time interaction $F_{30,286} = 0.77$, $p = .799$; due to pattern of missing data, results are of a two-way ANOVA with no repeated measures). Response accuracy (Figure 5-10, middle panel) increased as a function of response latency $F_{4,104} = 19$, $p < .001$, but L-741,626 altered response accuracy $F_{3,104} = 6.6$, $p < .001$ with no dose by response latency interaction $F_{12,104} = 1.4$, $p = .188$. A dose of 3.2 mg/kg L-741,626 significantly decreased response accuracy compared with vehicle. Premature responses were also increased at

this dose (Figure 5-10, bottom panel; dose main effect $F_{3,21} = 3.1$, $p = .045$), along with a large increase in trials omitted (Table 5-2; dose main effect $F_{3,21} = 10$, $p < .001$). Lever bias was not altered across the doses tested (Table 5-1; $F_{3,30} = 0.11$, $p = .957$).

The D_4 antagonist L-745,870 had little effect on most of the dependent measures assessed, but did have a small effect on latencies (Figure 5-11, top panel; dose main effect $F_{3,210} = 1.2$, $p = .350$, dose by response time interaction $F_{30,210} = 1.7$, $p = .015$). L-745,870 did not affect the response-latency-dependent increase in accuracy (Figure 5-11, middle panel; dose main effect $F_{3,93} = 0.25$, $p = .864$, response latency main effect $F_{4,93} = 30$, $p < .001$, dose by response latency interaction $F_{12,93} = 0.62$, $p = .818$), premature responses (Figure 5-11, bottom panel; $F_{3,21} = 0.03$, $p = .994$), lever bias (Table 5-1; $F_{3,27} = 0.23$, $p = .874$), or trials omitted (Table 5-2).

Haloperidol was administered as pretreatments to 0.1 mg/kg pramipexole to assess whether the increase in latency observed with pramipexole could be reversed. The dose of 0.032 mg/kg haloperidol, which had no effect when given alone (Figure 5-8), partially reversed the increase in latency caused by 0.1 mg/kg pramipexole (Figure 5-12, top panel; dose main effect $F_{3,210} = 41$, $p < .001$, dose by response time interaction $F_{30,210} = 9.1$, $p < .001$). A dose of 0.1 mg/kg haloperidol, which increased response latencies when given alone, also increased latencies when given as a pretreatment to 0.1 mg/kg pramipexole. Pramipexole given alone or in combination with haloperidol did not alter the increase in accuracy that coincided with increases in response latency (Figure 5-12, middle panel; dose main effect $F_{4,139} = 0.84$, $p = .499$, response latency main effect $F_{4,139} = 32$, $p < .001$, dose by response latency interaction $F_{16,139} = 0.58$, $p = .894$). A dose of 0.1 mg/kg pramipexole did not increase premature responses (Figure 5-12, bottom panel)

or trials omitted (Table 5-2) when administered alone, but the addition of 0.1 mg/kg haloperidol caused significant increases in both these measures (premature responses main effect $F_{3,21} = 3.1$, $p = .048$; trials omitted main effect $F_{3,21} = 9.8$, $p < .001$). Lever bias was not altered across these dose conditions (Table 5-1; dose main effect $F_{3,24} = 1.0$, $p = .405$).

The $D_{2\text{-preferring}}$ antagonist L-741,626 partially reversed the increases in response latency caused by 0.1 mg/kg pramipexole, although in a non-dose-dependent manner (Figure 5-13, top panel; dose main effect $F_{4,280} = 7.0$, $p < .001$, dose by response time interaction $F_{40,280} = 2.2$, $p < .001$). In the subset of animals tested under these dose conditions, 0.1 mg/kg pramipexole significantly decreased response accuracy, an effect which was not reversed by L-741,626 (Figure 5-13, middle panel; dose main effect $F_{4,144} = 3.7$, $p = .007$, response latency main effect $F_{4,144} = 19$, $p < .001$, dose by response latency interaction $F_{16,144} = 1.1$, $p = .346$). Premature response (Figure 5-13, bottom panel; $F_{4,28} = 7.7$, $p = .017$) and trials omitted (Table 5-2; $F_{4,28} = 5.0$, $p = .004$) were both increased by 0.1 mg/kg pramipexole in the subset of animals tested under these conditions. A dose of 0.1 mg/kg L-741,626 significantly reversed the increase in premature responses and 0.32 mg/kg L-741,626 reversed the increase in trials omitted. This set of dosing conditions did not affect lever bias (Table 5-1; $F_{4,36} = 1.3$, $p = .272$).

The $D_{3\text{-preferring}}$ antagonist PG01037 did not reverse the increase in latencies caused by administration of 0.1 mg/kg pramipexole (Figure 5-14, top panel; dose main effect $F_{4,280} = 6.1$, $p < .001$, dose by response time interaction $F_{40,280} = 3.7$, $p < .001$). This set of dosing conditions did not alter in the increase in accuracy that coincided with increases in response latency (Figure 5-14, middle panel; dose main effect $F_{4,158} = 1.6$, p

= .178, response latency main effect $F_{4,158} = 16$, $p < .001$, dose by response latency interaction $F_{16,158} = 0.55$, $p = .915$). Premature response (Figure 5-14, bottom panel; $F_{4,28} = 1.9$, $p = .136$), lever bias (Table 5-1; $F_{4,36} = 0.95$, $p = .445$, and trials omitted (Table 5-2; $F_{4,28} = 1.9$, $p = .140$) did not significantly differ across these dosing conditions.

Administration of 1.0 mg/kg of the $D_{1\text{-like}}$ agonist SKF 81297 increased response latencies (Figure 5-15, top panel; dose main effect $F_{3,210} = 5.8$, $p = .005$, dose by response time interaction $F_{30,210} = 1.6$, $p = .032$). Accuracy was significantly affected by SKF 81297 dose (Figure 5-15, middle panel; dose main effect $F_{3,113} = 4.6$, $p = .005$, response latency main effect $F_{4,113} = 42$, $p < .001$, dose by response latency interaction $F_{12,113} = 1.0$, $p = .418$), but no dose significantly differed from vehicle either overall or at a specific response latency. Premature responses (Figure 5-15, bottom panel; $F_{3,21} = 1.4$, $p = .262$) and lever bias (Table 5-1; $F_{3,30} = 1.8$, $p = .175$) were not significantly altered by SKF 81297, but 1.0 mg/kg increased trials omitted (Table 5-2; $F_{3,21} = 5.2$, $p = .008$).

The $D_{1\text{-like}}$ antagonist SCH 23390 increased response latencies with the largest effect at 0.01 mg/kg (Figure 5-16, top panel; dose main effect $F_{3,210} = 3.2$, $p = .045$, dose by response time interaction $F_{30,210} = 1.1$, $p = .338$). SCH 23390 did not alter the increase in accuracy observed as response latency increased (Figure 5-16, middle panel; dose main effect $F_{3,89} = 2.2$, $p = .089$, response latency main effect $F_{4,89} = 21$, $p < .001$, dose by response latency could not be computed due to pattern of missing data). Premature responses were increased slightly (Figure 5-16, bottom panel; $F_{3,21} = 5.1$, $p = .008$), but only at a dose that dramatically increased trials omitted (Table 5-2; $F_{3,21} = 127$, $p < .001$). Lever bias was also reduced at 0.032 mg/kg SCH 23390 (Table 5-1; $F_{3,27} = 3.0$, $p = .047$).

SCH 23390 was co-administered with 1.0 mg/kg SKF 81297, and at the doses tested, reversed the increase in response latency caused by 1.0 mg/kg SKF 81297 (Figure 5-17, top panel; dose main effect $F_{4,280} = 6.1$, $p = .001$, dose by response time interaction $F_{40,280} = 1.6$, $p = .019$). No significant effect on accuracy was noted over the dose conditions tested (Figure 5-17, middle panel; dose main effect $F_{4,148} = 1.6$, $p = .173$, response latency main effect $F_{4,148} = 30$, $p < .001$, dose by response latency interaction $F_{16,148} = 1.6$, $p = .073$). There was a significant effect of dose condition on premature responses (Figure 5-17, bottom panel; $F_{4,28} = 4.4$, $p = .007$), but 1.0 mg/kg SKF 81297 did not differ from vehicle, nor was the level of premature responses elicited by 1.0 mg/kg SKF 81297 altered by any of the doses of SCH 23390 tested. A dose of 0.01 mg/kg SCH 23390 did reverse the increase in trials omitted caused by 1.0 mg/kg SCH 23390, while the addition of 0.032 mg/kg SCH 23390 increased trials omitted (Table 5-2; $F_{4,28} = 42$, $p < .001$). In the subset of animals tested under these dose conditions, 1.0 mg/kg SKF 81297 significantly decreased lever bias, which was not reversed by SCH 23390 at the doses tested (Table 5-1; $F_{4,44} = 4.7$, $p = .003$).

The nonselective dopamine agonist apomorphine dose-dependently increased response latency at 0.32 mg/kg (Figure 5-18, top panel; dose main effect $F_{3,210} = 21$, $p < .001$, dose by response time interaction $F_{30,210} = 4.9$, $p < .001$), and decreased accuracy at this same dose (Figure 5-18, middle panel; dose main effect $F_{3,103} = 3.1$, $p = .031$, response latency main effect $F_{4,103} = 35$, $p < .001$, dose by response latency interaction $F_{12,103} = 0.51$, $p = .906$). Apomorphine tended to dose-dependently decrease premature responses, although the main effect of dose was not statistically significant (Figure 5-18, bottom panel; $F_{3,21} = 2.5$, $p = .085$). Apomorphine did not significantly affect lever bias

(Table 5-1; $F_{3,27} = 1.4$, $p = .255$), while 0.32 mg/kg increased trials omitted (Table 5-2; dose main effect $F_{3,21} = 20$, $p < .001$).

Discussion

In general, rats learned the UVD task and the uncertain visual stimuli signaled differential behavior patterns. As a function of response latency, response accuracy closely tracked the within-trial increase in the probability that the stimulus above the levers correctly predicted reinforcement delivery (Figure 5-2, middle panel). Further evidence that the rats were sensitive to the presence of the visual stimuli came from the probe trial with the stimuli correlated with the correct lever throughout the trial. During this single session, response accuracy remained high (>80%) throughout the trial, did not depend on response latency, and was significantly higher than in the uncertain visual stimuli condition (Figure 5-2, middle panel). Response bias, or percent of responses that occurred on the preferred lever, also decreased in this probe trial, indicating that the improved correlation of the stimuli with the correct response lever in this session helped to overcome lever biases (Table 5-1).

Response latency, a purported measure of impulsive preparation (Evenden, 1999a), was either unaffected or dose-dependently increased by all the dopaminergic drugs tested. The only decrease in latency distribution that was observed occurred when the lever insertion duration prior to stimuli onset was increased. As the pre-stimulus lever duration was increased to values greater than the training duration of 8 s latency decreased, reaching significance at a duration of 12 s. Both the agonist and antagonist tested that bind most selectively to $D_{1\text{-like}}$ (SKF 81297 and SCH 23390), D_2 (sumanirole and L-741,626), and D_3 (pramipexole and PG01037) receptors, as well as the dopamine

transporter ligands (*d*-amphetamine and GBR 12909), increased latency at in a dose-dependent manner. No dose of any of these drugs decreased latency. The D_4 agonist and antagonist tested (ABT-724 and L-745,870) had no appreciable effect on this measure. While L-745,870 significantly altered latency, this effect was very small in magnitude and did not appear dose-dependent. Increases in latency caused by 0.1 mg/kg pramipexole were partially antagonized by doses of haloperidol and L-741,626 but not PG01037, suggesting D_2 receptor activation is important for this effect. The increase in latency caused by 1.0 mg/kg SKF 81297 was not reversed by the doses of SCH 23390 tested. It seems as though sufficient activation or deactivation of $D_{1\text{-like}}$, D_2, or D_3 receptors increases response latency. As a model of impulsive preparation, this pattern of results is difficult to interpret. It has been found that individual differences in baseline and drug-altered latency on this task strongly correlates with latency to respond on the delay discounting task (Chapter 6). On the delay discounting task, the stimuli signaling reinforcer availability are presented at the beginning of a trial and signal availability with a constant probability of 1.0 throughout the trial. No processes approximating impulsive preparation seem to be associable with low response latencies on the delay discounting task. That response latency was strongly correlated across these tasks suggests that response latency on the UVD task may not be related to impulsive preparation. Instead, response latency on this task may more closely approximate latency to respond on simple reaction time experiments. This assertion is further supported by the stimulus certainty condition, where removing the probabilistic nature of the stimuli had no effect on response latency (Figure 5-2). With the uncertainty removed from the stimulus presentations, no information could be gained by waiting to respond. Response

latency remaining the same under both certain and uncertain conditions suggests "impulsive preparation" was not a governing force in the behavior of the subjects on these tasks.

Premature responses on the 5-CSRT task are an often-studied model of impulsive action (Dalley et al., 2008). While the UVD task has received less attention, there is good reason to believe premature responses are similar on the two tasks. Increasing the duration of time between the onset of a trial and the presentation of visual stimuli reliably increases premature responses on the 5-CSRT task (e.g., Dalley et al., 2007), and the same effect was found by increasing the lever insertion duration prior to stimulus onset in the current experiment (Figure 5-1, bottom panel). In addition, *d*-amphetamine reliably increases premature responses on the 5-CSRT task (Cole & Robbins, 1987; van Gaalen et al., 2006), and a significant, dose-dependent increase was noted with *d*-amphetamine in the current experiment (Figure 5-3, bottom panel). Other than the lever insertion duration manipulation and *d*-amphetamine, 3.2 mg/kg L-741,626 and 0.032 mg/kg SCH 23390 increased percent premature responses in the current experiment. These same doses also produced large increases in trials omitted, however, reducing the number of trials on which these percentage data were based. Since premature responses are expressed as a percent of responses in the current analysis and total responses were decreased with these drugs, there is discordance between these increases and the absolute number of premature responses recorded in the session. In absolute terms, premature responses were not altered by L-741,626 over the dose range tested, and decreased by 0.032 mg/kg SCH 23390 (data not shown). The main effect of apomorphine trended toward significance, and a *post hoc* test suggested a decrease in premature responses with 0.32 mg/kg

apomorphine (Figure 5-18, bottom panel). Apomorphine has not been tested previously on premature responding in either the 5-CSRT task or the UVD task. On a paced fixed consecutive number schedule, another purported measure of impulsive action (Evenden, 1999a), apomorphine decreased impulsive action as defined by this task (Chapter 4). In both cases, 0.32 mg/kg was the active dose, suggesting this dose range may function to reduce impulsive action. However, it should be noted that this same dose increased trials omitted (Table 5-2) and produced atypical, biased responding on a delay discounting task (Chapter 3), potentially limiting its usefulness as a therapeutic.

Response accuracy was very resilient to the effects of the drugs tested, and followed a similar pattern throughout the experiment. Accuracy closely followed the probability that the uncertain stimuli signaled the correct response location (Figure 5-2, middle panel), and this pattern remained relatively undisturbed, even after high doses of drugs that caused large increases in trials omitted and response latency. For example, 0.1 mg/kg haloperidol dramatically increased trials omitted (Table 5-2) and response latency (Figure 5-8, top panel), but had no significant effect on response accuracy in the latency-based bins in which there were enough responses to compute accuracy (Figure 5-8, middle panel). Doses of 3.2 mg/kg L-741,626 and 0.32 mg/kg apomorphine did decrease response accuracy somewhat, as did 0.1 mg/kg pramipexole in the same subgroup of animals that showed an abnormal increase in premature responses to this same dose.

In conclusion, further research is needed to determine if the UVD task is an appropriate model of impulsive preparation. The pattern of results with response latencies on this task suggest that the relationship of this measure to tasks measuring impulsive preparation in humans may be dubious, but it's quite possible that administration of

dopaminergic drugs is not the best way of determining this relationship. Premature responses on the UVD task appear to be analogous to premature responses on the 5-CSRT task, with increases in premature responses seen after *d*-amphetamine administration or an increase in the pre-stimulus lever insertion duration. Of the dopaminergic drugs tested, only apomorphine tended to decrease impulsive action as defined by this task, but the therapeutic relevance of this finding is likely moot.

Table 5-1. Average percent responding on the preferred lever (±SEM) for each condition and drug tested. These data include rats that demonstrated extreme lever biases (<90% responding on one lever during vehicle sessions), which were excluded from other data analyses.

Pre-stimulus Lever Insertion Duration (n = 11)	Dur.	8 sec	10 sec	12 sec		
	Bias	82.2 (±3.9)	81.8 (±3.5)	79.2 (±4.3)		
Stimulus Certainty (n = 11)	Cond.	Uncertain	Certain *			
	Bias	79.2 (±4.6)	69.8 (±5.9)			
d-Amphetamine (n = 10)	Dose	Vehicle	0.1	0.32	1.0	
	Bias	77.9 (±4.7)	78.0 (±5.4)	79.6 (±5.0)	74.9 (±4.0)	
GBR 12909 (n = 10)	Dose	Vehicle	1.0	3.2	10	
	Bias	73.6 (±5.4)	77.5 (±5.0)	75.5 (±5.3)	75.9 (±5.9)	
Pramipexole (n = 10)	Dose	Vehicle	0.032	0.1	0.32	
	Bias	70.6 (±3.8)	67.8 (±4.1)	64.7 (±3.2)	63.9 (±3.0)	
Sumanirole (n = 9)	Dose	Vehicle	0.32	1.0	3.2 **	
	Bias	77.6 (±4.7)	76.6 (±4.3)	74.6 (±4.2)	66.1 (±3.0)	
ABT-724 (n = 12)	Dose	Vehicle	0.1	0.32	1.0	3.2
	Bias	75.9 (±4.5)	74.1 (±5.0)	76.8 (±4.8)	78.1 (±4.4)	74.9 (±5.4)
Haloperidol (n = 10)	Dose	Vehicle	0.032	0.1		
	Bias	76.7 (±4.1)	66.5 (±3.2)	70.2 (±5.0)		
PG01037 (n = 11)	Dose	Vehicle	10	32	56	
	Bias	73.8 (±4.9)	75.3 (±4.3)	75.1 (±4.3)	72.9 (±4.3)	
L-741,626 (n = 11)	Dose	Vehicle	0.32	1.0	3.2	
	Bias	78.5 (±4.3)	79.0 (±4.4)	78.5 (±4.4)	76.3 (±5.5)	
L-745,870 (n = 10)	Dose	Vehicle	0.32	1.0	3.2	
	Bias	73.0 (±5.0)	72.6 (±5.2)	72.7 (±5.5)	73.8 (±5.1)	
Haloperidol + 0.1 Pramipexole (n = 9)	Dose	Vehicle	0.1 Pram	+ 0.032 Hal	+ 0.1 Hal	
	Bias	74.1 (±3.6)	64.6 (±3.7)	68.6 (±4.9)	72.3 (±3.9)	
L-741,626 + 0.1 Pramipexole (n = 10)	Dose	Vehicle	0.1 Pram	+ 0.1 L-741	+ 0.32 L-741	+ 1.0 L-741
	Bias	76.6 (±4.9)	69.3 (±4.4)	76.1 (±6.1)	75.9 (±5.4)	73.1 (±4.7)

PG01037 + 0.1 Pramipexole (n = 10)	Dose	Vehicle	0.1 Pram	+ 10 PG	+ 32 PG	+ 56 PG
	Bias	78.9 (±5.0)	74.3 (±5.2)	73.4 (±5.9)	72.0 (±6.1)	73.0 (±5.0)
SKF 81297 (n = 11)	Dose	Vehicle	0.1	0.32	1.0	
	Bias	76.1 (±5.1)	74.2 (±5.4)	75.7 (±5.5)	67.9 (±4.6)	
SCH 23390 (n = 10)	Dose	Vehicle	0.0032	0.01	0.032 *	
	Bias	79.5 (±4.6)	78.7 (±5.0)	73.8 (±5.1)	70.9 (±4.5)	
SCH 23390 + 1.0 SKF 81297 (n = 12)	Dose	Vehicle	1.0 SKF **	+ 0.0032 SCH	+ 0.01 SCH	+ 0.032 SCH
	Bias	78.1 (±3.8)	67.3 (±4.2)	67.9 (±4.0)	66.6 (±3.3)	68.5 (±3.0)
Apomorphine (n = 10)	Dose	Vehicle	0.032	0.1	0.32	
	Bias	75.7 (±5.1)	75.0 (±5.1)	75.8 (±4.9)	69.6 (±5.0)	

Cond. = Condition, Dur. = duration. Hal = haloperidol, L-741 = L-74,626, PG = PG01037, Pram = pramipexole, SCH = SCH 23390, SKF = SKF 81297.
* $p < .05$, ** $p < 0.01$, *** $p < .001$ compared to vehicle in Bonferroni-corrected *post hoc* tests.

Table 5-2. Mean number of trials omitted (±SEM) for each condition and drug tested. These data exclude rats that demonstrated extreme lever biases (<90% responding on one lever during vehicle sessions); *n* = 8 for all conditions.

Pre-stimulus Lever Insertion Duration	Dur.	8 sec	10 sec	12 sec		
	Omi.	0 (±0)	0 (±0)	0 (±0)		
Stimulus Certainty	Cond.	Uncertain	Certain			
	Omi.	0 (±0)	0.1 (±0.1)			
d-Amphetamine	Dose	Vehicle	0.1	0.32	1.0	
	Omi.	0 (±0)	0 (±0)	0.1 (±0.1)	0.6 (±0.4)	
GBR 12909	Dose	Vehicle	1.0	3.2	10	
	Omi.	0 (±0)	0 (±0)	0 (±0)	0 (±0)	
Pramipexole	Dose	Vehicle	0.032	0.1	0.32 ***	
	Omi.	0 (±0)	0.9 (±0.8)	11.1 (±4.9)	54.0 (±4.9)	
Sumanirole	Dose	Vehicle	0.32	1.0	3.2 ***	
	Omi.	0 (±0)	0.1 (±0.1)	0 (±0)	30.0 (±7.7)	
ABT-724	Dose	Vehicle	0.1	0.32	1.0	3.2
	Omi.	0 (±0)	0 (±0)	0 (±0)	0 (±0)	0 (±0)
Haloperidol	Dose	Vehicle	0.032	0.1 ***		
	Omi.	0.1 (±0.1)	0 (±0)	73.4 (±2.4)		
PG01037	Dose	Vehicle	10	32	56	
	Omi.	0 (±0)	0 (±0)	0 (±0)	15.6 (±10.3)	
L-741,626	Dose	Vehicle	0.32	1.0	3.2 ***	
	Omi.	0 (±0)	0 (±0)	0 (±0)	41.3 (±12.9)	
L-745,870	Dose	Vehicle	0.32	1.0	3.2	
	Omi.	0 (±0)	0 (±0)	0 (±0)	0 (±0)	
Haloperidol + 0.1 Pramipexole	Dose	Vehicle	0.1 Pram	+ 0.032 Hal	+ 0.1 Hal ††	
	Omi.	0 (±0)	6.4 (±3.3)	0.9 (±0.7)	40.0 (±11.7)	
L-741,626 + 0.1 Pramipexole	Dose	Vehicle	0.1 Pram **	+ 0.1 L-741	+ 0.32 L-741 †	+ 1.0 L-741
	Omi.	0.4 (±0.4)	32.9 (±10.7)	23.5 (±9.8)	7.3 (±5.5)	10.9 (±6.7)

PG01037 + 0.1 Pramipexole	Dose	Vehicle	0.1 Pram	+ 10 PG	+ 32 PG	+ 56 PG
	Omi.	0 (±0)	10.3 (±5.6)	8.5 (±7.0)	17.8 (±8.4)	10.6 (±7.9)
SKF 81297	Dose	Vehicle	0.1	0.32	1.0 *	
	Omi.	0 (±0)	0 (±0)	0.3 (±0.2)	17.0 (±7.4)	
SCH 23390	Dose	Vehicle	0.0032	0.01 ***	0.032 ***	
	Omi.	0 (±0)	0 (±0)	28.9 (±5.7)	75.5 (±2.2)	
SCH 23390 + 1.0 SKF 81297	Dose	Vehicle	1.0 SKF **	+ 0.0032 SCH	+ 0.01 SCH †	+ 0.032 SCH †††
	Omi.	0 (±0)	21.4 (±7.3)	20.0 (±5.7)	5.8 (±2.4)	63.9 (±3.5)
Apomorphine	Dose	Vehicle	0.032	0.1	0.32 ***	
	Omi.	0 (±0)	0 (±0)	0 (±0)	23.4 (±5.2)	

Cond. = Condition, Dur. = duration. Hal = haloperidol, L-741 = L-74,626, PG = PG01037, Pram = pramipexole, SCH = SCH 23390, SKF = SKF 81297.
* $p < .05$, ** $p < 0.01$, *** $p < .001$ compared to vehicle in Bonferroni-adjusted *post hoc* tests.
† $p < .05$, †† $p < 0.01$, ††† $p < .001$ compared to agonist alone in Bonferroni-adjusted *post hoc* tests.

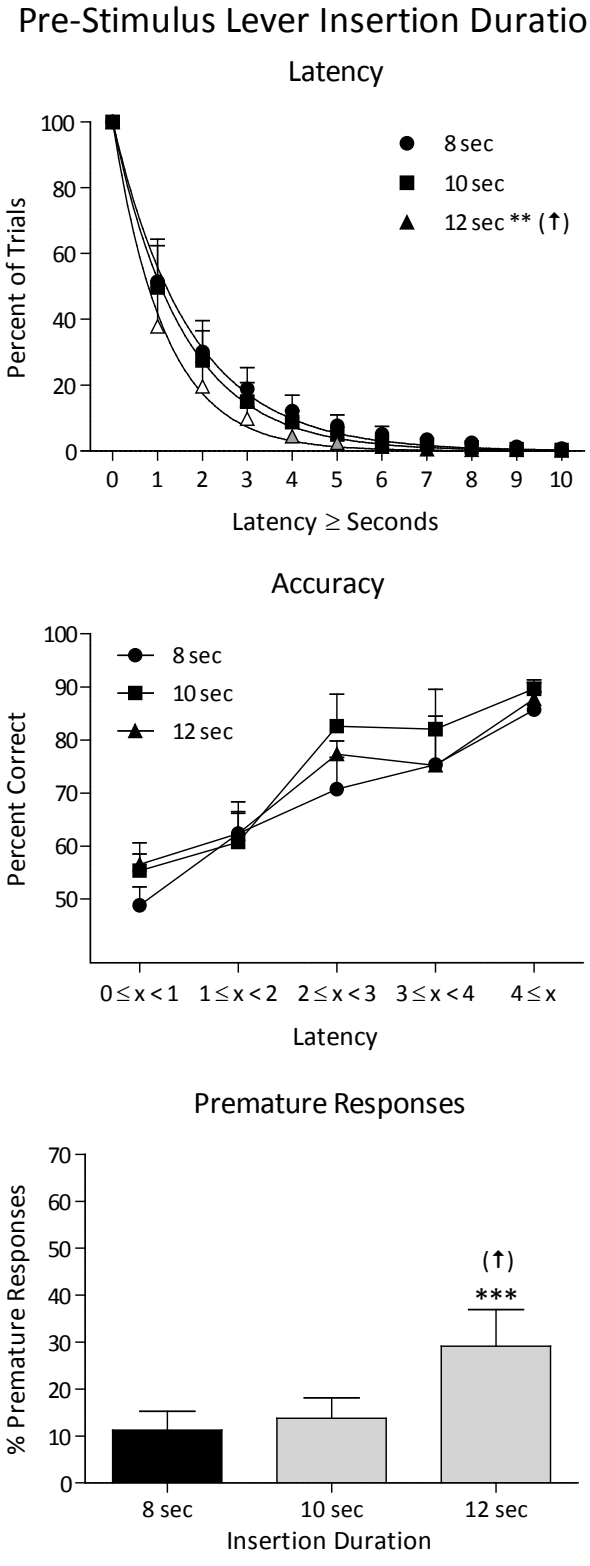

Figure 5-1. Changes in performance after altering the duration that the levers were inserted into the chamber prior to stimulus onset. Top panel: Distribution of latencies to respond after onset of stimuli as a function of the lever insertion duration prior to stimulus onset. Data are presented as percent of total responses meeting or exceeding the delay indicated on the *x* axis under each lever insertion duration condition. Asterisks in the legend indicate a significant difference from the 8-s condition (* $p < .05$, ** $p < .01$, *** $p < .001$), while shading of individual points indicates a significant difference from the corresponding 8-s condition point (black, n.s.; gray, $p < .05$; white, $p < .001$). Selective effects on latency corresponding to an increase (↑) or decrease (↓) in impulsive preparation, or a disruption in behavior (✕), is also indicated in the legend. Middle panel: Accuracy of responses as a function of latency to respond and the pre-stimulus lever insertion duration. Bottom panel: Premature responses as a function of pre-stimulus lever insertion duration. Asterisks above bars indicate statistical significance compared to the 8-s condition, as described above. Selective effects on premature responses corresponding to an increase (↑) or decrease (↓) in impulsive action, or a disruption in behavior (✕), is also indicated above each bar.

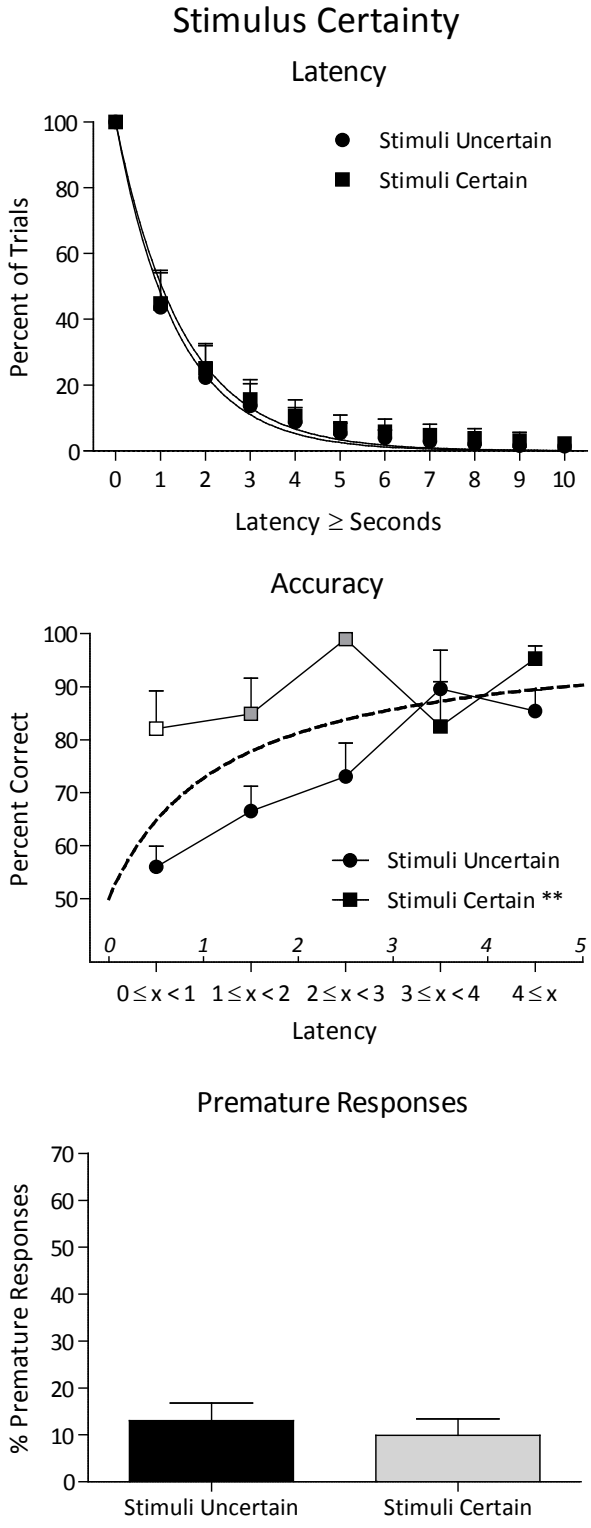

Figure 5-2. Changes in performance when stimuli were correlated with the food lever with a probability of 1.0 throughout the trial, compared to the uncertain probabilities used for all other tests. Top panel: Distribution of response latencies under both stimulus certainty conditions. Middle panel: Accuracy of responses as a function of response latency and stimulus certainty. Asterisks in the legend (* $p < .05$, ** $p < .01$, *** $p < .001$) and symbol shading (black, n.s.; gray, $p < .05$; white, $p < .001$) indicate statistically significant differences from the uncertain stimuli condition. The bold, dashed line represents the programmed probability of the uncertain stimuli accurately predicting the reinforcer location as a function of trial duration. Trial duration for the purposes of this analysis is indicated by the upward-deflecting tick marks on the *x*-axis and italicized axis labels, and corresponds to the latency bins of the response accuracy data. Bottom panel: Premature responses as a function of stimulus certainty.

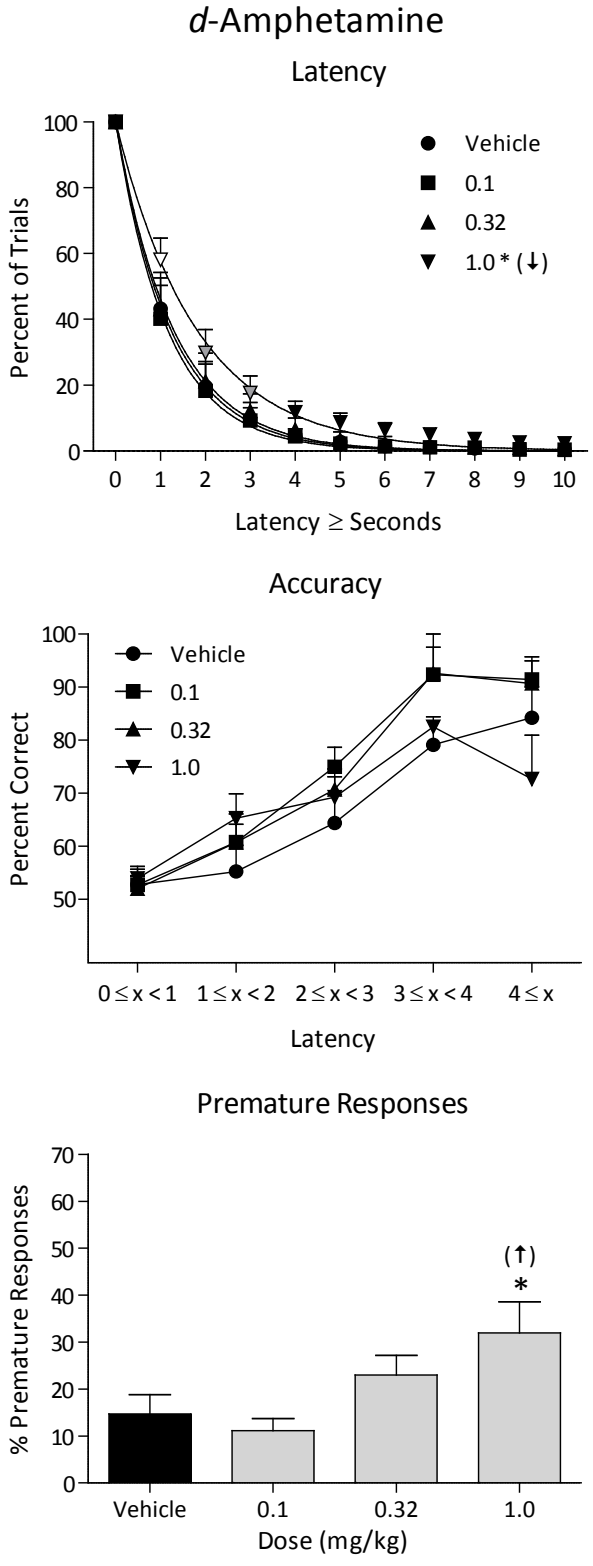

Figure 5-3. Effects of *d*-amphetamine pretreatments on performance. Top panel: Distribution of latencies to respond as a function of drug dose in mg/kg. Data are presented as percent of total responses meeting or exceeding the delay indicated on the *x* axis after each dose indicated by symbol shape. Asterisks in the legend indicate a significant difference from vehicle (* $p < .05$, ** $p < .01$, *** $p < .001$), while shading of individual points indicates a significant difference from the corresponding vehicle point (black, n.s.; gray, $p < .05$; white, $p < .001$). Selective effects on latency corresponding to an increase (↑) or decrease (↓) in impulsive preparation, or a disruption in behavior (✕), is also indicated in the legend. Middle panel: Accuracy of responses as a function of latency to respond and drug dose in mg/kg. Asterisks appearing in the legend and symbol shading indicate statistical significance as described above. Bottom panel: Premature responses as a function of drug dose. Asterisks appearing above bars indicate a statistically significant difference from vehicle (* $p < .05$, ** $p < .01$, *** $p < .001$). Selective effects on premature responses corresponding to an increase (↑) or decrease (↓) in impulsive action, or a disruption in behavior (✕), is also indicated above each bar.

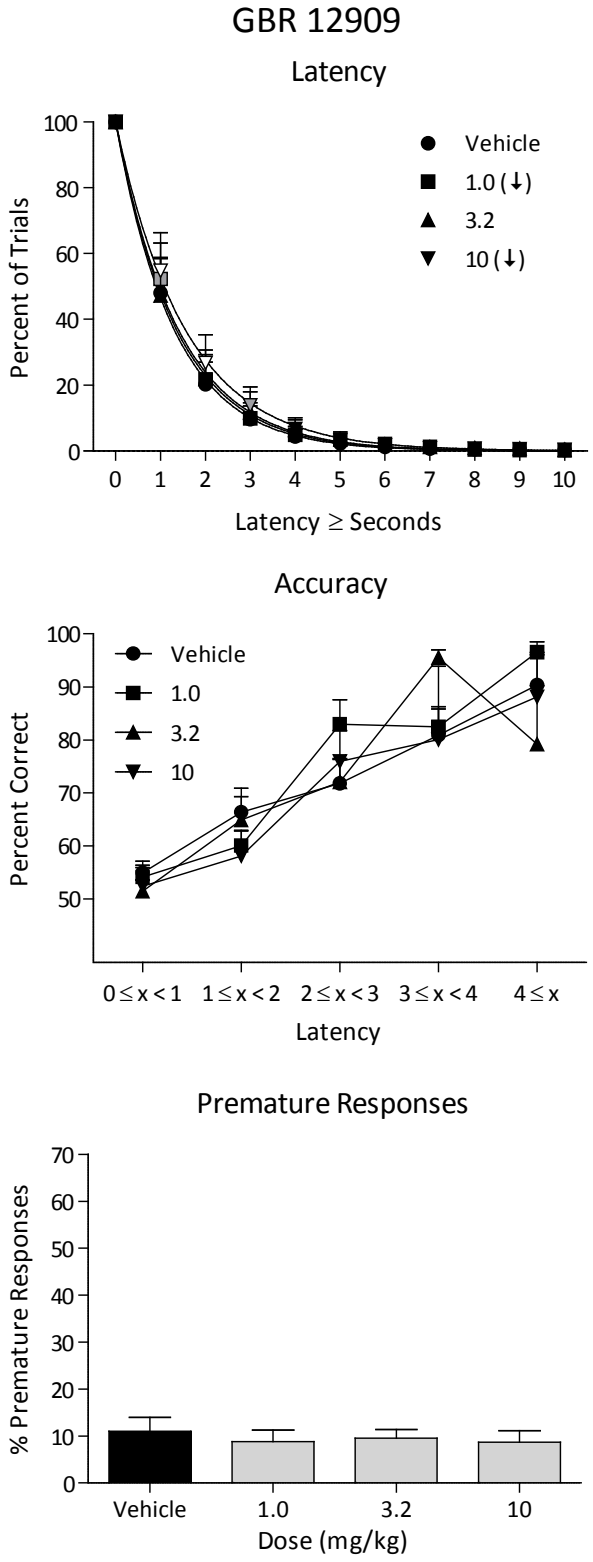

Figure 5-4. Effects of GBR 12909 pretreatments on performance. All other details as in Figure 5-3.

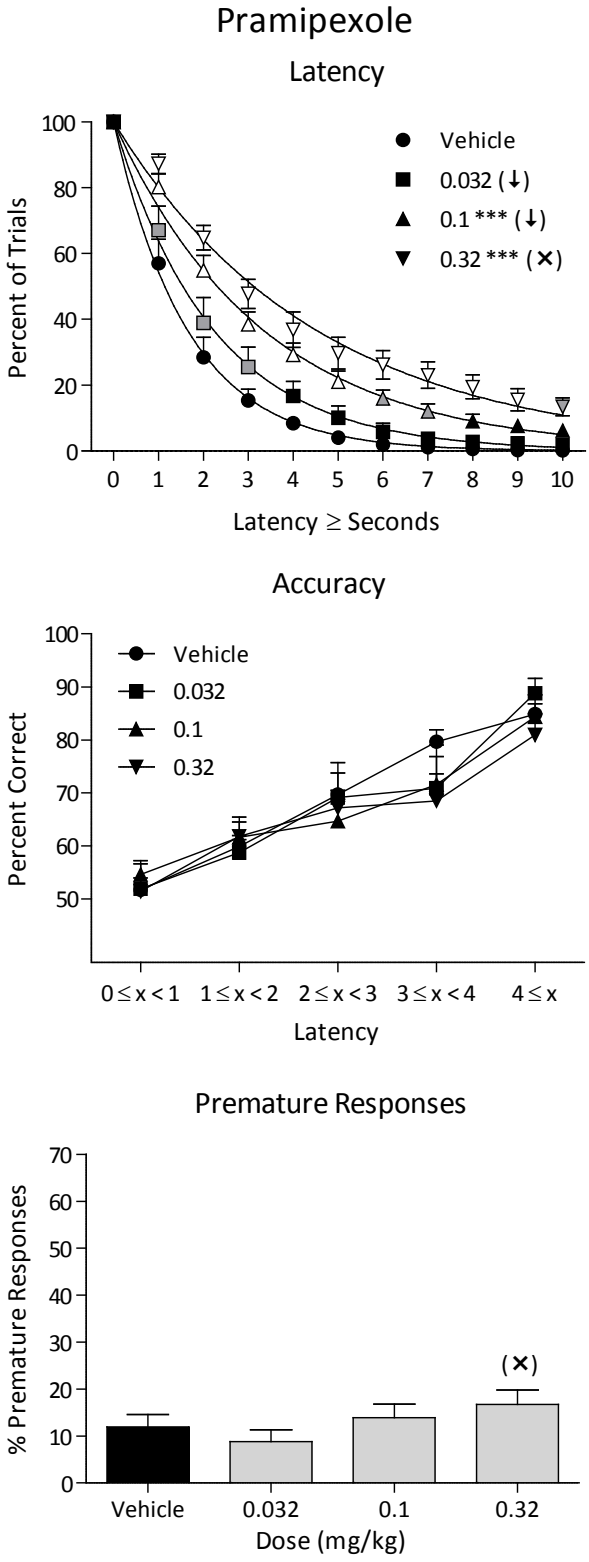

Figure 5-5. Effects of pramipexole pretreatments on performance. All other details as in Figure 5-3.

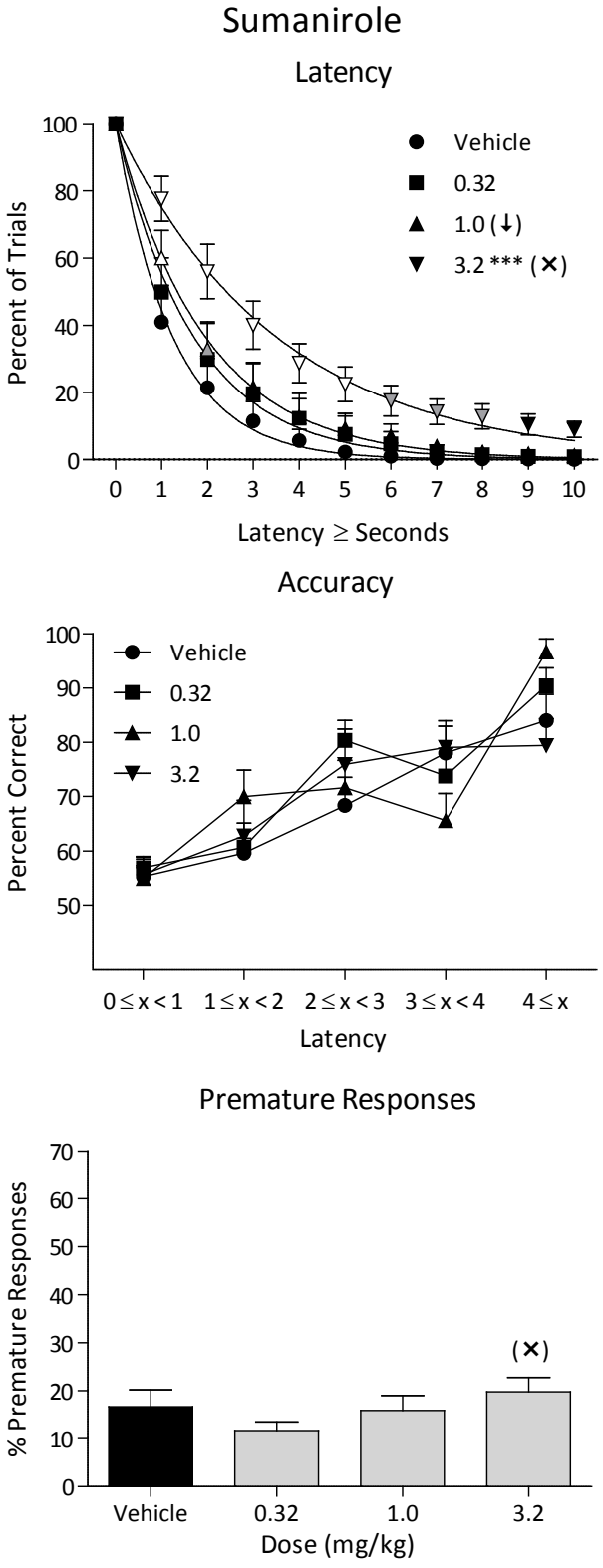

Figure 5-6. Effects of sumanirole pretreatments on performance. All other details as in Figure 5-3.

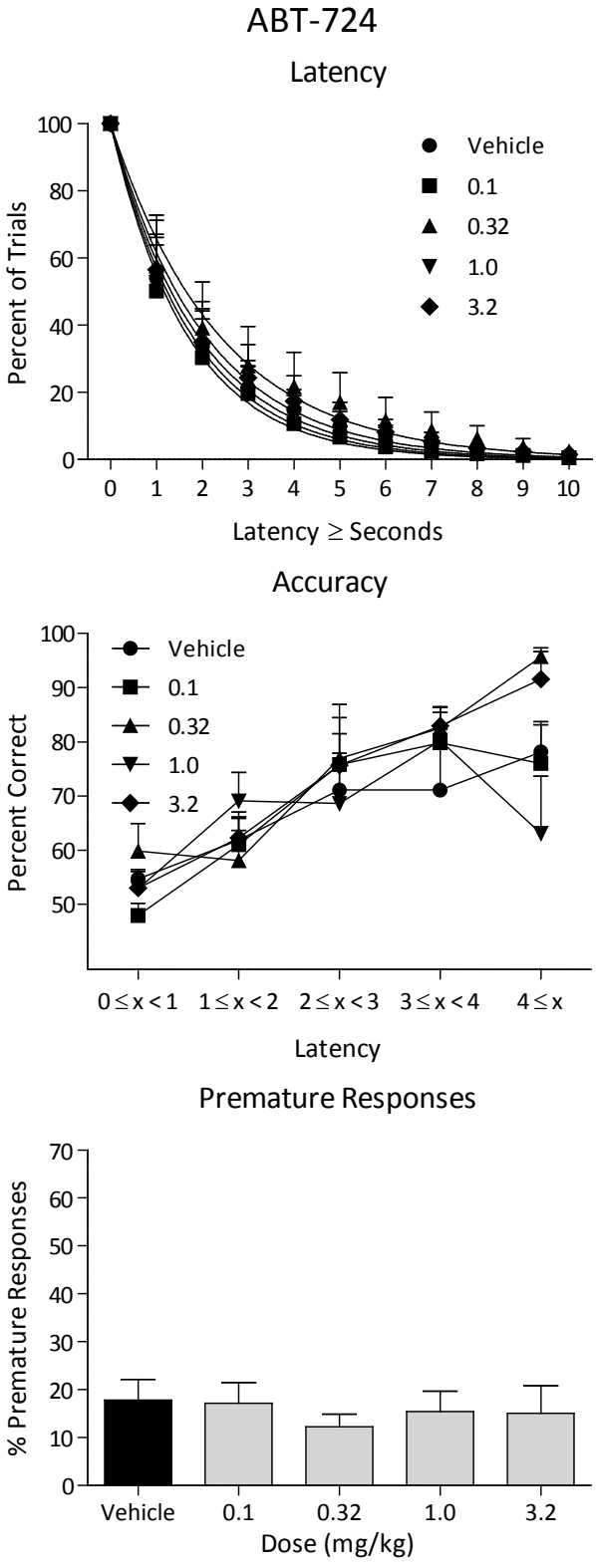

Figure 5-7. Effects of ABT-724 pretreatments on performance. All other details as in Figure 5-3.

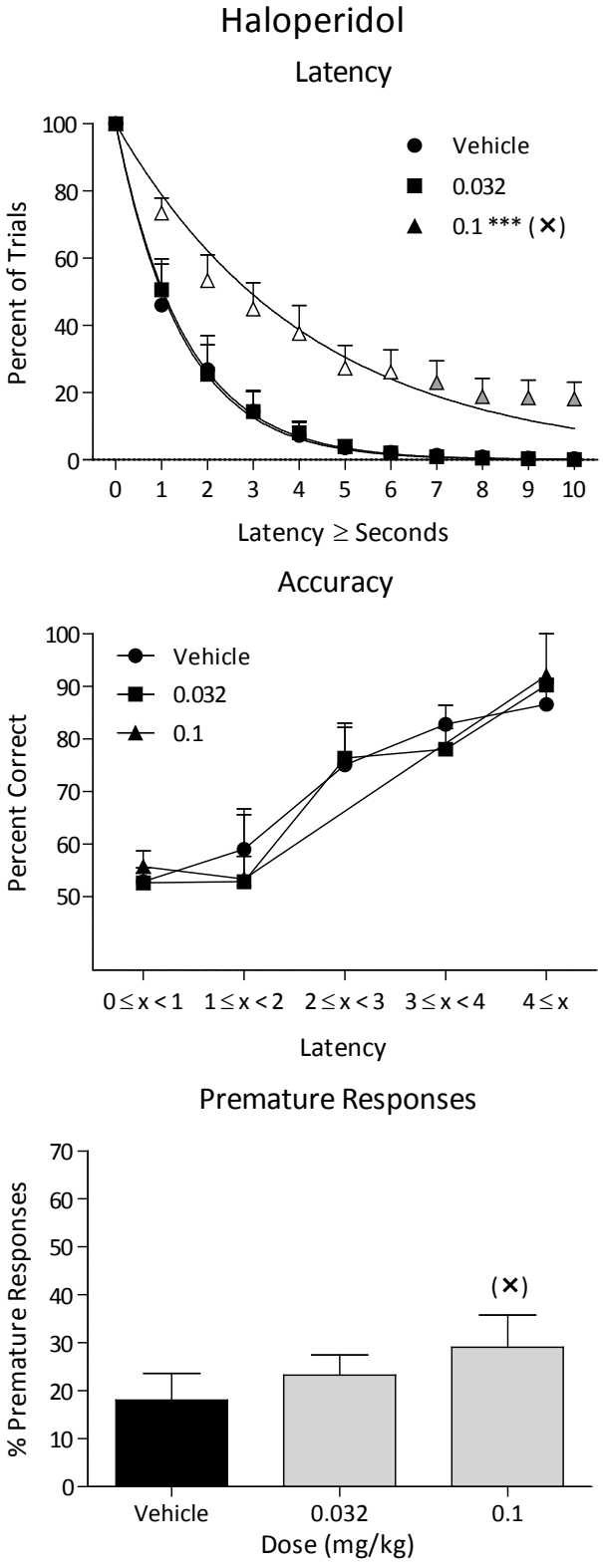

Figure 5-8. Effects of haloperidol pretreatments on performance. All other details as in Figure 5-3.

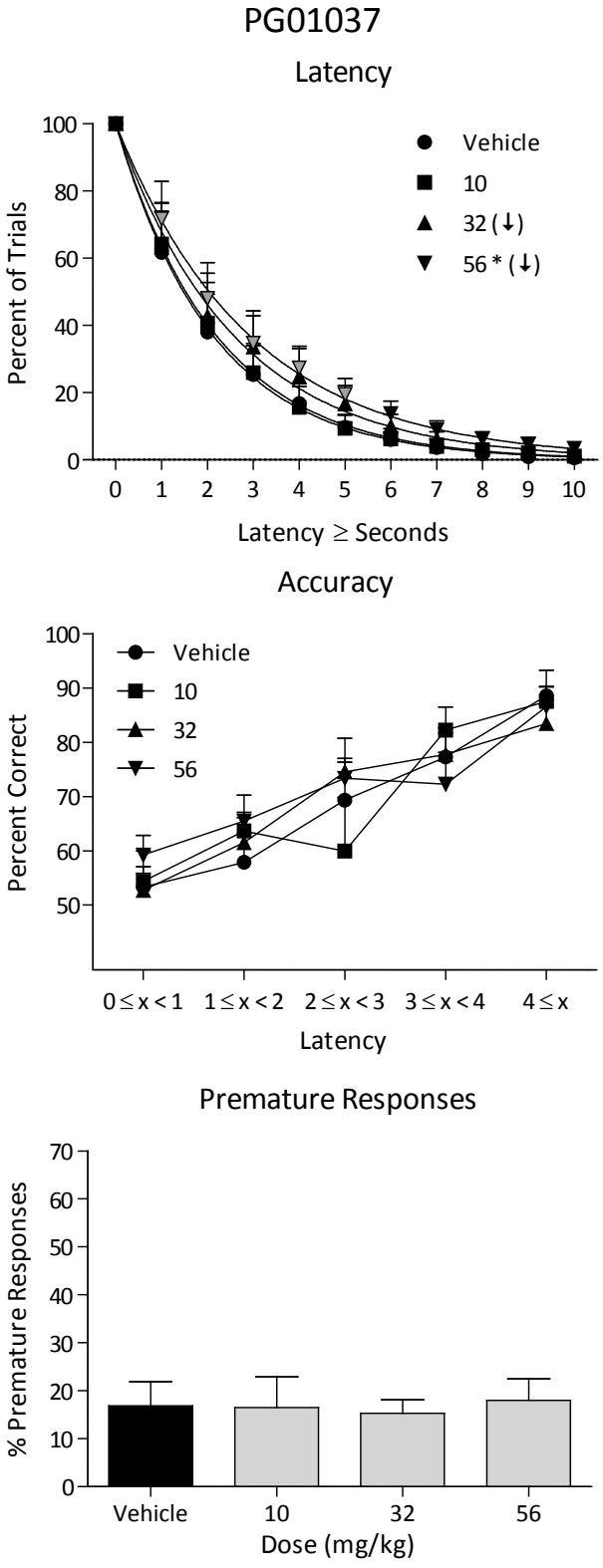

Figure 5-9. Effects of PG01037 pretreatments on performance. All other details as in Figure 5-3.

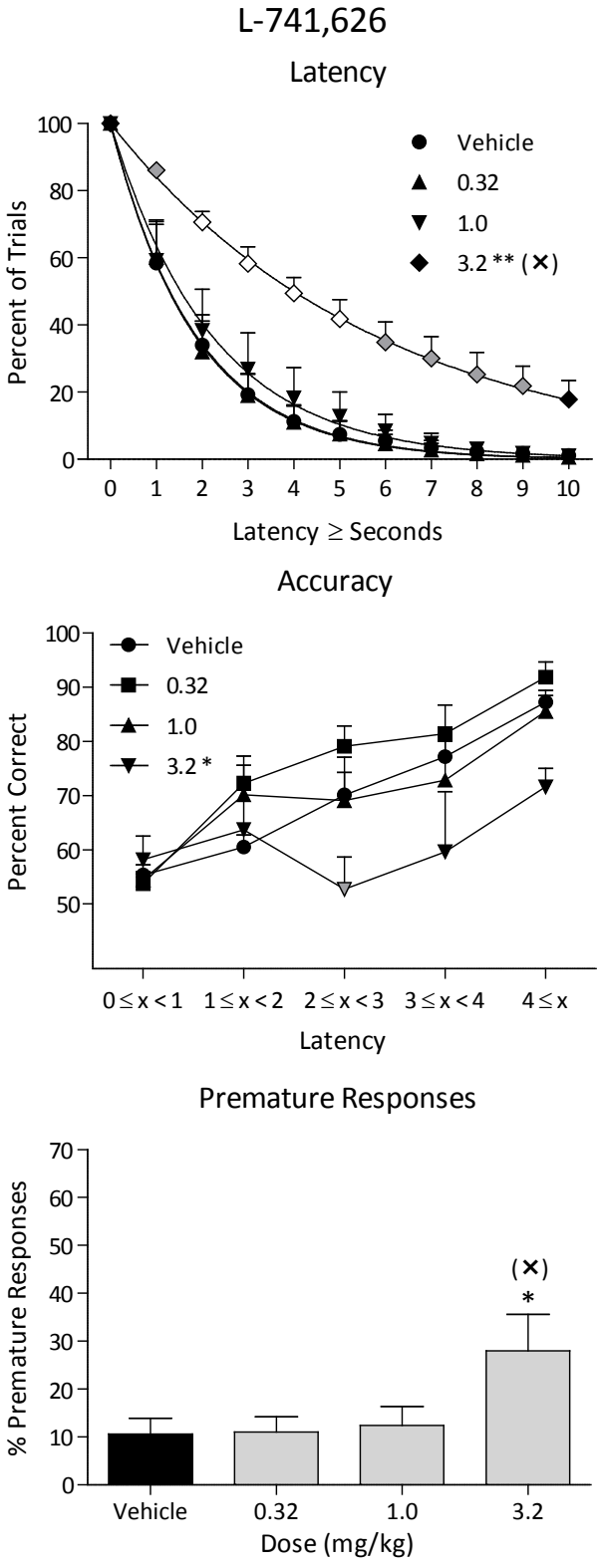

Figure 5-10. Effects of L-741,626 pretreatments on performance. All other details as in Figure 5-3.

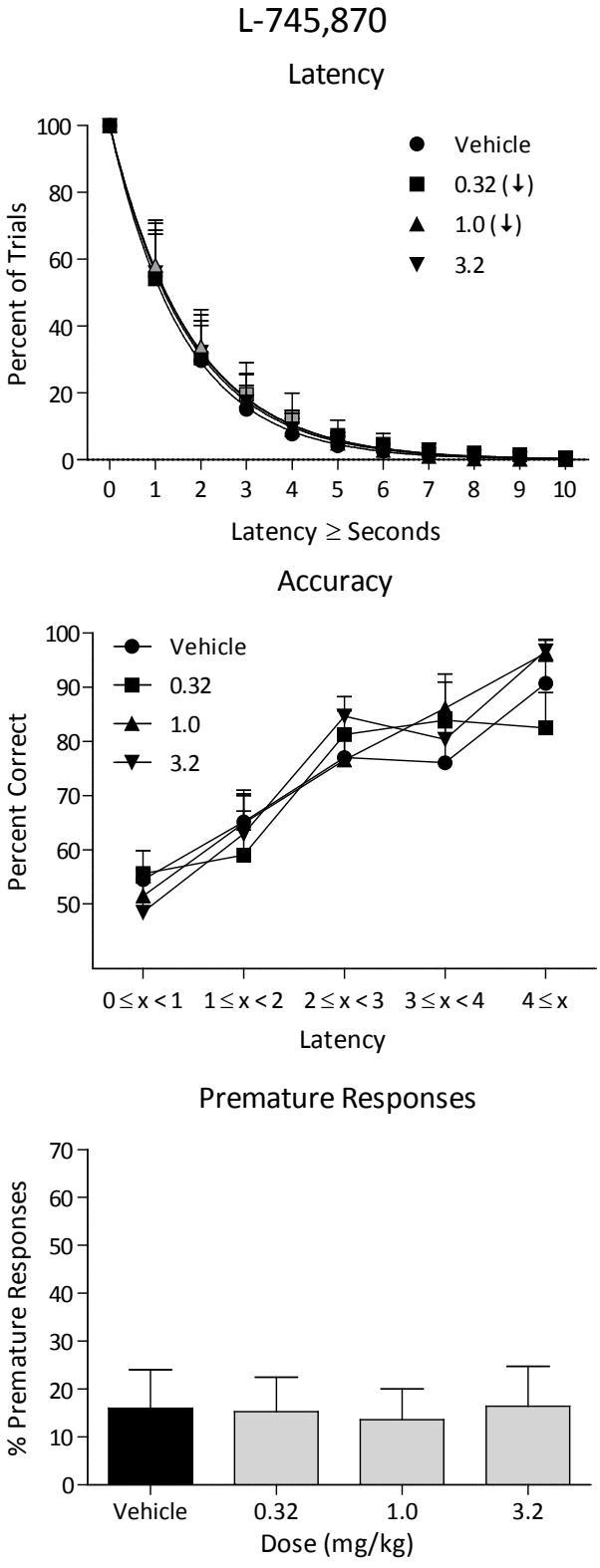

Figure 5-11. Effects of L-745,870 pretreatments on performance. All other details as in Figure 5-3.

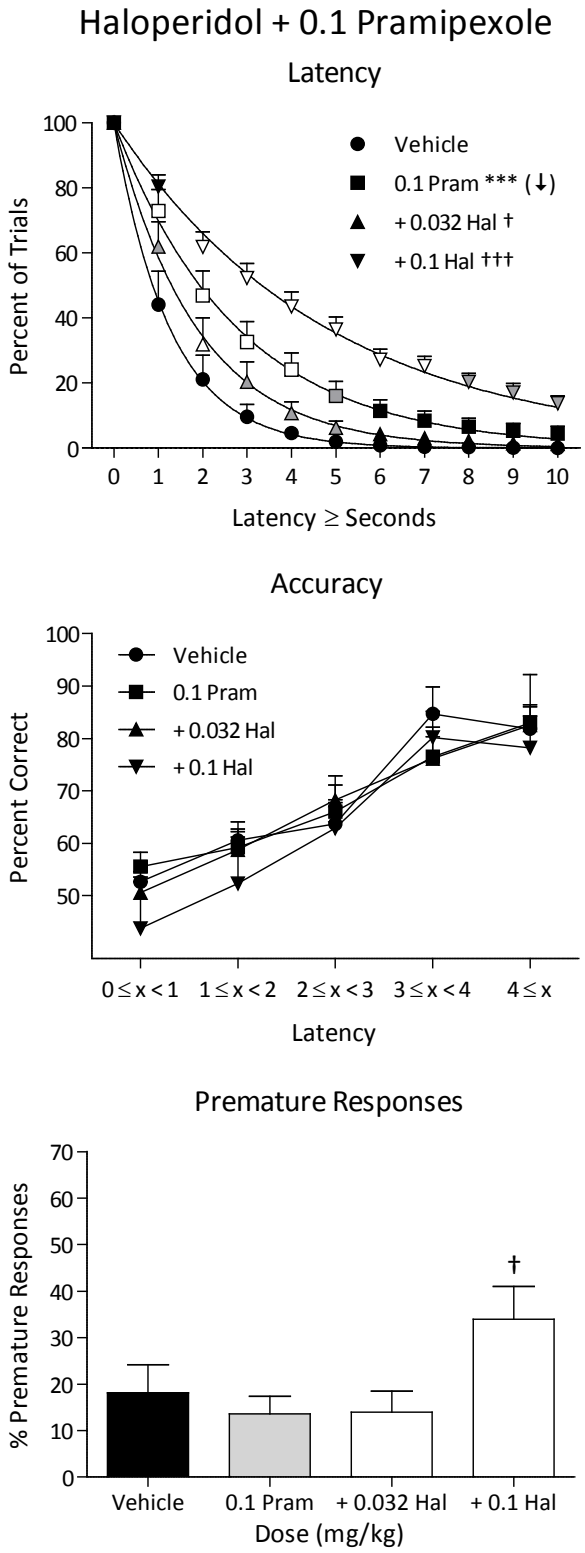

Figure 5-12. Effects of haloperidol pretreatments on the effects of 0.1 mg/kg pramipexole. Top panel: Distribution of latencies to respond as a function of drug dose. Data are presented as percent of total responses meeting or exceeding the delay indicated on the *x* axis after each dose indicated by symbol shape. Asterisks in the legend indicate a significant difference from vehicle (* $p < .05$, ** $p < .01$, *** $p < .001$), while daggers indicate a significant difference from the effects of the agonist alone († $p < .05$, †† $p < .01$, ††† $p < .001$). Shading of individual points in the agonist alone curve indicates a significant difference from the corresponding vehicle point, while shading of the antagonist + agonist points indicates a significant difference from the corresponding agonist alone point (black, n.s.; gray, $p < .05$; white, $p < .001$). Selective effects on latency corresponding to an increase (↑) or decrease (↓) in impulsive preparation, or a disruption in behavior (✕), is also indicated in the legend near the agonist alone condition. Middle panel: Accuracy of responses as a function of latency to respond and drug dose. Asterisks appearing in the legend and symbol shading indicate statistical significance as described above. Bottom panel: Premature responses as a function of drug dose. Asterisks appearing above agonist alone bars indicate a statistically significant difference from vehicle (* $p < .05$, ** $p < .01$, *** $p < .001$), while daggers above antagonist plus agonist bars indicate a statistically significant difference from the agonist alone condition († $p < .05$, †† $p < .01$, ††† $p < .001$). Selective effects on premature responses corresponding to an increase (↑) or decrease (↓) in impulsive action, or a disruption in behavior (✕), is also indicated above the agonist alone bar.

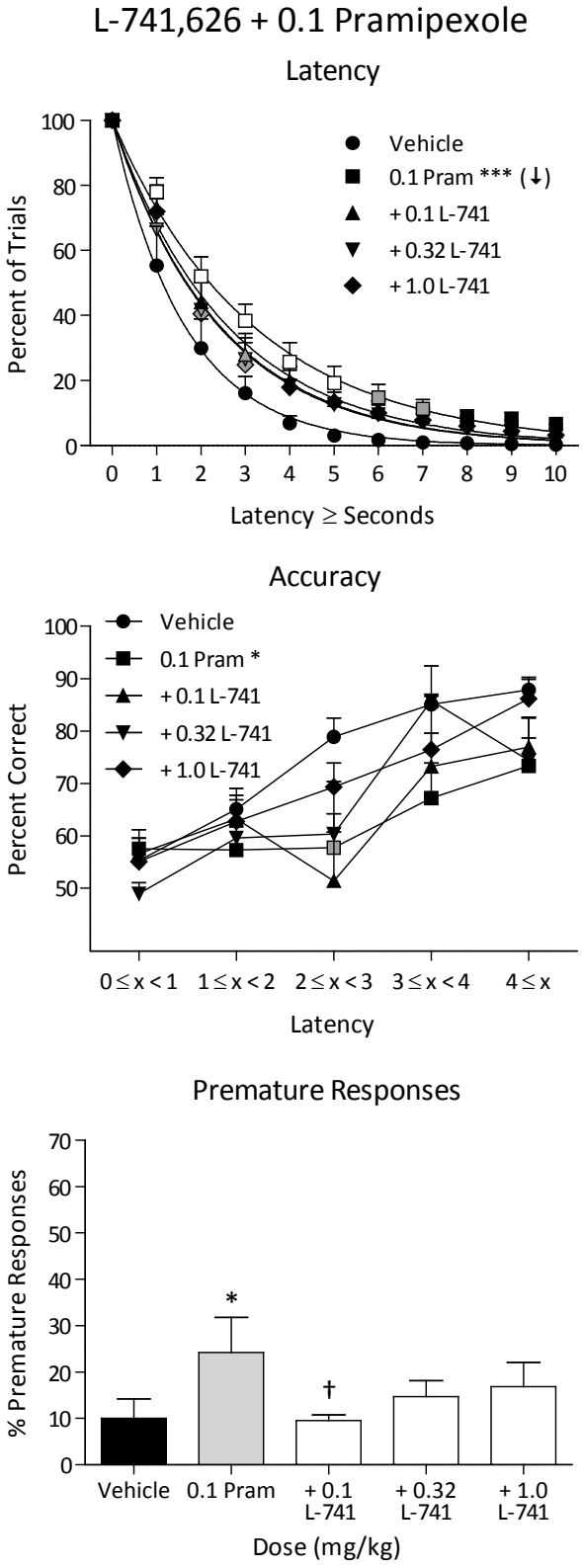

Figure 5-13. Effects of L-741,626 pretreatments on the effects of 0.1 mg/kg pramipexole. All other details as in Figure 5-12.

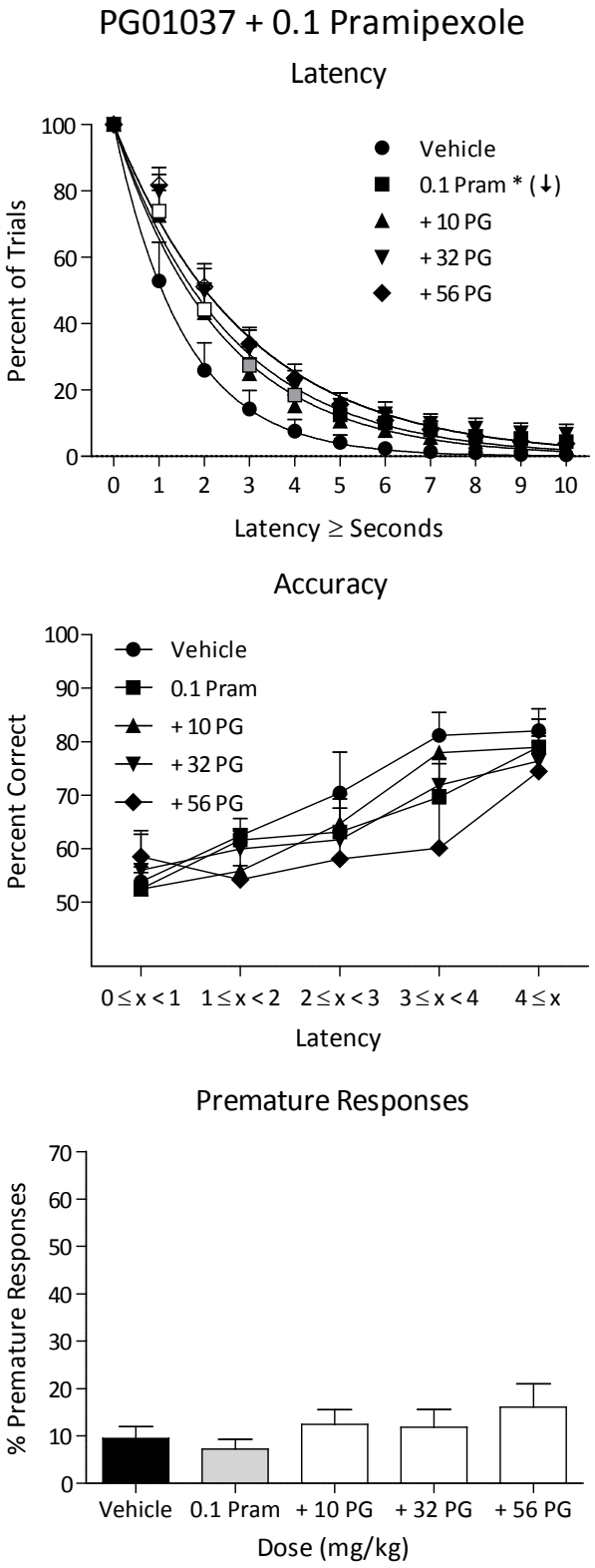

Figure 5-14. Effects of PG01037 pretreatments on the effects of 0.1 mg/kg pramipexole. All other details as in Figure 5-12.

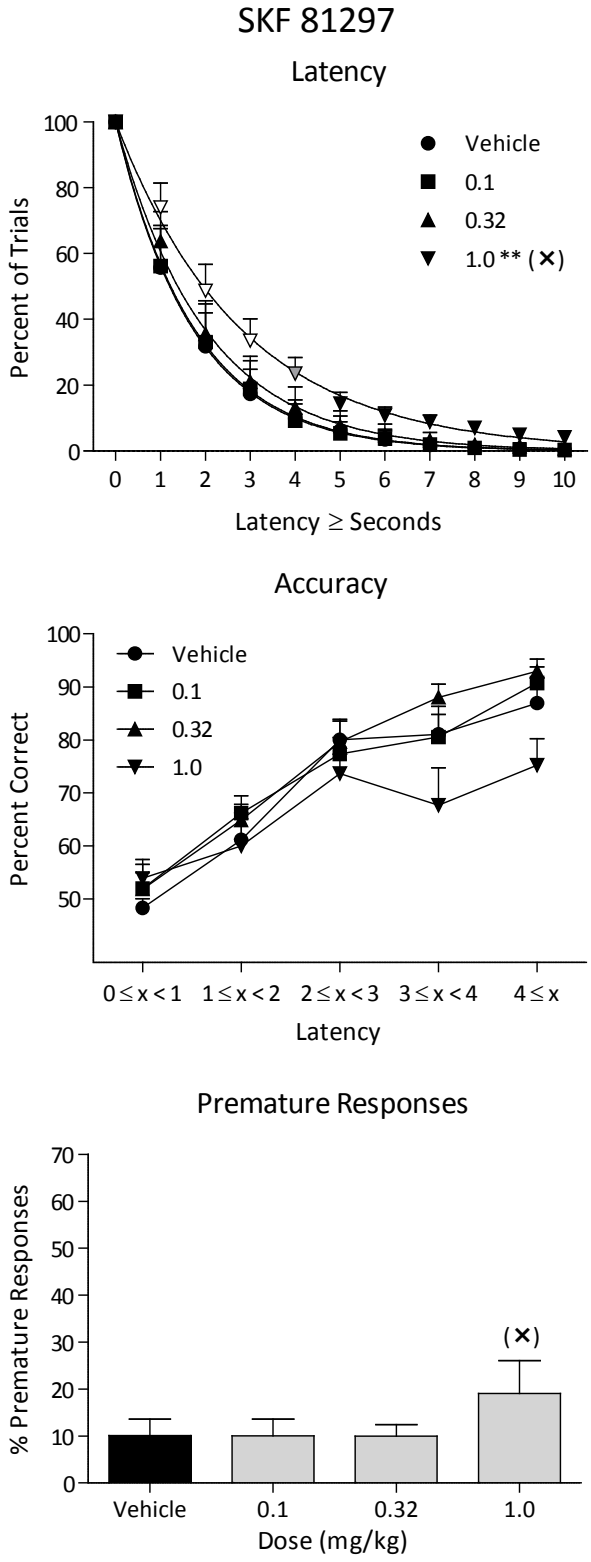

Figure 5-15. Effects of SKF 81297 pretreatments on performance. All other details as in Figure 5-3.

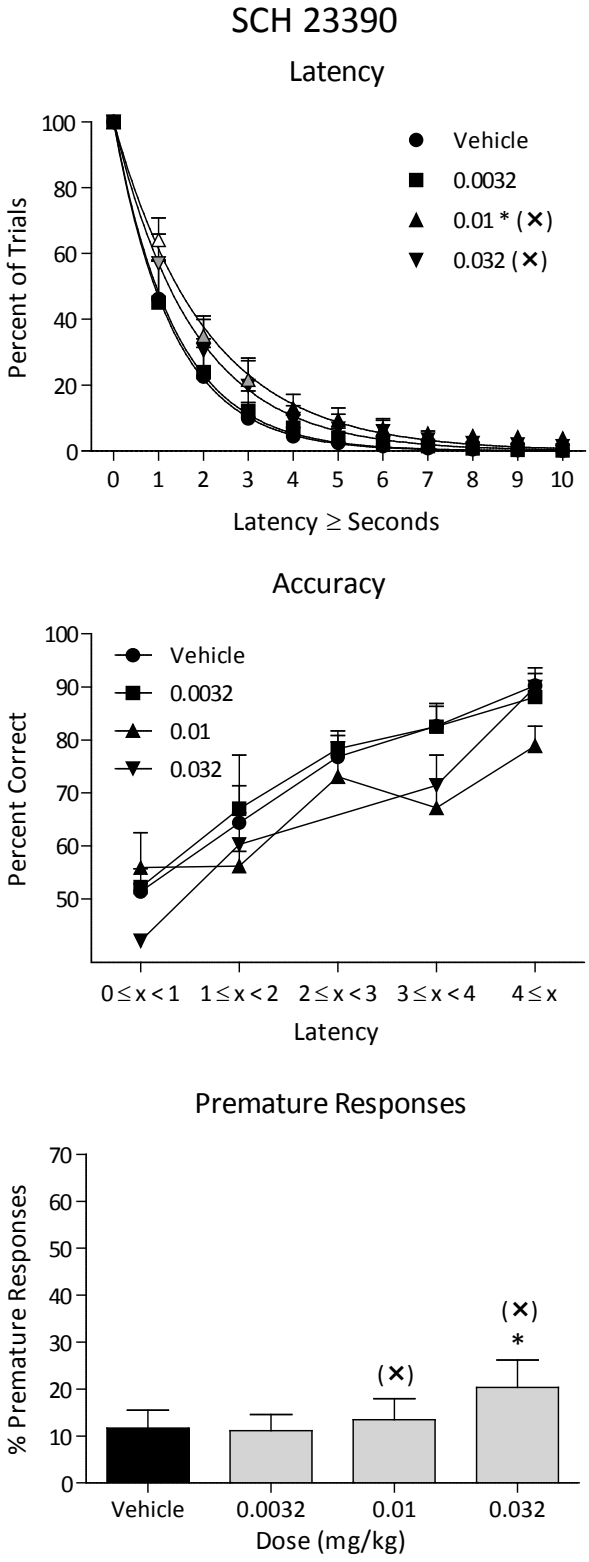

Figure 5-16. Effects of SCH 23390 pretreatments on performance. All other details as in Figure 5-3.

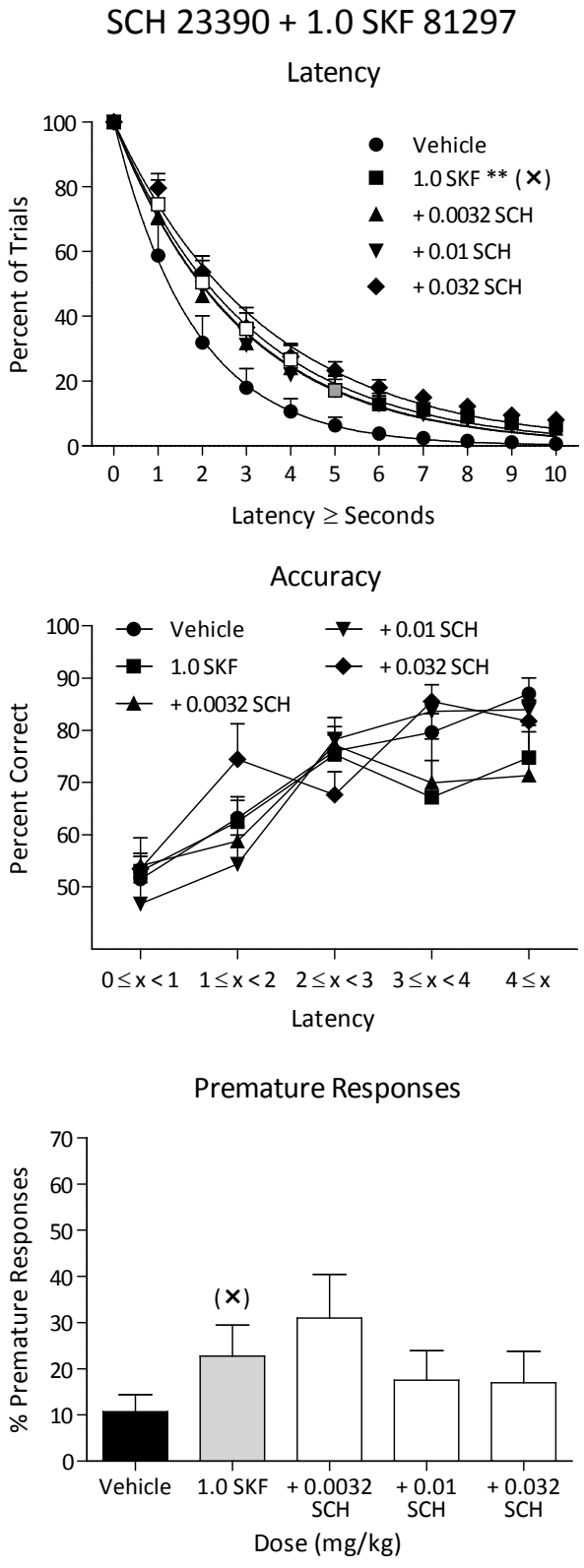

Figure 5-17. Effects of SCH 23390 pretreatments on the effects of 1.0 mg/kg SKF 81297. All other details as in Figure 5-12.

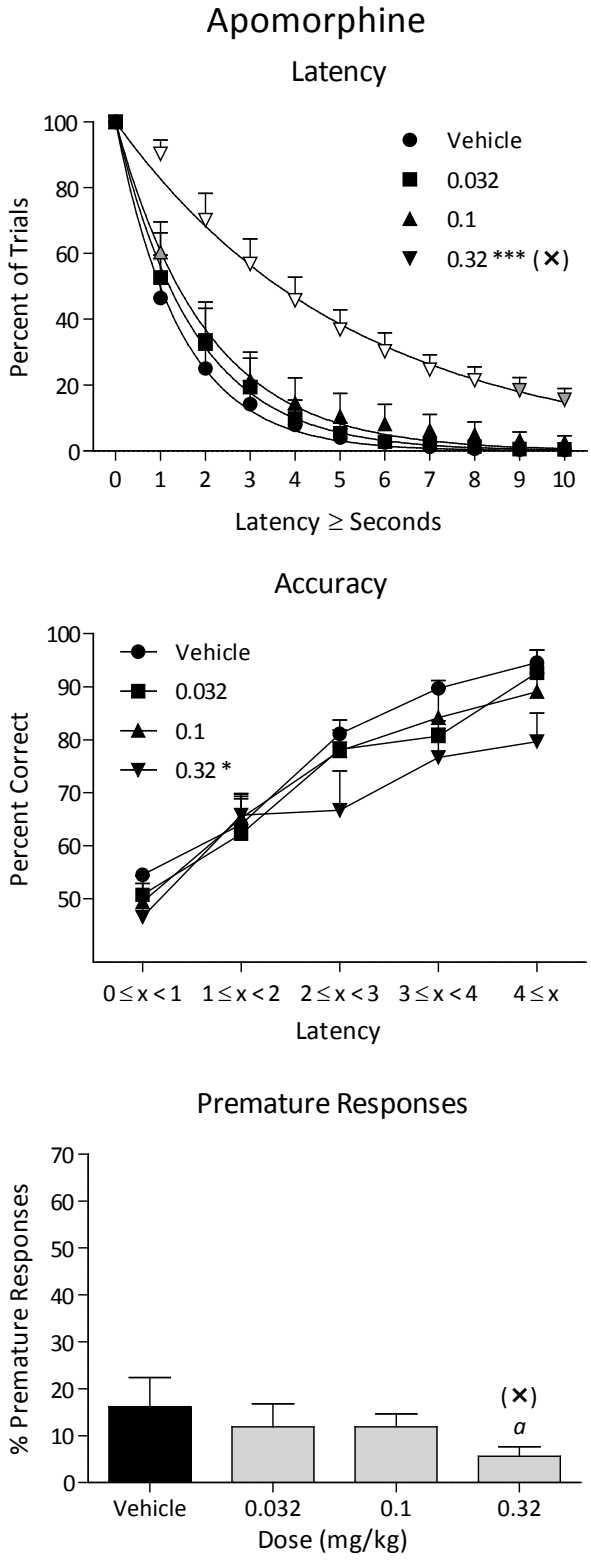

Figure 5-18. Effects of apomorphine pretreatments on performance. All other details as in Figure 5-3.

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CHAPTER 6

ASSESSING INTER-MODEL CONGRUITY OF ANIMAL MODELS OF IMPULSIVE BEHAVIOR: DELAY DISCOUNTING, UNCERTAIN VISUAL DISCRIMINATION, AND PACED FIXED CONSECUTIVE NUMBER SCHEDULES

Impulsivity and self control are constructs used to describe what is increasingly apparent to be more than one class of behaviors. Although as many as 15 subtypes of impulsive behavior patterns have been posited (Gerbing, Ahadi, & Patton, 1987), two or three subtypes have been argued more frequently. Based on operant and neurobiological experiments in humans and animals, a growing consensus largely agrees on two types of impulsive behavior: impulsive choice and what is termed impulsive action or behavioral inhibition (Dalley, Mar, Economidou, & Robbins, 2008; de Wit, 2008; Evenden, 1999a; Perry & Carroll, 2008; Winstanley, Eagle, & Robbins, 2006). Impulsive choice is the tendency to be hypersensitive to delays to reward, while impulsive action refers to the inability to withhold or inhibit a prepotent response. In addition to these two, a third component of impulsivity has been proposed by some. Impulsive preparation or reflection impulsivity, acting before gathering and processing all necessary information, has been argued to encompass impulsive-like responding on a variety of cognitive tasks used in humans and an UVD task in rats (Evenden, 1999a). Lapses in attention which do not necessarily coincide with poor attentional performance overall have also been proposed as a component of impulsivity (de Wit, 2009).

Impulsive choice is typically measured using procedures that provide choice opportunities between a smaller amount of a reinforcer delivered after little or no delay and large amount of the same reinforcer delivered after a longer delay (Ainslie, 1975). Procedures to measure impulsive choice fall into two categories: those that make within-session adjustments the amount of one reinforcer or the delay to one reinforcer based on the subject's behavior (Mazur, 1987; Richards, Mitchell, de Wit, & Seiden, 1997), or those that arrange choices between a predefined set of delays and amounts (Evenden & Ryan, 1996). In both types of procedures, the tendency to choose the smaller, more immediate reinforcer over the larger, delayed reinforcer is interpreted as impulsive choice.

Impulsive action has been modeled using a number of procedures, including but not limited to the go/no-go task, the stop signal reaction time (SSRT) task, the 5-choice serial reaction time (5-CSRT) task, differential reinforcement of low rates (DRL) schedules, and FCN schedules. Performance on each of these tasks required suppressing or withholding a response that is reinforced in another context. The go/no-go task and SSRT task are very similar (for review, see Band & van Boxtel, 1999). Both reinforce responding in the presence of a stimulus, but punish responding if a distinct, second stimulus is present. In the go/no-go task, the second "no-go" stimulus is presented prior to or simultaneously with the "go" stimulus. In the SSRT task, the second "stop signal" is presented briefly after the first stimulus. The 5-CSRT task, originally developed as a model of sustained attention, reinforces responding in the presence of brief visual stimuli (Robbins, 2002). Responses that occur prior to the presentation of these brief stimuli are punished with a timeout, and have been studied as a model of impulsive action. DRL

schedules and FCN are also conceptually similar (for review, see Monterosso & Ainslie, 1999). Responding is reinforced on a DRL schedule based on the time that has elapsed since the previous response. For example, responses are reinforced on a DRL 60-s schedule if a fixed 60-s interval has elapsed since the previous response. On a FCN schedule, responses on a "reinforcement lever" are reinforced based on the number of responses made on a "chain lever" since the previous reinforcement-lever response. For example, a single response on the reinforcement lever is reinforced on a FCN 8 schedule if at least eight responses have been recorded on the chain lever prior to the reinforcement-lever response. Responses made prior to the time interval on a DRL schedule, or prior to the response requirement on a FCN schedule, are punished with a timeout and interpreted as impulsive action. Evenden (1998) developed a variant of this task, dubbed a paced FCN schedule, that controls for the rate-increasing or rate-decreasing effects many drugs have on schedule-maintained behavior. By withdrawing the levers after every response and reinserting them into the chamber after a specified interval, the maximum response rate can be controlled.

Subtypes of impulsivity other than impulsive choice and impulsive action have been proposed. Impulsive preparation, or acting before obtaining and processing all necessary environmental stimuli, has been proposed as a component of impulsive behavior (Evenden, 1999a). The UVD task mentioned above is an interesting model of impulsivity in rats, as behavior on this task may include components of impulsive action and impulsive preparation (Dalley et al., 2008; Evenden, 1999b). In a two-lever operant chamber, responses on one lever are reinforced while responses on the other lever are punished with a timeout. The reinforced lever is determined randomly at the beginning of

each trial, and visual stimuli that probabilistically correlate with the correct lever are illuminated above the levers. The probability that the stimuli are correct increases as the trial progresses, such that withholding a response for a few seconds greatly increases the likelihood of a correct response. This behavior pattern is hypothesized to model cognitive tasks such as the Matching Familiar Figures Test and the Tower of London, which have been used to study impulsivity in humans (Evenden, 1999a). Responses made prior to the illumination of the uncertain stimuli, or premature responses, on this task are also punished with a timeout similar to premature responses on the 5-CSRT task. Therefore, the UVD task provides two distinct measures of impulsivity within a single session.

While tasks used to model impulsive behavior in the laboratory are typically grouped into categories such as these, little is known about the relationship among the dependent measures on these tasks. If tasks that measure impulsive choice are distinct from those that measure impulsive action or impulsive preparation, then one would expect choices on a DD task, for example, to be uncorrelated with premature responses on the UVD task. One would also expect premature responses on the UVD task and chain length on a FCN schedule, for example, to correlate as these tasks are both hypothesized to measure impulsive action. Finally, one would expect that a manipulation that alters performance on one task, such as administration of a psychoactive drug, to affect performance similarly on models within a subtype. Relationships such as these have received little attention in the animal literature. There are numerous examples of the same drug or environmental or neural manipulation assessed on separate tasks, but to the author's knowledge, no reports exist relating these effects in individual subjects trained to respond on multiple tasks. A single report compared within-subject baseline performance

of rats trained to respond on multiple models of impulsive behavior (Delly-Hagedorn, 2006). Comparing performance within-subject on the DD task, a FCN 8 schedule, and a multiple fixed-interval extinction (mult FI EXT) schedule (thought to be a model of hyperactivity, for review see Sagvolden, Russel, Aase, Johansen, & Fishbaf, 2005), general activity was found to correlate across tasks. Impulsive choice on the DD did not correlate with impulsive action on the FCN 8 schedule or hyperactivity on the mult FI EXT schedule, but impulsive action on the FCN 8 schedule did correlate with hyperactivity in the extinction component of the mult FI EXT schedule. No environmental or pharmacological manipulations were assessed on these tasks.

The current experiments were designed to assess the underlying similarities and differences among the dependent measures of three purported models of impulsivity. Rats were trained on either the DD task, a paced FCN schedule, or the UVD task and drug effects were examined (for a complete account of drug effects, see Chapter 3, Chapter 4, and Chapter 5). Rats were then retrained on a different task, and selected drug effects were redetermined. Assuming that behavior maintained on tasks that measure the same underlying process will correlate and react similarly to pharmacological challenges, data were used to assess two questions: 1. Do individual differences in baseline performance correlate across the dependent measures of these tasks? 2. Do individual differences in changes in performance after drug administration correlate across the dependent measures of these tasks?

Method

Subjects

Twenty-four male Sprague Dawley rats served as subjects (Harlan, Indianapolis, IN). Rats were approximately 10 weeks old at the start of the experiment. A food restriction protocol was in place to maintain the rats at approximately 325 g throughout the experiment. This weight was chosen as it is approximately 85% of the mean adult weight supplied by the manufacturer for this strain, and this weight was not changed once established. When not in session, rats were housed in accordance with institutional animal care and use guidelines in polycarbonate cages with fresh water continuously available. The lights in the housing colony were on from 7:00 AM to 7:00 PM, and sessions were conducted between 8:00 AM and 6:30 PM. These protocols were approved by the University of Michigan Committee on the Use and Care of Animals and conformed to the guidelines established by the NIH Guide for the Use of Laboratory Animals.

Apparatus

Sessions were conducted in two sets of similarly equipped rodent operant conditioning chambers with an area of 30.5 cm x 24.1 cm x 21.0 cm and stainless steel grid floors (ENV-008; Med-Associates Inc., St. Albans, VT). Both sides of the front panel of the chamber held a retractable lever (E23-17, Coulbourn Instruments, Whitehall, PA or ENV-112CM, Med-Associates, Inc.). Between the levers was a food tray connected to a 45 mg pellet dispenser (ENV-200R1AM and ENV-203M-45, Med-Associates, Inc.). Above both of the levers and the food tray were triple stimulus lights containing a red, green, and yellow LED (ENV-222M, Med-Associates, Inc.). A houselight was located near the top of the opposite wall to provide illumination to the chamber (ENV-215M, Med-Associates, Inc.). The chambers used in the second phase of

the experiment also contained a nose-poke hole on the back wall which was not used (ENV-114BM, Med-Associates, Inc.). Chambers were connected to a computer running Med-PC IV software (Med-Associates, Inc.) to control experimental events and record data.

Procedure

A schematic of the procedure is displayed in Figure 6-1, and was split into five phases (A-E). After response training, each rat was trained to respond on two of the three tasks chosen in a counterbalanced order, with the same five drug tests performed on each task so baseline performance and drug effects could be compared across task within subject.

Response training (Phase A). All rats were exposed to a common magazine- and lever-training procedure. Rats were trained to respond on a mixed fixed-time 60 s FR 1 schedule of reinforcement, with the active lever alternating each session between the left and right levers. This schedule arranged one sucrose pellet to be delivered every 60 s independent of behavior, with every lever press also producing a pellet. This was continued for four sessions, at which point the schedule was switched to a FR 1 with no response-independent pellet deliveries. Rats were allowed to respond on this schedule until 80 responses or more were recorded on two consecutive 20-min sessions.

Delay discounting (Phase B). The sessions were then extended to 75 min and split into five components of ten discrete-choice trials each. Total trial duration was 90 s and began with one or both levers extending into the chamber. If a single response was made within 20 s, the levers retracted and the consequence programmed for that lever was delivered. If no response was made within 20 s, that trial was recorded as an omission

and the levers retracted for the remaining 70 s of that trial. The first two trials of each component were always forced-choice trials where only one lever was extended into the chamber, forcing the subject to sample the contingencies for that component. The remaining eight trials were free-choice trials where both levers were extended into the chamber, allowing the rat to respond on either. The three stimulus lights above each lever were lit whenever that lever was inserted in the chamber, and the stimulus lights above the pellet tray were lit during sucrose pellet deliveries. Initially, the consequences for both levers were immediate deliveries of either one or three 45-mg sucrose pellets, with the side associated with each amount counterbalanced across subjects. This condition was continued until rats chose the three-pellet option on at least 85% of free-choice trials. The three-pellet and one-pellet levers were then switched two times, with each new lever assignments in place until rats responded on the three-pellet option on at least 85% of trials. When this training regimen was completed, delays were introduced between responses made on the three-pellet lever and the delivery of the three pellets. The delays to the three-pellet option were 0, 10, 20, 40, or 60 s and were always presented in ascending order with one delay in effect in each of the five 10-trial components.

Uncertain visual discrimination (Phase B). Rats were trained to discriminate visual stimuli presented above the levers. In a series of discrete trials, the three stimulus lights above one of the levers were lit and both levers were extended into the chamber. The location of the lights was determined randomly at the start of each trial. A response to the lever below the illuminated stimulus lights was recorded as a correct response and led to both levers retracting, a 45-mg sucrose pellet delivery, and a 5-s timeout period. Responses to the lever with no stimulus lights was recorded as an incorrect response and

resulted in lever retraction and the timeout only. If no response occurred within a limited hold of 30 s, an omission was recorded, the levers were retracted, and a 5-s timeout occurred. After four sessions, a pre-stimulus lever insertion duration was added such that the levers were inserted into the chamber 1 s before the randomly-determined stimulus light was illuminated. Responses made before the stimulus presentation, regardless of lever, led to the levers retracting and a 5-s timeout. Over a number of sessions, the duration that the levers were inserted into the chamber before a stimulus was lit was extended to 8 s. Rats were allowed to respond with these contingencies until at least 85% of responses made after stimulus illumination were on the lever under the stimulus light.

The test procedure was similar to the final training procedure, with the exception that the stimuli did not predict the correct lever with a probability of 1.0. Once each trial began, 8 s after the levers were inserted into the chamber, a series of 0.2-s cycles began with the stimulus location during each cycle determined on a probabilistic basis. During the first cycle, any of the three stimulus lights ("correct," the light above the lever with the active FR 1 schedule; "incorrect," the light above the other lever; or "irrelevant," the light above the food cup that did not differentially signal food availability) had an equal probability of being illuminated. With each subsequent cycle (n), the probability that the "correct" light was illuminated increased such that the correct probability (p_c) was

$$p_c = \frac{2+n}{8+n} \tag{6-1}$$

and the probability that the incorrect or irrelevant stimulus was illuminated (p_i) was

$$p_i = \frac{1-\frac{2+n}{8+n}}{2}. \tag{6-2}$$

When $n = 1$, both Equation 6-1 and Equation 6-2 equal $.\overline{3}$ and the probability that each of the three stimuli being lit was the same. The probability that the lit stimulus was

above the correct lever increased to approximately .8 after 4 s elapsed ($n = 21$). A response on the correct lever at any point after stimuli were lit was reinforced with a food pellet, while a response on the other lever led to the 5-s timeout period. Sessions ended after 60 min or 144 trials, whichever occurred first.

Paced fixed consecutive number schedule (Phase B). Paced FCN schedule training began with the subjects placed in the operant chambers and both levers extended. Left and right levers were randomly assigned to each subject as either the "chain lever" or the "sucrose lever", and these assignments did not change over the course of the experiment. The FCN contingency reinforced responding on the chain lever a number of times equal to or greater than the FCN schedule value followed by a single response on the sucrose lever. Training started with an FCN 1 schedule, where one or more responses on the chain lever followed by one response on the sucrose lever resulted in a 45-mg sucrose pellet delivery and both levers being retracted for 5 s. After each response, both levers were retracted and reinserted such that the maximum response rate was controlled, but with no minimum response rate, as described in detail by Evenden (1998b). Sessions were also split into five components, separated by 1-min blocks with the houselight off and the levers retracted. Components 1, 3, and 5 were 10 min in duration with a pacing interval of 2.5 s, and components 2 and 4 were 20 min in duration with a pacing interval of 5.0 s. The FCN schedule value was then gradually increased over a number of sessions to FCN 8, where eight or more responses on the chain lever were required before one response on the sucrose lever was reinforced with a food pellet. At each FCN schedule value, more responses than required on the chain lever before switching to the sucrose

were reinforced with a sucrose pellet, but fewer responses than required led to both levers being retracted for 5 s and no sucrose pellet delivery.

Drug Testing (Phase C). Drug testing began in each group after no increasing or decreasing trend in performance was apparent over a period of five sessions. Sessions were generally conducted five days per week with vehicle injections administered on the first and fourth days of the week, drugs administered on the second and fifth days, and no injections given on the third day. Vehicle injections always matched the schedules drug injections for the following day in number, substance, and time relative to the experimental session. Each session contained a vehicle or drug injection five minutes before the start of the session with the rat then immediately placed in the darkened experimental chamber. Pramipexole, *d*-amphetamine, SKF 81297, and SCH 23390 were administered at this 5-min pretreatment point, while PG01037 or its vehicle was administered 30 min before session start. When an injection was administered 30 min before session start, the rat was placed back in his home cage for the intervening 25 min before the second vehicle injection was given. SCH 23390 injections were immediately followed by a second saline injection before the rat was placed in the chamber. These rats were the same included in reports detailing the effects of various dopamine agonists and antagonists on these behavioral tasks. Those results are reported elsewhere (Chapter 3, Chapter 4, and Chapter 5).

Task reassignment (Phase D). After drug effects were determined as described above, all subjects were reassigned to another task. Four rats from each task were reassigned to each of the other two tasks (see Figure 6-1). This reassignment was not random; instead attempts were made to equalize the distribution of rats in each task based

on baseline performance. For example, of the eight DD rats, four were assigned to the UVD task and four were assigned to the paced FCN task. Rats were reassigned such that the effect of delay on choices of the delayed, three-pellet lever were roughly equal in the two sets of four rats, both in range and mean effect size of delay. Similar considerations were made when reassigning the UVD rats and paced FCN rats. Attempts were made to equalize range and mean response latency and premature responses in the UVD rats and mean chain lengths in the paced FCN rats. Once rats were reassigned, they went through an abbreviated training regimen as described above. They were first placed on the original response training schedule for five days, with responses reinforced on an FR 1 schedule on either the left or right lever on alternating days. This was followed by training on the second task, as described above.

Drug Testing (Phase E). After final schedule criteria were met and no increasing or decreasing trend in performance was noted on each of the tasks, the five drug tests and associated vehicles were readministered as described above. One subject died prior to Phase E (Figure 6-1).

Drugs

Pramipexole was generously provided by Drs. Jianyong Chen and Shaomeng Wang (University of Michigan, Ann Arbor, MI) and PG01037 by Drs. Amy H. Newman (Medicinal Chemistry Section – National Institute on Drug Abuse, Baltimore, MD) and Peter Grundt (University of Minnesota – Duluth, Duluth, MN). SKF 81297 and SCH 23390 were obtained from Sigma-Aldrich (St. Louis, MO) and *d*-amphetamine was obtained by the National Institute on Drug Abuse (Bethesda, MD). All drugs were dissolved in sterile saline except PG01037 which was dissolved in 20% β-cyclodextrin.

All drugs were administered subcutaneously in a volume of 1.0 ml/kg except 56 mg/kg PG01037 which was administered in of volume of 1.75 ml/kg due to solubility limits.

Data Analysis

On each task, two or three measures were selected to characterize performance on that task. Performance was measured in the absence of any drug administrations for five consecutive sessions. For the DD task, the percent choice of the three pellet option was plotted as a function of the delay to that option. A linear regression line was drawn through those data with GraphPad Prism 5 (La Jolla, CA), and the slope and y-intercept of that line was recorded. The latency to respond after levers were inserted into the chamber was selected as an additional measure of interest for this task. For the UVD task, the average latency to respond after illumination of the uncertain stimuli was selected as the first measure. Premature responses, those responses recorded before the illumination of any stimuli, was the second measure of interest. For the paced FCN schedule, three measures were selected. The first two were derived measures obtained by first plotting chain length data as survival plots, or the percent of chains of at least *X* responses. Summarized in this manner, data were well-approximated by the sigmoidal equation

$$Y = \frac{100}{1+10^{(C_{50}-X)*S}} \quad (6\text{-}3)$$

where *Y* is the percent chains meeting *X* or more responses and C_{50} and *S* are derived parameters, C_{50} indicating the chain length that 50% of chains met or exceeded, and *S* indicating the slope of the curve at point C_{50}. The value of C_{50} was computed for the short and long pacing-interval components separately, and these values were two of the measures used to characterize this task. The third measure was perseverative sucrose-

lever responses, defined as the percent of sucrose-lever responses occurring with no chain-lever responses preceding them.

Each of these measures of interest was then compared within tasks (e.g., UVD latency and UVD premature responses) and between tasks (e.g., UVD latency and paced FCN perseverative responses). Baseline measures obtained in the absence of any drug over a period of five sessions were compared with a Pearson product-moment correlation in Systat SigmaStat 3.5 (San Jose, CA). Changes in performance after drug administrations (change in performance = performance on test session – performance on corresponding vehicle session) were also compared across tasks with Pearson correlations.

Results

The results of all correlations are shown in Table 6-1. Baseline performance was significantly correlated within a task in only one instance. Perseverative responses on the paced FCN schedule was negatively correlated with the derived C_{50} parameter from Equation 6-3 in the long components (r = -.845, n = 16, p < .001). However, examination of the associated scatter plot of this correlation (not shown) revealed a single outlier that was responsible for this apparent correlation. The C_{50} in the long component for one subject was 4.03 (range for the rest of the group was 8.86 to 13.03) and the percent perseverative responses for this same subject was 24.0 (range for the rest of the group was 1.0 to 7.5). With this outlier removed, no relationship existed between these variables (r = -.039, n = 15, p = .892). The C_{50} parameter did not correlate between the long and short component, nor baseline levels of C_{50} during the short components correlate amount of perseverative responses. On the DD task, the slope of a best-fit curve

fit to the individual rats' choice data, the y-intercept of this line, and the average latency to respond did not correlate. On the UVD task, no significant correlation was found between premature response and response latency.

When the selected dependent measures were compared across tasks, a significant positive correlation was found between latency to respond on the UVD task and latency to respond on the DD task (r = .823, n = 8, p = .012). All other pairs of variables across tasks were not significantly correlated (see Table 6-1).

Changes in performance after administration of five drugs known to affect performance on these tasks in varied ways (1.0 mg/kg *d*-amphetamine, 0.1 mg/kg pramipexole, 56 mg/kg PG01037, 1.0 mg/kg SKF 81297, and 0.01 mg/kg SCH 23390) were compared within and across tasks (Table 6-1, shaded portion). Within the DD task, a negative correlation was found between the slope and y-intercept of the regression lines fit through the choice data (r = -.665, n = 72, p < .001), meaning when a drug increased the slope of the discounting line it also tended to decrease the y-intercept of that line in the same subject, and vice-versa. Within the paced FCN task, changes in each of the three measures after drug administrations were associated with a change in the other two. A positive correlation was found between drug effects on the derived C_{50} parameter from Equation 6-3 in the long and short components (r = .660, n = 56, p < .001), indicating that these drugs typically affected performance in each component similarly. In addition, perseverative responses was negatively correlated with the derived C_{50} parameter in both the short (r = -.300, n = 71, p = .011) and long (r = -.438, n = 56, p < .001) components. Drug administrations that increased perseverative responses also tended to decrease chain lengths in both components.

Comparing the effects of the chosen drugs between tasks, only one set of variables was significantly correlated. Just as with baseline performance correlations, changes in latency to respond on the UVD task after drug administrations were positively correlated with changes in latency to respond on the DD task ($r = .458$, $n = 37$, $p < .001$). Drug administrations tended to increase or decrease latency to respond on both tasks similarly within a given subject.

Discussion

Subjects learned the contingencies of each of the three tasks both in the original training, and retraining to a second task. This experiment represents the first assessment of psychoactive drugs on multiple rodent impulsivity tasks on a within-subject basis.

Latency to respond on the UVD task and DD task were correlated at baseline, and drug effects on these measures were also correlated. This suggests the same underlying processes control these behaviors. Latency on both tasks represents time since the presentation of response levers and visual stimuli together (DD) or visual stimuli alone with levers already extended for 8 s (UVD). That this measure is correlated within subjects at baseline and after drug administration is not surprising, but raises interpretation questions about the UVD task. Latency on the UVD task has been hypothesized to measure impulsive preparation, or acting with incomplete information (Evenden, 1999a). In this regard, the UVD task has face validity. Since the visual stimuli are presented probabilistically, with the probability of correctly predicting reinforcer location increasing as trial duration increases, waiting on this task could be construed as processing or gathering information conveyed by the discriminative stimuli. The DD task, however, has no such features. Stimuli and levers are presented simultaneously and

signal the consequences of each choice option with the same probability (1.0) on each trial. Since latency to respond was highly correlated on both tasks, it is likely that latency on the UVD task is measuring a similar behavioral trait as latency on the DD task. The selected drugs also affected latency similarly on both tasks, indicating that these drug effects on the UVD task had little to do with enhancing propensity to gather information and prepare for a response. Instead, it seems likely that the drugs were affecting reaction time to discriminative stimuli in both tasks, and likely governed by similar processes as those in simple reaction time experiments.

On the DD task, the slope and y-intercept of the best-fit regression lines fit through the choice data were not correlated significantly at baseline, but drug effects on these two measures were negatively correlated. A decrease in slope of the discounting curve is typically interpreted as a decrease in impulsive choice, but if this is also accompanied by a decrease in y-intercept, it is typically interpreted as a failure to discriminate amount through loss of stimulus control or similar mechanism (Acheson et al., 2006; Pitts & Febbo, 2004; note that since slopes were negative as plotted, a "reduction" in slope is an increase in absolute value, leading to a negative correlation for the described scenario). For the doses of drugs tested, this was the normal occurrence, as there was a robust negative correlation between these measures.

On the paced FCN schedule, drug-induced changes in chain lengths were positively correlated in the short and long components, and drug-induced changes in perseverative responses were also correlated with chain lengths in both components. It is not surprising that changes in chain lengths were correlated between components, as the only difference between short and long components was the pacing interval that

controlled maximum response rate. That perseverative responses, or proportion of sucrose-lever responses not preceded by a chain lever response, were negatively correlated with chain lengths may be a function of how these responses were operationally defined. Perseverative responses could be conceptualized as chains of zero responses in length, or chains not preceded by a chain-lever response. Thought of in this way, it is not surprising that drugs that tended to reduced chain lengths overall also increased the proportion of the shortest chain length possible, zero responses.

One set of correlations that is absent from these results is notable. There were no significant correlations between chain lengths in either component on the paced FCN schedule and premature responses on the UVD task, nor did the selected drugs affect these measures similarly. Premature responses and chain length are both purported measures of "impulsive action" (Dalley et al., 2008; Evenden, 1999a). That individual rats do not respond similarly on these two measures, nor react similarly with respect to these measures after drug challenges, raises doubt that these are simply two manifestations of the same behavioral construct. Group-level data also show differences between these tasks. The spontaneously hypertensive rat (SHR), selective bred from Wistar Kyoto (WKY) rats, is a much-studied rodent model of attention-deficit/hyperactivity disorder (for review see Sagvolden et al., 2005). On the 5-CSRT task, SHR emit the same number of premature responses as WKY rats (De Bruin, Kiliaan, De Wilde, & Broersen, 2003; van den Bergh, Bloemarts, Chan, Groenink, Olivier, & Oosting, 2006), but have shorter chain lengths on a paced FCN schedule (Evenden & Myerson, 1999). Drug effects on a group level also occasionally correlated between premature responses on the UVD task and chain length on the paced FCN

schedule (e.g., *d*-amphetamine, see Cole & Robbins, 1987, Evenden, 1998; Chapter 4, Chapter 5), but other times a discordance is found (e.g., pramipexole, see Chapter 4 and Chapter 5).

Impulsivity is often described as a multidimensional trait, and dependent measures on behavioral models of impulsivity are often assigned to one of these trait subtypes. The present experiment represents one attempt at determining whether these model assignments are valid. Many of the dependent measures on the DD, UVD, and paced FCN models of impulsivity did not correlate, as theory predicts. However, the correlation between response latency on the UVD and DD tasks brings into question the validity of the UVD task as a model of impulsive preparation. In addition, the lack of correlation between baseline measures and drug effects on premature responses on the UVD task and chain length on the paced FCN brings into question the grouping of both these measures as impulsive action.

Table 6-1. Pearson *r* correlations between measures of interest and the number of data points included in each correlation. Numbers in the unshaded, upper-right portion of the table represent correlations between baseline performance for each measure of interest, computed over five days of responding in the absence of any injections. Numbers in the shaded, lower-left portion of the table represent correlations between drug effects on performance for each measure.

	DD			UVD		Paced FCN		
	Latency	Slope	Y-int	Latency	Prem.	Short C_{50}	Long C_{50}	Persev. Resp.
DD								
Lat.		-.394 (n = 16)	.077 (n = 16)	.823* (n = 8)	-.571 (n = 8)	.188 (n = 8)	.122 (n = 8)	-.156 (n = 8)
Slope	.106 (n = 72)		-.330 (n = 16)	-.506 (n = 8)	.282 (n = 8)	-.197 (n = 8)	-.132 (n = 8)	.212 (n = 8)
Y-int.	-.145 (n = 72)	-.665** (n = 72)		.280 (n = 8)	.362 (n = 8)	.337 (n = 8)	-.132 (n = 8)	.177 (n = 8)
UVD								
Lat.	.458** (n = 37)	.093 (n = 37)	-.208 (n = 37)		-.380 (n = 16)	-.045 (n = 8)	-.255 (n = 8)	.138 (n = 8)
Prem. Resp.	-.178 (n = 37)	.137 (n = 37)	-.071 (n = 37)	.125 (n = 79)		-.066 (n = 8)	.451 (n = 8)	.222 (n = 8)
PFCN								
Short C_{50}	-.059 (n = 34)	-.083 (n = 34)	-.081 (n = 34)	.098 (n = 31)	-.064 (n = 31)		.405 (n = 16)	.021 (n = 16)
Long C_{50}	.086 (n = 25)	-.044 (n = 25)	.076 (n = 25)	.092 (n = 26)	.066 (n = 26)	.660** (n = 56)		-.845**[a] (n = 16)
Persev Resp.	-.266 (n = 34)	.093 (n = 34)	-.079 (n = 34)	.213 (n = 31)	.208 (n = 31)	-.300* (n = 71)	-.438** (n = 56)	

* $p < .05$; ** $p < .001$

[a] This correlation was driven by a single outlier that when removed, reduces the correlation from -.845 to a nonsigificant -.039.

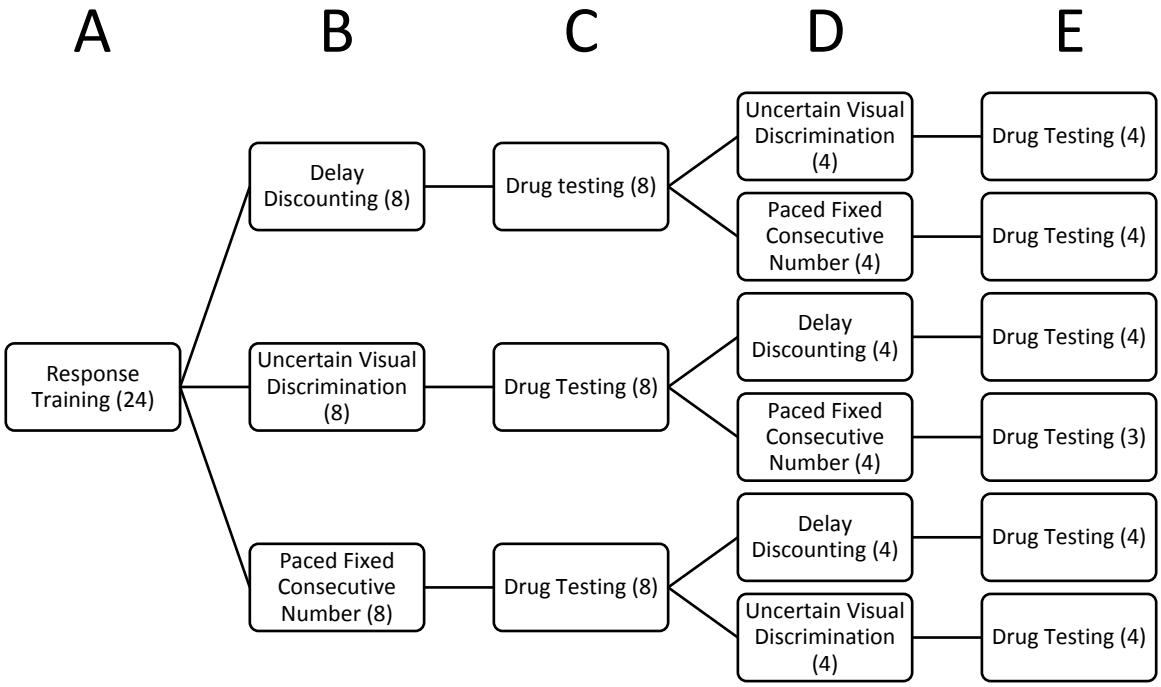

Figure 6-1. Schematic of the experimental procedure and number of rats (*n*) in each subgroup of each Phase. The 24 subjects were split into subgroups at each phase of the experiment as indicated. A: Response and magazine training. B: Training on one of the three impulsivity tasks. C: The drugs listed described in Chapters 3, 4, and 5 were administered. D: The three groups were each split into two groups, each of which was assigned to a new task. This resulted in three counterbalanced groups of rats, each of which experienced two of the three tasks. E: The drugs listed in the Method section were re-administered on the new task.

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CHAPTER 7

CONCLUSIONS

The experiments in the preceding chapters represent steps toward validating three behavioral models of impulsive behavior. In Chapter 2, impulsive choice was found to be associated with demand for self-administered cocaine without being associated with demand for sucrose, a relationship relevant to the increased impulsive choice noted in human substance abusers. In the next three chapters, the effects of agonists and antagonists selective for specific dopaminergic receptor subtypes were assessed on three purported models of impulsivity. Dopamine $D_{1\text{-like}}$ antagonism and D_4 agonism were found to have similar effects on impulsive choice in Chapter 3. In Chapter 4, D_2 and D_3 receptors appeared to be important, with selective decreases in impulsive action with administration of either a D_2 agonist or D_3 antagonist. Agonists or antagonists at $D_{1\text{-like}}$, D_2, or D_3 receptors reduced the purported measure of impulsive preparation in Chapter 5, raising questions about the validity of this result. These concerns were addressed more directly in Chapter 6, which challenged parts of the classification system used to assign models of impulsivity to theoretical categories.

Task Validity

Assessing the validity of the delay discounting (DD) task, paced fixed consecutive number (FCN) schedules, and the uncertain visual discrimination (UVD) task was a goal of the current set of experiments. Three evaluative criteria proposed for the assessment of animal models include face validity, construct validity, and predictive validity (Sagvolden, Russell, Aase, Johansen, & Fashbaf, 2005; Sarter, Hagan, & Dudchenko, 1992). Face validity, or the degree to which a model resembles the associated clinical condition, was not directly assessed in the current experiments. Behavior maintained by the contingencies in each of these models had at least some face validity. On the delay discounting task, choices are made between large, delayed reinforcers and small, immediate reinforcers. Similar choices are made by people every day. We are continuously confronted with choices between an immediate piece of chocolate cheesecake versus delayed, improved health; or between an immediate bout of television-watching versus delayed, better grades that could result from additional studying. The DD task resembles such choices to a large degree. The paced FCN schedule is less-obviously related to impulsive action in people, although similarities exist. Impulsive action, or failure to inhibit a prepotent response, is present in both the clinic and the paced FCN schedule. Rats must respond repeatedly on the chain lever, a response that has never been directly reinforced (except during training), while continuously inhibiting responses on the sucrose lever, a response that is available and has been reinforced repeatedly in the past. Similarly, premature responses on the UVD task require the subject to initially inhibit a response on the levers when they are presented, despite such lever presses being reinforced many times previously. Response latency on the UVD task

also has face validity with respect to impulsive preparation in people. To respond optimally on this task, subjects must withhold a response for a period of time to observe the sequence of stimulus presentations above the two levers. When a sufficient number of stimulus presentations have been observed to discriminate the correct response location, an accurate response can be emitted. Responses made before a sufficient number of stimulus presentations are observed are faster and less accurate, a pattern that typifies impulsive preparation in people.

A model with predictive validity should be affected by pharmacological and behavioral manipulations in an analogous way as in the clinic, including for previously-unknown manipulations (Sarter et al., 1992). Assessing predictive validity is therefore a two-step process. Potential treatments should be assessed in the behavioral model, and those that show promise need to then be evaluated in the target human population. A number of previously-untested dopaminergic agonists and antagonists were assessed in the current experiments, with some results that warrant future study in either animal- or human-subjects research. Table 7-1 and Table 7-2 detail the effects of these compounds on the purported measures of impulsive behavior in each of the three tasks. In these tables, only those effects of drugs that were considered selective are highlighted. Relatively high doses of drugs often had significant effects on the measure of impulsive behavior on these tasks, but the relevance of these effects are questionable if corresponding behavioral disturbance was noted on a secondary measure. If response latency was significantly increased or if sensitivity to amount was significantly decreased on the DD task, behavior was considered disrupted. Behavior was similarly considered disrupted if total trials completed were significantly reduced on the paced FCN schedule

or if trials omitted were significantly increased on the UVD task. Organizing results in this way allows for an easier assessment of selective effects on the purported measures of impulsivity. The only drug assessed with known efficacy in the clinic was *d*-amphetamine, which is a popular ADHD treatment (Table 7-1). The only model that demonstrated decreased impulsive behavior after administration of *d*-amphetamine was on the impulsive preparation measure of the UVD task. While this lends support to the predictive validity of this measure, the pattern of other results and the correlations with response latency on the DD task (Chapter 6) limit the generalizability of this result. In the DD task, *d*-amphetamine had no selective effect, and it selectively increased impulsive action on the paced FCN schedule and on the UVD task. These results, which do not correspond with the effectiveness of *d*-amphetamine as a treatment for ADHD, raise doubts regarding the predictive validity of these tasks. While others have found reductions in impulsive choice with *d*-amphetamine (Floresco, Tse, & Chods-Sharifi, 2008; van den Bergh, Bloemarts, Groenink, Olivier, & Oosting, 2006; van Gaalen, van Koten, Schoffelmeer, & Vanderschuren, 2006; Wade, de Wit, & Richards, 2000; Winstanley, Theobald, Dalley, & Robbins, 2005; but see Evenden & Ryan, 1996; Helms, Reeves, & Mitchell, 2006; Stanis, Avila, White, & Gulley, 2008; Uslaner & Robinson, 2006), *d*-amphetamine only been shown to increases impulsive action on paced FCN schedules (Evenden, 1998; Evenden & Myerson, 1999) and on the UVD task (Evenden, 1999b).

With these effects with *d*-amphetamine noted, a set of findings with the paced FCN still warrants further attention. The $D_{2\text{-preferring}}$ agonist sumanirole and the $D_{3\text{-preferring}}$ antagonist PG01037 selectively decreased impulsive action at low doses. Conversely,

The $D_{3\text{-preferring}}$ agonist pramipexole and the $D_{2\text{-preferring}}$ antagonist L-741,626 increased impulsive action, also at low doses. These results suggest a D_2/D_3 modulation of impulsive action, with either a D_2 agonist or D_3 antagonist being potential therapeutics. These or related compounds would require assessment in humans with impulse-control disorders to comment further about the relevance of these findings to the predictive validity of the paced FCN schedule.

A model has construct validity if it shares underlying theoretical and neural mechanisms with the clinical condition being modeled. Construct validity was assessed with distinct approaches in each of the three specific aims of the preceding chapters. Substance abuse is defined by the *Diagnostic and statistical manual of mental disorders-IV-TR* (American Psychiatric Association, 2000) as an impulse-control disorder. The demonstration that choices on the DD task are associated with demand for self-administered cocaine injections improves the construct validity of the DD task and drug demand as models of impulsive choice and drug abuse, respectively. Importantly, this relationship was restricted to cocaine demand, with no relationship between choices on the DD task and demand for sucrose. The specificity of the relationship to impulsive choice and cocaine demand, demonstrated by excluding a relationship between impulsive choice and sucrose demand, indicates greater construct validity of these models (Sarter et al., 1992). Aspects of construct validity of the DD task and paced FCN schedule were also demonstrated in Chapter 3 and Chapter 4 with the administration of selective dopamine agonists and antagonists to rats performing on these tasks. Based on neurological experiments in humans and animals, it was predicted that compounds binding to $D_{1\text{-like}}$ and D_4 receptors would be more involved in impulsive choice on the

DD task, and that D_2 and D_3 receptors would be more involved in impulsive action on the paced FCN schedule and UVD task (see Chapter 1). The results with the DD task and the paced FCN schedule match these predictions. The $D_{1\text{-like}}$ antagonist and D_4 partial agonist increased impulsive choices on the DD task, and D_2 and D_3 compounds showed opposing, selective effects on impulsive action on the paced FCN schedule (see Table 7-1 and Table 7-2). Since these findings agree with neurological correlates of impulsive choice and impulsive action, the construct validity of these tasks is improved.

Construct validity of these tasks was also assessed in Chapter 6. The DD task, the paced FCN schedule, and the UVD task have been hypothesized to model the human behavior patterns of impulsive choice, impulsive action, and both impulsive action and preparation, respectively (Evenden, 1999a). This classification system was assessed in Chapter 6 by comparing individual differences in behavior on these tasks, both at baseline and after pharmacological challenges. Discrepancies were found between the theoretical classification system proposed and the results of this experiment, challenging the construct validity of these tasks in some cases and supporting it in others. Most notably, response latency on the UVD task, a purported measure of impulsive preparation, correlated with response latency on the DD task both at baseline and after pharmacological challenges. This suggests the UVD task may not be a measure of impulsive preparation. Also notable was the finding that premature responses on the UVD task were not correlated with chain length on the paced FCN schedule, both purported measures of impulsive action. This finding suggests that either at least one of these measures is not a valid model of impulsivity, or the theoretical construct of impulsive action is not as unified as hypothesized. Finally, choices on the DD task were

not correlated with the other impulsivity measures, supporting the assertion that this represents a distinct subtype of impulsivity.

Subtypes of Impulsivity Revisited

The theoretical classification system proposed by Evenden (1999a) is appealing in that it provides a framework in which the vast majority of tasks used to model impulsivity in both humans and animals can be classified with respect to Skinner's (1953) three-term contingency. Skinner's three-term contingency has been widely successful in describing the interrelationship between behavior and the consequences of behavior, and the stimuli that signal this relationship. Evenden (1999a) envisioned behavior that is abnormal with respect to discriminative stimuli as impulsive preparation, behavior that is abnormal in its execution as impulsive action, and behavior that is abnormal with respect to valuation of consequences as impulsive choice.

The validity of this classification system was directly assessed in Chapter 6. Impulsive choice, as measured by the DD task, was distinct from the measures of impulsive action and impulsive preparation, supporting Evenden's framework. Two purported models of impulsive action were assessed: premature responses on the UVD task and chain length on the paced FCN schedule. These were found to be uncorrelated, both at baseline and after drug administration. This result leads to one of three conclusions regarding Evenden's hypothesis: impulsive action is not a unitary construct and is also composed of multiple subtypes, at least one of these tasks is not a model of impulsive action, or the procedure of Chapter 6 does not provide a valid test of Evenden't hypothesis. While both of these tasks involve a component of behavioral inhibition, they differ in many respects. On the paced FCN schedule, the animal is actively emitting a

behavior almost continuously, and must inhibit a shift in behavior to a second response manipulandum. On the UVD schedule, behavior must be suppressed at the presentation of response manipulana, and withheld until the illumination of visual stimuli. Perhaps the inhibition of behavior in these contexts is sufficiently distinct that subtypes of impulsive action should be proposed. Further experimentation would be required to determine if this is the case. It may also be the case that either the paced FCN schedule or the UVD task is not a valid measure of impulsive action. Direct analogues of these two tasks have not been studied in humans with impulse control disorders known to involve deficits of behavior inhibition. Such an experiment would help determine which of these models is better suited for the study of impulsive action in animals. Finally, it may be that the experiment described in Chapter 6 is not a valid test of these models. While the evidence for dopaminergic pathways in the expression of impulsive behavior is quite extenstive (Chapter 1), the effects of systemically administered dopaminergic ligands may not be adequately or selectively affecting these pathways. Dopamine receptors are distributed throughout the brain, and it is possible that any effects of these compounds on impulsive behavior were overshadowed by behavioral effects mediated through other brain systems. Furthermore, it is possible that both tasks were measuring impulsive action but with differences in sensitivity. Since a small subset of drug doses was assessed in Chapter 6, it might not be expected that similar effects should be observed on both tasks. Significant effects on chain length in the paced FCN schedule were observed at much lower doses of each drug tested than were seen on premature reponses on the UVD task. Perhaps these two tasks are both models of impulsive action, but the paced FCN schedule and UVD

task show changes in impulsive action across different dose ranges, and the limited doses used in Chapter 6 did not find a correlatiosn between these tasks for that reason.

The results of Chapters 5 and 6 suggest the UVD task is not a measure of impulsive preparation. While this suggests that the UVD task requires rethinking, it does not necessarily mean Evenden's (1999a) hypothesis regarding the classification system of impulsive behavior was incorrect with respect to impulsive preparation being a subtype of impulsivity. Impulsive preparation has been studied extensively in people, with convincing evidence supporting this construct as a component of impulsivity (Chapter 1). Attempting to model impulsive preparation in animals was a worthwhile endeavor, and it is the view of this author that it should not be abandoned despite the apparent lack of validity of the UVD task. The UVD task appears to have face validity, so perhaps modifications of this task could improve its predictive and construct validity. As originally designed (Evenden, 1999b; Chapter 5), the UVD task provides response opportunities that, depending on response latency, are reinforced between roughly 50% and 85% of the time. It may be that the difference between these probabilities is not sufficient to influence waiting behavior that is central to the contruct of impulsive preparation. Without such influence, response latencies appear to be similar to other tasks that signal response availability (e.g., the DD task). If the UVD task was modified to increase the advantage of waiting, its validity may be improved. This could be done by ranging the reinforcement percentage from 0% to 85%, for example, to increase the benefit of waiting. In addition, the consequence of incorrect responses could be made more salient by adding a punisher such as mild shock to the timeout that is currently the consequence of incorrect responding.

Future Directions

The prevalence of impulsive behavior both in a normal behavioral repertoire and in many psychological disorders assures that further research on impulsive behavior will be required for quite some time. The results of the experiments described in the preceding chapters suggest some specific follow-up experiments that may prove fruitful.

The experiments described in Chapter 5 and Chapter 6 suggest that the UVD task is not a valid model of impulsive preparation, despite the phenomenon of impulsive preparation being well documented in people (Evenden, 1999a). Developing a model of impulsive preparation that has face, construct, and predictive validity with respect to the human condition would be very useful to the further understanding of this subtype of impulsivity in humans. The UVD task has face validity, but does not seem to measure the behavior pattern intended. Impulsive preparation is studied in people using tasks originally developed to model aspects of executive function. Perhaps impulsive preparation is unique to situations involving complex stimuli and cognitive processes, and would be better-modeled using animals with more complex behavioral repertoires such as non-human primates.

The results of Chapter 2 demonstrate that impulsive choice on the DD task is associated with demand for cocaine, resembling the relationship in people between substance abuse and impulsive choice (see Chapter 1; for review, see Reynolds, 2006). Although less extensively documented, impulsive action and impulsive preparation in people have also been shown to correlate with substance abuse (e.g., Clark, Robbins, Ersche, & Sahakian, 2006; Ersche, Clark, London, Robbins, & Sahakian, 2006; Lane, Moeller, Steinberg, Buzby, & Kosten, 2007; Yakir et al., 2007; but see Li, Milivojevic,

Hong, & Sinha, 2006). Determining whether individual differences in impulsive action or impulsive preparation (should a suitable model be developed) are associated with demand for drugs of abuse would be informative.

A fourth subtype of impulsivity, lapses in attention, has been proposed (de Wit, 2009). Lapses in attention are assessed by measuring the skew of a distribution of reaction times on an attention task. Sustained attention tasks are commonly used in animals (e.g., Robbins, 2002), and adapting one to measure lapses in attention as a model of impulsivity may be quite straightforward, and could be the impetus for important findings.

Occasionally engaging in behavior patterns that appear impulsive is normal, but when these patterns become excessive the results can be devastating. Through rigorously conducted behavioral experiments in animal subjects, it may be possible to discover new treatment mechanisms to assist those with impulse-control disorders interact more effectively with their environment.

Table 7-1. Summary of effects of environmental manipulations, *d*-amphetamine, GBR 12909, apomorphine, SKF 81297, and SCH 23390 on selected measures from Specific Aim 2. Symbols indicate the effects of that dose (s.c.) on the dependent measure indicated. Changes in impulsivity as defined for each task without a corresponding disruption of behavior are indicated with arrows representing an increase (↑) or decrease (↓). Behavior was considered disrupted (×) if there was a reduced choice of the large reinforcer when not delayed (DD Choice), if response latency was increased (DD Choice), if total trials were decreased (PFCN C_{50} Short and Long), or if trials omitted were increased (UVD premature responses and latency). Conditions or doses that had no significant effect (–) or were not tested (·) are also indicated.

	DD Choice	PFCN C_{50} Short	PFCN C_{50} Long	UVD Premature	UVD Latency
Pre-stimulus insertion dur.					
10 s	·	·	·	–	–
12 s	·	·	·	↑	↑
Stimulus certainty					
Stimuli Certain	·	·	·	–	–
d-Amphetamine					
0.032 mg/kg	–	·	·	·	·
0.1 mg/kg	–	–	↑	–	–
0.32 mg/kg	–	↑	↑	–	–
1.0 mg/kg	×	↑	↑	↑	↓
GBR 12909					
1.0 mg/kg	–	↓	↓	–	↓
3.2 mg/kg	–	–	–	–	–
10.0 mg/kg	–	↓	–	–	↓
Apomorphine					
0.032 mg/kg	–	↓	↓	–	–
0.1 mg/kg	–	–	↑	–	–
0.32 mg/kg	×	×	×	×	×
SKF 81297					
0.1 mg/kg	–	↓	–	–	–
0.32 mg/kg	×	↓	–	–	–
1.0 mg/kg	×	↑	↑	×	×
SCH 23390					
0.001 mg/kg	–	–	·	·	·
0.0032 mg/kg	–	–	–	–	–
0.01 mg/kg	↑	×	×	×	×
0.032 mg/kg	×	×	×	×	×

DD = Delay discounting task; PFCN = paced fixed consecutive number schedule; UVD = uncertain visual discrimination task; C_{50} = C_{50} from Equation 4-1.

Table 7-2. Summary of effects drugs acting as agonists (sumanirole, pramipexole, and ABT-724) and antagonists (haloperidol, L-741,626, PG01037, and L-745,870) at $D_{2\text{-like}}$ receptors on selected measures from Specific Aim 2. All details as in Table 7-1.

	DD Choice	PFCN C_{50} Short	PFCN C_{50} Long	UVD Premature	UVD Latency
Sumanirole					
0.032 mg/kg	·	↓	–	–	–
0.56 mg/kg	·	–	×	·	·
1.0 mg/kg	–	×	×	–	↓
3.2 mg/kg	×	·	·	×	×
Pramipexole					
0.01 mg/kg	·	–	↑	·	·
0.032 mg/kg	–	↑	×	–	↓
0.1 mg/kg	–	×	×	–	↓
0.32 mg/kg	×	×	×	×	×
ABT-724					
0.1 mg/kg	·	·	·	–	–
0.32 mg/kg	·	↑	–	–	–
1.0 mg/kg	–	–	–	–	–
3.2 mg/kg	↑	↓	–	–	–
Haloperidol					
0.01 mg/kg	–	↓	–	·	·
0.032 mg/kg	–	↑	↑	–	–
0.1 mg/kg	×	×	×	×	×
L-741,626					
0.32 mg/kg	–	–	–	–	–
1.0 mg/kg	×	–	↑	–	–
3.2 mg/kg	×	×	×	×	×
PG01037					
10 mg/kg	–	–	↓	–	–
32 mg/kg	–	↓	↓	–	↓
56 mg/kg	×	↓	↑	–	↓
L-745,870					
0.32 mg/kg	–	↓	–	–	↓
1.0 mg/kg	–	–	–	–	↓
3.2 mg/kg	–	–	↑	–	–

DD = Delay discounting task; PFCN = paced fixed consecutive number schedule; UVD = uncertain visual discrimination task; C_{50} = C_{50} from Equation 4-1.

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