THE EFFECTS OF CHRONIC COCAINE ON DELAY-DISCOUNTING IN RATS AND THE POTENTIAL ROLE OF THE D2 RECEPTOR

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THE EFFECTS OF CHRONIC COCAINE ON DELAY-DISCOUNTING IN RATS AND THE POTENTIAL ROLE OF THE D2 RECEPTOR

Impulsive behavior is a heterogeneous construct characterized by numerous behaviors involving the inability to delay gratification and acting without forethought (e.g., Evenden & Ryan, 1996). Stimulant medications are commonly used in the treatment of impulse control disorders such as attention deficit hyperactivity disorder (e.g., Chronis, Jones & Raggi, 2006; Pattij & Vanderschuren, 2008), and when administered acutely (or in low doses) decrease impulsive behavior in human and non-human animals. However, when administered chronically (or at higher doses), stimulant drugs can increase impulsive behavior (e.g., Seeman and Madras, 2002; Winstanley, LaPlant, Therobald, Green, Bachtell & Perrotti et al., 2007). One illicit stimulant drug which has been implicated in increasing impulsive behavior in human and non-human animals is cocaine (e.g., Logue, Tobin, Chelonis, Wang, Geary & Schachter., 1992; Coffey, Gudleski, Saladin & Brady, 2003; Paine, Dringenberg & Olmstead, 2003). I investigated the effects chronic cocaine has on impulsive behavior, using a delay-discounting choice task, and the potential role the dopamine (DA) system plays in mediating the effects of cocaine on this behavior. By understanding the ways in which drugs of abuse, such as cocaine, affect impulsive behavior, researchers may gain a better understanding of the relationship between behavior and corresponding pharmacological mechanisms.

Impulsive Behavior

Impulsive behavior has been defined in numerous ways for use in both clinical and laboratory settings. According to the Diagnostic and Statistical Manual (DSM-IV) the American Psychiatric Association (1994) defines impulsiveness as the "failure to resist an impulse, drive or temptation to perform an act that is harmful to the person or to others." Although this definition

is advantageous in aiding professionals in the clinical field to diagnose problem behaviors or instances of mental illness, this definition is not ideally suited to test impulsive behavior in a laboratory setting for two main reasons. One reason is that it lacks an operational definition needed for laboratory testing. A second reason is that this definition fails to distinguish between impulsive and aggressive acts (Ho, Mobini, Chiang, Bradshaw & Szabadi, 1999). Furthermore, this definition implies that impulsive behavior is "negative" or "sub-optimal," but this cannot be said for all acts of impulsive behavior. Take, for example, an animal foraging for food in the wild. The animal may encounter a situation that will provide a small amount of food immediately. However, if the animal waits and continues to forage, it may find a larger amount of food; of course, it may also find no food and starve. The act of choosing the smaller reinforcer over a potentially larger reinforcer is *one type* of impulsive behavior. For most animals in the wild, it may be optimal to eat when they find food and not wait to find a larger meal. Therefore, impulsive behavior may be either beneficial or detrimental depending on the situation (e.g., Winstanley, Eagle & Robbins, 2006); acting in an impulsive manner may "allow us to seize a valuable opportunity, or to make a disastrous decision". (Winstanley et al., 2006).

Because impulsive behavior is a heterogeneous construct (Evenden & Ryan, 1996; Pattij & Vanderschuren 2008), numerous behaviors are characterized as being "impulsive." As discussed in the above example, the choice of a smaller-sooner reinforcer over a larger-later reinforcer is an act of impulsivity, as are acts of behavioral disinhibition, delay of gratification, acting without forethought, and failures to respond during an extinction schedule (see Ho, Mobini, Chiang, Bradshaw & Szabadi, 1999 for review). Due to the complexity of this behavioral construct, several experimental techniques have been developed to study each aspect of impulsivity using animal models.

Animal Models of Impulsive Behavior

Tasks that measure impulsive behavior can be divided in to two main categories, those that measure impulsive action, or motoric impulsivity, and those that measure impulsive choice, or decision-making (see Wintanley et al., 2006 for review). Impulsive action is defined as the "inability to withhold making a response" (or acting without forethought), whereas impulsive choice is characterized as a decision-making processes, as opposed to an act of motoric inhibition (Winstanley et al., 2006). For instance, *impulsive choice* may be characterized as making the decision between driving a motor vehicle while intoxicated or calling a cab because it represents the choice of a smaller-sooner reinforcer (getting home fast) versus a larger-later reinforcer (having to wait for a ride but getting home safe). *Impulsive action* may be characterized as effectively stopping a motor vehicle at a red light and accelerating at a green light because it involves the ability to motorically operate the motor vehicle once the decision to drive it has been made. Common techniques used to assess impulsive action are the Go/No-Go Task, Stop Signal Reaction Test (SSRT) and 5-Choice Serial Reaction Time Test (5-CSRTT). The primary means by which researchers test impulsive choice and decision-making is with a Delay-Discounting Task (Winstanley et al., 2006).

Because each task targets a different aspect of impulsivity, findings across tasks may vary. For instance, rats may be characterized as impulsive on a delay-discounting task, but not characterized as impulsive on a Go/No-Go task (e.g., Paine et al., 2003). Therefore, researchers should exercise caution when generalizing findings of "impulsivity" across tasks. When assessing impulsivity, researchers should utilize a task that will best target the specific aspect of impulsivity they are interested in studying.

Go/No-Go and SSRT. Two of the most commonly used tasks to assess impulsive action are the Go/No-Go and Stop-Signal Reaction Time Tests (SSRT; Winstanley et al., 2006). In a standard Go/No-Go task, with rats as subjects, rats learn to make a response (e.g. press a lever in an operant chamber) in the presence of a "go" signal (e.g., green light) and inhibit making a response in the presence of a "no-go" signal (e.g., red light). The no-go signal is presented concurrently with the go signal or immediately preceding it. This task is advantageous for measuring how a variety of environmental factors (e.g., drugs of abuse) affects behavioral inhibition, or the inability to inhibit a response (e.g., Winstanley et al., 2006; Pattij et al., 2008).

Similar to the Go/No-Go task is the SSRT task, which also measures behavioral inhibition but in addition provides information regarding the latency to inhibit a response. The SSRT task requires rats to respond accurately on a single lever in the presence of a "go signal", and then on two additional levers. A correct pattern of responding on these levers results in reinforcement. The average time it takes to complete this task is calculated as the mean go reaction time (mRT). To assess behavioral inhibition, on 20% of trials a "stop-signal" (e.g., tone) is presented following response on the first lever, but preceding responding on the last two levers. Subjects must inhibit responding on the last two levers following the tone in order to receive reinforcement. If behavior is not inhibited, rats do not receive reinforcement and incur a 5-s time-out. The SSRT (amount of time taken to inhibit the go response) is calculated, and serves as a measure of inhibitory control. Because the latency to make a response that does not occur cannot be measured directly, SSRT is calculated with a formula that uses the mRT score to estimate the SSRT. SSRT scores average approximately 200 ms for adult humans, 400 ms for young children and elderly adults and 300 ms for rats (Winstanley et al., 2006).

The Go/No-Go and SSRT tasks are advantageous for assessing behavioral inhibition, yet they reveal nothing about other behaviors that may be related to impulsive action. Another popular task used to assess behavioral inhibition, and related behaviors, is the 5-CSRTT.

5-CSRTT. The 5-CSRTT was originally developed to measure visiospatial attention (Robbins, 2002), but has since become popular for testing animal models of impulsive action (behavioral inhibition). In a standard 5-CSRTT procedure, with rats as subjects, a response must be made on one of five manipulandum in an operant chamber. However, rats must learn to make a response only in the presence of an illuminated light associated with each manipulandum. A 5-s intertrial interval (ITI) precedes the start of each trial, during which time the rat must not make a response. Premature responding (before presentation of the light) results in no reinforcer delivery and a 5-s time-out. These premature responses serve as a measure of behavioral disinhibition (lack of inhibiting a response). This task is particularly advantageous when attempting to assess multiple aspects of behavior. In addition to assessing impulsive action, the task also assesses attention, motivation and response strength (Winstanley et al., 2006). The 5-CSRTT lends itself well to separating the effects of various central nervous system (CNS) manipulations on a variety of different behaviors. For instance, the 5-CSRTT task is useful in both the diagnosis of disorders such as Attention Deficit Hyperactivity Disorder and assessment of the effectiveness of different stimulant medications to treat this disorder (e.g., Robbins, 2002; Winstanley et al., 2006).

The 5-CSRTT, and the other tasks described above, only target behaviors related to impulsive action, they reveal no information about impulsive choice and decision-making. This aspect of behavior is an important one to consider given that on a daily basis people are faced

with dozens of choices that must be made. To assess impulsive choice and decision-making, delay-discounting tasks are used.

Delay-Discounting Task. During a delay-discounting procedure, subjects are required to choose between two simultaneously available, mutually exclusive, schedules of reinforcement to obtain reinforcement (Ainslie, 1974). Tasks originally designed to assess choice behavior with rats included runways and T-mazes (e.g., Logan, 1965). However, discounting tasks for pigeons and rats have more recently been developed using standard operant chambers (e.g. Rachlin & Green, 1972, Ailslie, 1974, Tobin, Chelonis & Logue 1993).

When rats are used, two manipulandum (e.g., levers) in a standard operant chamber are available simultaneously. Emitting a lever-press to one lever leads to a small but immediately delivered reinforcer (e.g., 2 pellet of food following no delay) and a lever-press to the other lever leads to a larger but more delayed reinforcer (e.g., 6 pellets of food following a 6 s delay). In this type of situation, subjects tend to choose the smaller reinforcer (e.g., Tobin et al., 1993). However, when the delay between the availability of only the *smaller* reinforcer is increased, preferences begin to shift and subjects will typically choose the larger reinforcer (Rachlin & Green, 1972; Bradshaw & Szabadi, 1992). The choice of the smaller reinforcer, over the larger reinforcer is an impulsive choice. This task tells us nothing about behavioral inhibition, but is advantageous for assessing factors (e.g., drugs of abuse) that may alter human and non-human animals' decision-making abilities.

In the present study, I am primarily interested in assessing impulsive choice; therefore, impulsivity is defined as the selection of a smaller more immediately available reinforcer, over a larger but more delayed reinforcer (e.g., Rachlin & Green, 1972; Ainslie, 1974; King & Logue, 1987; Logue, 1988). Impulsivity will be assessed using a delay-discounting task.

Factors Influencing Impulsivity

Many factors play a role in whether an animal makes an impulsive choice, the two most prominent factors being reinforcer amount and delay (e.g., van Haaren, van Hest & van de Poll, 1988; Tobin et al., 1993). When given the choice, animals (e.g., rats and pigeons) will typically choose a smaller, more immediate reinforcer, over the larger, more delayed reinforcer, in a delay-discounting paradigm, unless delay to both reinforcers is simultaneously increased (e.g., Rachlin & Green,1972; Ainslie 1974; Logue, 1988; Tobin et al., 1993). Researchers therefore suggest that acts of impulsivity are the result of the inability of an animal to tolerate delay (e.g., Ainslie, 1974; Logue, 1988; Evenden & Ryan, 1996).

It is important to note that studies assessing the effects of delay on impulsivity using delay-discounting procedures were originally conducted with pigeons as subjects (e.g., Rachlin & Green, 1972; Ainslie, 1974), because Tobin et al. (1993) suggests that the paucity of work using rats is unfortunate since rats are phylogenically closer to humans than pigeons are, and because the pharmacology and neuroendocrinology of the rat brain is better understood than that of the pigeon brain. Research with rats might aid researchers in better assessing human problems related to impulse control. For example, Tobin et al. (1993) exposed male Long Evans rats to a delay-discounting procedure similar to those used with pigeons, and found that rats show impulsiveness under the *same conditions* in which pigeons show impulsiveness.

There are other species differences with respect to impulsivity, whereby pigeons exhibit a greater degree of impulsive behavior on delay-discounting tasks than rats, and humans exhibit less impulsive behavior than do both pigeons and rats (for review see Tobin & Logue, 1994). These discrepancies do not necessarily signify that rats are “less impulsive” than pigeons or “more impulsive” than humans. Rather, these findings suggest that species are more or less

sensitive to delay (van Haaren et al., 1988). For instance, incurring a delay of 10 s for a pigeon may be equivalent to a rat incurring a 15-s delay, or a human incurring a delay of 1 week. It is therefore important when testing impulsivity using delay-discounting tasks that delays to reinforcement are chosen with the type of species tested in mind. Overall, research reveals that whereas sensitivity to delays may vary across species, impulsivity still increases as a function of increasing delay (Tobin et al., 1993; Tobin & Logue, 1994).

Effects of Reinforcer Delay on Impulsivity. Several variations of the delay-discounting task exist, and can be categorized into two main types: procedures that use a concurrent-chain paradigm (Rachlin & Green, 1972; Peters, Hunt & Harper, 2004) and procedures that use a discrete-trial paradigm (as used in the present study; e.g., Mazur, 1987; Evenden & Ryan, 1996). Concurrent-chain procedures require subjects to emit multiple responses to obtain reinforcement, whereas discrete-trial procedures only require subjects to emit a single response to obtain reinforcement. Both procedures illustrate the importance that delay to reinforcement plays in influencing choice behavior.

In a concurrent-chains procedure, there is an extended choice period (i.e. initial link) prior to the choice of the smaller or larger reinforcer. In Rachlin and Green (1972), pigeons were presented with a choice between 2-s access to grain immediately or 4-s access to grain following a 4-s delay (terminal link). However, in order to receive access to either reinforcer, pigeons first had to distribute 25 key pecks between two different keys (initial link). At the start of a trial, pigeons' key pecks could be distributed on either of two white illuminated keys, but if the twenty-fifth peck occurred on the right key both keys and the houselights were darkened for T seconds (T varied across trials-see below) and were then re-illuminated. Upon re-illumination of the keys, the right key signaled the availability of 2-s access to grain immediately (small but

immediate reinforcer). The left key signaled the availability of a 4-s delay followed by 4-s access to grain (larger more delayed reinforcer). If, during the initial link, a pigeons' twenty-fifth peck was make on the left key, only the left key (larger reinforcer) was re-illuminated during the terminal link phase. This additional requirement is often referred to as 'pre-commitment'; the animal must complete the initial link before the next trial begins and in essence 'commit' to a later choice.

Overall, the finding from Rachlin and Green (1972) revealed that whenever subjects were presented with 2-s of immediate access to grain and 4-s of delayed access to grain, the 2-s access to grain was usually chosen. However, as 'T' increased, the key, which would only lead to the larger delayed reinforcer, was chosen more often (Rachlin & Green, 1972). This study illustrates the impact delay has on choice behavior; namely, that animals will typically choose the smaller-sooner reinforcer over the larger-later reinforcer, unless an added delay period between initial reinforcer choice and delivery is used. The delay period immediately preceding reinforcer delivery as well as the delay period between initial reinforcer choice and delivery are both important in mediating choice behavior. In contrast to the concurrent-chain procedure, during discrete-trial procedures only a single choice response (e.g., lever press) is necessary, and is made immediately preceding the delay to obtain reinforcement. In the above example from Rachlin and Green (1972), a discrete-trials procedure would encompass only the terminal link (choice of 2-s access of grain immediately versus 4-s access of grain following a delay). Discrete-trial procedures do not take into account how the delay period preceding reinforcer choice impacts impulsivity.

There are benefits and drawbacks to each of these procedures. Namely, procedures that require multiple responses to obtain reinforcement, as in the case of concurrent-chain procedures,

are advantageous for assessing not only what reinforcer may be preferred but also the degree to which a reinforcer is preferred. This information cannot be obtained using a discrete-trial procedure. Both procedures reveal a great deal about how delay to reinforcement affects impulsive behavior, however, because concurrent-chains procedures take into account how the total length of a choice period affects impulsivity, not just simply the delay to reinforcement itself, discrete-trial procedures are advantageous when attempting to isolate how only delay immediately preceding reinforcer delivery alters choice behavior.

The use of discrete-trial procedures also allows for the calculation of *indifference points*, or the point at which subjects are indifferent between two alternative forms of reinforcement (choice of the larger reinforcer 50% of the time and choice of the smaller reinforcer 50% of the time). Smaller indifference points signify higher discounting rates (e.g., greater impulsivity). For instance, an indifference point of 26 s indicates that an animal will tolerate up to a 26-s delay to obtain a larger reinforcer over a smaller reinforcer during a delay-discounting task. An indifference point of 35 s signifies that an animal will tolerate up to a 35-s delay to obtain a larger reinforcer; it is inferred that an animal that can tolerate a 35-s delay is less impulsive than an animal that can tolerate only a 26-s delay.

In 1987, Mazur developed an innovative procedure to calculate indifference points, called an *adjusting* delay-discounting procedure. Originally designed for use with pigeons, this procedure has since been modified and widely used with rats and humans (e.g., Logue et al., 1992; Tobin et al., 1993; Green, Fry & Myerson, 1994; Kirby & Petry, 2004; Roesch, Takahashi, Gugsa, Bissonette & Shoenbaum, 2007). During an adjusted-delay procedure (i.e. titration procedure) delay to one reinforcer (e.g., smaller reinforcer) remains fixed while delay to the other reinforcer (e.g., larger reinforcer) is adjusted (increased or decreased) according to choices

made by the subject. On any given trial, choosing the smaller reinforcer will decrease delay to the larger reinforcer on the following trial and choice of the larger reinforcer will increase delay to the larger reinforce on the following trial. Delays are adjusted until an indifference point is obtained.

One of the first studies to assess impulsivity in rats using an adjusting delay-discounting procedure was that of Tobin et al. (1993). Rats were exposed to a task in which one lever in an operant chamber corresponded to a 2-s reinforcer access period following a 1-s delay (impulsive choice) and the other lever corresponded to a 6-s reinforcer access period following a 6-s delay. Rats' mean proportion of larger reinforcer choices were significantly lower than their mean proportion of smaller reinforcer choices. In order to assess the role that reinforcer amount and delay each play separately on impulsivity, Tobin et al. (1993) expanded his first study by employing the use of a adjusting delay-discounting procedure, whereby delay to the larger reinforcer was adjusted for each rat until the subject was indifferent between the smaller and larger reinforcers. Results revealed that reinforcer delay controls impulsive behavior just as much as reinforcer amount does (Tobin et al., 1993). These findings are consistent with work from Richards, Mitchell, De Wit and Seiden (1997) who used a variation of the adjusting delay-discounting procedure, the adjusting-*amount* procedure, to assess the effects reinforcer delay had on choice behavior in rats. As with the adjusting delay-discounting procedure, the adjusting-amount procedure was also designed to assess reinforcer value. However, instead of altering delay to reinforcement in order to obtain indifference points, the magnitude of reinforcement was altered.

During an adjusted-amount procedure, larger and smaller reinforcers are available after a fixed delay, and the magnitude for the smaller reinforcer is increased or decreased based on

subjects' choices. If a subject chooses the larger reinforcer, the amount of the smaller reinforcer is increased. If the smaller reinforcer is chosen, its amount is decreased. In Richards et al. (1997), rats chose between a large amount of water (100 µl) after a fixed delay (0, 2, 4, 8, 16 s) or a smaller amount of water (35-71 µl) available immediately. The magnitude of the smaller amount of water was increased or decreased 10% following each reinforcer choice. Choice for immediately delivered water approached indifference as a function of delay. When the larger reinforcer (100 µl) was available following no delay, rats adjusted the amount of the smaller reinforcer to approximately 100 µl. When delay to the larger reinforcer was increased, rats adjusted the amount of the immediate reinforcer in direct proportion to the duration of the delay. For example, 100 µl of water delayed 16 s was chosen just as often as 25 µl of water delivered immediately.

Because work with humans suggests that smaller reinforcers (e.g., $1,000) are often discounted at a faster rate than larger reinforcers (e.g., $10,000; see Green et al., 1994), Richards et al. (1997) also assessed whether reinforcer amount was controlling choice behavior as much as reinforcer delay was controlling behavior. Richards et al. (1997) assessed several magnitudes of the larger, fixed, reinforcer (100, 150 and 200 µl of water). Results revealed no significant differences between reinforcer amounts, suggesting that rats did not discount smaller amounts of water more rapidly than larger amounts of water. These findings further emphasize that delay to reinforcement, and not reinforcer amount, controls discounting behavior under these conditions.

Results from Tobin et al. (1993) and Richards et al. (1997) are in accord with numerous studies (e.g., Logue, 1988; Evenden and Ryan, 1996; Bradshaw & Szabadi, 1992; Anderson & Woolverton, 2005), revealing that impulsivity increases as a function of increasing delay. These findings provide support for the theory that impulsive behavior arises due to an inability to

tolerate delay. The present study is primarily concerned with how delay immediately preceding choice affects impulsivity. Therefore, I will utilize a discrete-trials delay-discounting task, with adjusting delays. However, one must be careful when assessing the effects of delay on impulsive behavior because delay, the amount of time that elapses to receive reinforcement, is often confounded with response cost, the amount of responding (e.g., lever presses) required to obtain reinforcement.

Time versus Response Cost. Impulsivity increases as a function of increasing delay (e.g. Logue, 1988; Bradshaw & Szabadi, 1992). However, an increase in response requirement may also lead to increases in impulsive responding. The larger the response requirement for a task, the more time it takes to complete (Neuringer & Schneider, 1968). It may be the case that rats learn to lever press during the delay period to receive reinforcement and that lever pressing, and not delay to reinforcement, is what is driving increases in impulsivity during discounting tasks. It is true that under some circumstances response cost and time are confounded variables; however, this problem is not unique to discrete-trials operant procedures. Extraneous, or "superstitious" behaviors are potential confounds in all human and animal experimentation. Pierce, Hanford and Zimmerman (1972) provides evidence to suggest that the use of retractable and fixed levers in discrete-trials procedures yield comparable results.

In Pierce et al. (1972), rats were exposed to a discrete-trials delay-discounting procedure, whereby responding during the delay to reinforcement was allowed (using fixed levers) or not allowed (using retractable levers). Rats were trained to press a lever to receive food reinforcement following a delay which increased from 0.5 to 10, 30 and 100 s. Results revealed that response rates decreased as delay to reinforcement increased. There were no systematic differences in performance because of the different procedures. Specifically, similar effects were

obtained on a discrete-trials delay-discounting task when responding during the delay was prevented, as was the case with retractable levers, or not prevented, as was the case with the fixed levers (Pierce et al., 1972). Overall, these findings support the idea that the *amount of time* between response and reinforcement controls the probability of a given response, whether or not other responses intervene.

In addition, several studies using pigeons have assessed the degree to which responding is controlled by time (e.g., delay) versus response cost (key presses; e.g., Neuringer & Schneider, 1968). Because delay and response cost are correlated, Neuringer and Schneider (1968) manipulated each independently to assess the degree to which each controlled behavior. Overall, results of the study revealed that the latency to respond for reinforcement is not controlled by the number of responses made as much as it is controlled by the delay to receive that reinforcer. This is not to say, however, that response requirement cannot serve as discriminative stimuli for a future behavior (e.g., Pliskoff & Goldiamond, 1966). This is an important point because it emphasizes that while response cost does not necessarily determine what choice will be made, it does suggest that past behavior can serve as a marker for future behaviors to take place (e.g., placing four quarters in a soda machine creates the condition to press a button to receive a soda).

Together, studies that have investigated the effects of delay on impulsive behavior reveal that impulsivity increases as a function of increasing delay on delay-discounting tasks (e.g., Ainslie, 1974; Tobin et al., 1993). More recently, these delay-discounting procedures have been used to assess how various drugs of abuse affect impulsive behavior (e.g., Logue et al., 1992; Paine et al., 2003; Roesch et al., 2007). In order to investigate how drugs of abuse affect impulsive behavior, we must first understand the biological properties mediating this behavior.

The Biological Properties of Impulsivity

As mentioned above, impulsivity is not a unitary construct. It is characterized by several distinct behaviors and psychological processes, many of which have independent biological mechanisms which can be dissociated both neuroanatomically and neuropharmacologically (Winstanley et al., 2006; Pattij et al., 2008). However, even though different acts of impulsivity may have distinct biological mechanisms, interconnected networks often regulate these behaviors (Winstanley et al., 2007). Key brain areas which mediate impulsivity are the frontal cortex (e.g., prefrontal cortex [PFC], orbitofrontal cortex [OFC], and infralimbic region), as well as the ventral striatum, namely the nucleus accumbens (NAc; e.g., Winstanley et al., 2006).

Neuroanatomy. Most work assessing impulsivity has been conducted using the 5-CSRTT and delay-discounting tasks (Logue et al., 1992; Robbins, 2002; Krishnan-Sarin, Reynolds, Duhig, Smith, Liss & McFetridge et al., 2007; Paine et al., 2003; Pattij et al., 2008). As discussed above, these tasks assess very distinct aspects of impulsivity; specifically, behavioral inhibition and decision making. Although similar brain structures are involved in mediating both of these behaviors, performance on these tasks are often not correlated (e.g., Winstanley et al., 2007). These findings hint at the idea that damage or stimulation of similar brain areas affect impulsivity differently, depending on the specific behavior being assessed (see Winstanley et al., 2006 for review). For instance, damage to the NAc increases impulsivity on delay-discounting tasks but has no effect on performance of the SSRT (Cardinal, Pennicott, Sugathapala, Robbins & Everitt, 2001; Winstanley et al., 2006).

Frontal and striatal systems are heavily implicated in mediating all forms of impulsivity (e.g., Robbins, 2000). Children with Attention Deficit Hyperactivity Disorder, a condition characterized by the manifestation of inattentive, hyperactive and impulsive behaviors (e.g.,

behavioral disinhibition and impulsive choice) have atypical frontal-striatal loop activation (Vaidya, Austin, Kirkirian, Ridlehuber, Desmond, & Glover, 1998). The frontal-striatal-loop (PFC to the NAc) is involved in mediating both behavioral inhibition and delay-discounting behaviors. However, the role that each area of the loop plays in the manifestation of each of these impulsive behaviors differs. For instance, researchers know that the OFC and NAc largely influence impulsive choice. In particular, lesions to the OFC makes rats less impulsive on delay-discounting tasks, yet has no effect on impulsive action (Pattij et al., 2008). Interestingly, the OFC and NAc are also both implicated in drug addiction. For example, research has shown that recently abstinent cocaine addicts have a hyperactive OFC (Volkow & Fowler, 2000), suggesting that these brain structures play a role in mediating impulsivity associated with drug abuse. However, it is still debated whether persons are pre-disposed to act impulsively, thus leading to the compulsive use of drugs, or if the use of drugs leads to the performance of impulsive behavior.

Primary brain regions involved in mediating impulsive behaviors are areas within the PFC (such as the OFC) and NAc (Winstanley et al., 2006; Winstanley, 2007; Pattij et al., 2008). The PFC and basolateral amygdala project to the NAc; lesions to both the PFC and basolateral amygdala can lead to striatal dysfunction, which is shown to alter performance on delay-discounting tasks (Cardinal et al., 2001; Solanto, 2002; Winstanley & Theobald, 2004; Pattij et al., 2008).

The NAc is separated into two distinct parts, the core and shell; the core, but not shell, is shown to be involved in mediating impulsivity (Winstanley et al., 2006). For example, Pothuizen, Jongen-Relo, Feldon and Yee (2005) showed that NAc core lesions reduce the choice for smaller continually delivered reinforcement over larger, but only partially delivered

reinforcement. It is well established that accumbal DA in this area is involved in regulating impulsive choice (e.g, Hernandez & Hoebel, 1988). However, studies assessing the effects of DA on impulsive behavior have found that both increases and decreases in extracellular DA in the NAc lead to increases in impulsivity on delay-discounting tasks (e.g., Cardinal et al., 2001; van Gaalen, Brueggma, Bronius & Schoffelmeer, 2006).

Neuropharmacology. Distinct, yet converging, neuropharmacological pathways regulate impulsivity (Winstanley et al., 2006). The serotonin (5HT), norepinephrine (NE) and DA systems all play a role in mediating impulsive behavior (e.g., Winstanley et al., 2007). However, for the purpose of the current study I will focus on the role the DA system plays in the mediation of this behavior.

Winstanley et al. (2006) showed that rats performing a delay-discounting task had higher levels of DA in the PFC when the larger reinforcer had shorter delays, and that DA levels decreased as delay to the larger reinforcer increased. This was not seen in yoked controls, suggesting that DA function is involved in more than just signaling the expectation of reinforcement, it is involved in the decision making processes to receive that reinforcement (Winstanley et al., 2006).

Much of what researchers know about the role of DA in impulsive behavior comes from studying impulse control disorders such as Attention Deficit Hyperactivity Disorder (Pattij et al., 2008). Stimulant drugs commonly used in the treatment of Attention Deficit Hyperactivity Disorder (e.g., methylphenidate and *d*-amphetamine) increase synaptic DA levels by binding to the dopamine transporter (DAT), and either inhibiting the reuptake of DA (e.g., methylphenidate) or through reversal of the transporter (e.g., *d*-amphetamine; e.g., Giros Jaber, Jones, Wightman & Caron, 1996; Seeman & Madras, 2002). Human and non-human studies

reveal that low doses of stimulants reduce impulsive behavior on delay-discounting tasks (e.g., Wade, de Wit & Richards, 2000; de Wit, Enggasser & Richards, 2002). In rats, treatment with low doses of amphetamine and methylphenidate decreased rates of discounting (e.g., Richards, Sabol & de Wit, 1999; Cardinal et al., 2000; Wade et al., 2000). Cardinal et al. (2000) suggested that these decreases in discounting were contingent upon presentation of a conditioned stimulus during delay to reinforcement. Specifically, Cardinal et al. (2000) found that *d*-amphetamine (0.3 mg/kg) increased choice for the larger reinforcer when a conditioned stimulus (i.e., houselight) was presented immediately following reinforcer choice, and throughout the delay period to that reinforcer. However, when no conditioned stimulus was presented during the delay, higher doses of amphetamine (1.0, 1.6 mg/kg) actually decreased preference for the larger reinforcer. No other studies to date, however, have replicated these findings. More common are findings which show that low to moderate doses of stimulants decrease impulsiveness regardless of conditioned stimulus presentation (e.g., Richards et al., 1999; Wade et al., 2000). For example, Wade et al. (2000) administered *d*-amphetamine (0.5-1.0 mg/kg) to rats preceding performance on a delay-discounting task and found that amphetamine dose-dependently increased rats indifference points on the task (decreased impulsivity) with no conditioned stimulus present; rats that received 1.0 mg/kg of amphetamine had significantly higher indifference points than rats that received saline.

The first study to assess this in normally functioning humans found similar results to those found with rats (de Witt et al., 2002). Healthy human volunteers were administered acute doses of *d*-amphetamine (10, 20 mg/kg), or placebo, and performed a delay-discounting task whereby they chose between small amounts of money immediately, or large amounts of money after a delay. For instance, participants were asked if they would prefer $2 immediately versus $10 in 30 days. Participants also performed a variation of this task, using an adjusting-amount

procedure, whereby they were asked if they would prefer a varying amount of money immediately or $10 delivered on a probabilistic basis (e.g., only 25% of the time). Participants who received *d*-amphetamine (20mg/kg) discounted the monetary rewards significantly less than participants whom received placebos and 10 mg/kg of d-amphetamine.

Based on the above research, it should come as no surprise that because stimulants increase extracellular DA levels, it was traditionally thought that the manifestation of impulsivity, and impulse control disorders such as Attention Deficit Hyperactivity Disorder, were due in part to a DA deficiency (Solanto, 2002). This hypothesis was further supported by imaging studies which found that adults with Attention Deficit Hyperactivity Disorder had increased numbers of dopamine transporters (DAT), but reduced binding of stimulant medications to DAT in striatal areas of the brain relative to control populations (e.g., Krause, Dresel, Krause, Kung & Tatsch, 2000; Dougherty, Bonab, Spencer, Rauch, Madras & Fischman, 1999, respectively). It was therefore suggested that increases in DA reuptake by DAT was causing a decrement of extracellular DA in striatal areas such as the NAc (Solanto, 2002).

More recently, there has been a shift in this theory, suggesting that impulsive behavior may actually manifest, in part, due to DA *hyperactivity* (Solanto, 2002; Seeman and Madras, 2002). How do stimulant medications, which increase extracellular levels of DA, alleviate behavior brought about by *heightened* levels of DA? One theory is that increased DAT seen in adult Attention Deficit Hyperactivity Disorder patients is an adaptive response, compensating for excess levels of DA (Solanto, 2002). This theory is supported by findings assessing stimulant abuse (e.g. cocaine). In particular, chronic cocaine use is also shown to up-regulate DAT; post-mortem studies in cocaine addicts reveal that persons whose DA system failed to up-regulate DAT and adapt to cocaine administration suffered from a fatal condition known as ‘excited

cocaine delirium' (Mash, Pablo & Quyang, 2002). These findings support the idea that DAT up-regulation is a compensatory mechanism brought about due to hyperactivity of the DA system.

This theory also better explains the biphasic nature of stimulant drugs (Seeman & Madras, 2002), whereby low to moderate doses of stimulants decrease impulsivity (e.g., van Gaalen et al., 2006), and too small or too large of a dose may over stimulate the central nervous system (CNS) and lead to the manifestation of impulsivity (e.g., Evenden & Ryan, 1996; Richards et al., 1999; van Gaalen et al., 2006). The above research assessing how stimulants are used in the treatment of Attention Deficit Hyperactivity Disorder and how they alter DA neurotransmission has been helpful in assessing how illicit stimulants, such as cocaine, affect impulsive behavior. Research shows that cocaine has profound effects on delay-discounting behavior in both human (e.g., Coffey et al., 2003) and non-human animals (e.g., Logue et al., 1992; Roesch et al., 2007).

Biological Properties of Cocaine

Cocaine is a highly abused central nervous system (CNS) psychomotor stimulant that readily passes the blood-brain barrier (Julien, 1999; Repetto & Gold, 2005). The onset of CNS drug effects following an i.p. injection of cocaine is approximately five minutes, with peak effects during the first 20 minutes after injection (Kalivas and Duffy, 1990). The bioavailability of the drug after five minutes is approximately 30% with the plasma half-life in the brain averaging 10–25 minutes. The metabolites of cocaine in the rest of the body have a half-life averaging 62 minutes (Benuck, Lajtha & Reith, 1987; Ma, Falk & Lau, 1999).

Cocaine was the first local anesthetic discovered, and has the same base structure as synthetic local anesthetics such as lidocaine (e.g., an ester of benzoic acid and nitrogen-containing base; Repetto & Gold, 2005). Peripherally, cocaine exerts its stimulant effects

through the potentiation of responses of sympathetically innervated nerve organs, primarily norepinephrine (Repetto & Gold, 2005). Centrally, cocaine exerts its effects by inhibiting the reuptake of norepinephrine, serotonin and dopamine, leading to increased synaptic levels of these neurotransmitters. Like many of the stimulants used to treat Attention Deficit Hyperactivity Disorder (e.g., methylphenidate), cocaine has a high affinity for DAT in areas such as the NAc. The NAc is one of the projections of the mesolimbic dopamine pathway which is heavily associated with chronic drug abuse and dependency of psychostimulant drugs (Julien, 1999). Knock-out studies reveal that binding to DAT is the primary mechanism by which cocaine exerts increased synaptic levels of DA (Seeman & Madras, 2002). Mice which lack DAT in the striatum do not exhibit extracellular rises in DA when administered cocaine (e.g., Giros et al., 1996).

It is important to note that even though the DA system is critical in mediating the rewarding properties of cocaine, research shows that this system does not function alone to mediate cocaine induced behaviors. Dopamine neurotransmission is *necessary* to induce cocaine use and seeking, but it is not *sufficient* (Repetto & Gold, 2005). For instance, pharmacological compounds that activate the DA system but have not effect on the 5-HT system do not generate the same self-administration behavior we see following cocaine use. Furthermore, compounds that activate the 5-HT system which do not affect the DA system do not induce reward behavior, such as self-administration, that is normally seen when the DA system is activated following drug use (Repetto & Gold, 2005).

With respect to cocaine's effects on impulsive behavior, Logue et al. (1992) suggests that drug abuse, including of cocaine, is an impulsive act because it often represents the choice of a smaller more immediate alternative (e.g., taking the drug) over a larger more delayed alternative

(e.g., not taking the drug in exchange for better health later in life). It is important to note, however, that not only is the choice to use cocaine itself an example of impulsive behavior, but the use of cocaine has also been shown to increase impulsive behavior in a variety of behavioral tasks using non-drug reinforcers (e.g., choice of a smaller versus larger food reinforcer) in both human and non-human animals (e.g. Logue et al., 1992; Coffey et al., 2003; Roesch et al., 2007). To date, few experiments have assessed the effects of cocaine on impulsive behavior with the use of a concurrent discrete-trials delay-discounting task.

Cocaine and Delay-Discounting

Not all choices are free to vary across several alternatives (e.g., choosing a place you would like to eat for dinner). There are also instances in which people are forced to make one choice at a single point in time (e.g., to eat chocolate cake or fruit salad for dessert at a particular meal). Because choice situations similar to the ones used in discrete-trials procedures present themselves daily in real life situations, it is important to assess the effects of cocaine on choice behavior using this paradigm.

Work using a delay-discounting task shows that cocaine-dependent individuals discount (or devalue) hypothetical monetary rewards faster than do non-cocaine dependent individuals (Coffey et al., 2003). For example, when asked to choose between $600 immediately or $1,000 delayed by 1 week, cocaine users chose the immediate option of $600 dollars more often than the non-cocaine users. Additionally, when given the choice between $1 of cocaine immediately, and $1,000 worth of cocaine delayed by 1 week, cocaine users preferred the immediate reward of $1 of cocaine (Coffey et al., 2003). Similar findings were obtained by Kirby and Petry (2004), who assessed the discounting behavior of cocaine addicts, heroin addicts and alcoholics using a similar delay-discounting survey. Participants were asked if they would prefer a small amount of

money which ranged from $11-$80 immediately, or a larger amount of money which ranged from $15-$85 following anywhere from a 1 week to a 6 month delay. Unlike Coffey et al. (2003), which used purely hypothetical questions, participants in Kirby and Petry (2004) had a 1 in 6 change of receiving the reinforcer they choose on any given trial. Results revealed that cocaine and heroin abusers discounted larger reinforcers significantly more than non-drug users.

This same type of delay-discounting task has been used in animal studies to examine the effects of chronic cocaine on impulsive behavior (e.g. Logue, 1992). The first documented study investigating the effects of chronic cocaine administration on impulsive behavior in rats was performed by Logue et al. (1992). Researchers exposed rats to daily experimental sessions in which they were injected with cocaine (15 mg/kg) or saline (1 mg/kg) proceeding each session. In each experimental session, rats were tested on a standard delay-discounting procedure whereby they pressed a lever to receive 2-s access to condensed milk following a 2-s delay or 6-s access to condensed milk following a 6-s *titrated delay*, whereby delay to the larger reinforcer was adjusted depending on choices made in the preceding trials. Under these particular parameters, chronic cocaine significantly reduced choices made for the larger reinforcer, leading to smaller adjusted delays to the larger reinforcer as days with cocaine treatment increased. Impulsivity decreased when cocaine administration ceased.

In a related study, Evenden and Ryan (1996) examined the effects of numerous psychoactive drugs on impulsive behavior using a delay-discounting procedure similar to Logue et al. (1992) which allowed several delays to reinforcement to be studied within a single session. However, unlike in Logue et al. (1992), the delays to reinforcement were chosen independently of the subject's responses. Delay to reinforcement was gradually increased across each experimental session in an attempt to describe the relationship between the magnitude of delay

and choice between a small, but immediate, reinforcer and a larger, but more delayed, reinforcer. Past work studying the effects of delay to reinforcement on impulsive behavior commonly did so using fixed-delay procedures whereby only one delay to reinforcement value was used instead of an adjusting delay (e.g. Tobin et al., 1993). Using the fixed delay may create rigid habits that are not readily altered by future shifts in delays to obtain reinforcement or reinforcer magnitude (see Evenden & Ryan, 1996). Although the titrated delay procedure implemented by Logue et al. (1992) successfully reduced rigid responding, Evenden and Ryan (1996) suggested that the procedure is still weak in that only one delay at a time is tested, and chosen by the rat, instead of the experimenter. To further reduce rats' rigid responding, Evenden and Ryan (1996) developed a procedure in which delay to reinforcement gradually increased as each experimental session progressed, regardless of the rat's choice behavior.

Rats were trained to press levers whereby a press to one lever lead to the delivery of a single food pellet immediately, while a press to the other lever lead to the delivery of five food pellets delivered after various programmed delays. Delay to the larger reinforcer increased over the course of each session. Rats constantly chose the lever leading to the larger reinforcer during shorter delays, but showed a significant preference for the smaller reinforcer at longer delays. This cannot as readily be seen using "steady-state" delay-discounting procedures which utilize only a single delay value to the larger reinforcer in each test session, and do not lead to long-term sensitivity to delayed reinforcement (Evenden & Ryan, 1996). Evenden and Ryan (1996)'s procedure which utilized several delays-to-reinforcement maintained rats' sensitivity to delay for several months. Based on this operant procedure, Paine et al. (2003) investigated the effects of chronic cocaine administration on the ability to delay reinforcement. Rats were treated with 15 mg/kg of cocaine or 1 mg/kg saline three times daily over the course of the study. Because this

dosing regimen caused behavioral sensitization, thus interfered with performance of the task, injections were given to animals 1-2 hours following testing. During baseline testing, rats chose the delayed reinforcer more often at shorter delays than at longer delays. When cocaine was administered, rats chose the delayed reinforcer significantly less over the 14 day administration period relative to saline rats. Similarly, cocaine administration led to a gradual decrease in rats' indifferent points. This implies that rats that received cocaine discounted the value of the larger reinforcer at a higher rate than did rats that received saline.

In this study, chronic cocaine administration led to task specific decreases in impulse control, though effects were not seen across the entire treatment regimen (only on day 7; Paine et al., 2003). It is important to note, however, that this procedure differs from Logue et al. (1992) in that impulsive behavior was assessed following previous cocaine exposure (given the day before) versus assessment of impulsive behavior while the drug was still biologically active. These results tell us how cocaine use, over time, affects impulsive behavior, that chronic administration produces sensitization to the drug prior to producing tolerance, however this study does not tell us anything about how cocaine affects choice behavior while drug is exerting its acute biological effects.

In a more recent study, Roesch et al. (2007) investigated the long-term effects of cocaine exposure on performance in a delay-discounting task using a titrating procedure similar to Logue et al. (1992). However, training on the delay-discounting task began 6 weeks following the final day of cocaine administration. Therefore, like Paine et al. (2003), this study did not assess the acute effects of cocaine on choice behavior, but rather assessed cocaine's long-term effects on choice behavior. Rats were given daily i.p. injections of 30 mg/kg of cocaine or saline (1 mg/kg) over a 14-day period. As expected, cocaine treated rats were more sensitive to delay lengths than

were saline controls. Cocaine treated rats shifted away from the larger reinforcer as delay to that reinforcer increased faster than did saline controls. Findings suggest that cocaine has a general effect on the mechanisms mediating reward assessment (Roesch et al., 2007).

Past work shows that cocaine alters impulsive behavior under a variety of different conditions (e.g., Logue et al., 1992, Paine et al., 2003, Roesch et al., 2007). The biological mechanisms by which cocaine exerts its effects, however, are numerous and complex. Recent theories postulate that cocaine may exert its effects on impulsivity, in part, through increased DA neurotransmission (Seeman & Madras, 2002).

Theory of Cocaine's Biological Effects on Delay Discounting: Role of the Dopamine System

Stimulants have biphasic effects on behavior, whereby individuals with high baseline activity show larger decreases in activity following stimulant administration than individuals with normal (or lower) baseline activity (Robbins & Sahakian, 1979; Solanto, 2002). This may give researchers insight into how low doses of stimulants help to decrease impulsive behavior, while chronically administered stimulants such as cocaine, increase impulsive behavior. Not surprising, one recent theory suggests this phenomenon is mediated by the accumbal DA system. D2 receptor activation in the NAc may mediate, at least in part, the effects of chronic cocaine on impulsivity (Seeman & Madras, 2002). In order to better understand the ways in which cocaine leads to alternations in impulsive behavior by means of DA transmission, normal DA function in the absence of drug administration must first be considered.

An important aspect of the DA system is that it is tonically 'on', meaning that in the absence of an inhibitory signal, DA is constantly being released at a steady *non-pulsatile* rate. However, DA is released in a pulsatile manner during nerve impulses. The basal resting level of DA is approximately 4 nM, and rises about 60-fold to 250 nM following a typical nerve impulse

(Seeman & Madras, 2002). Immediately following release of DA after a nerve impulse, extracellular levels of the neurotransmitter rise to 1.6 mM, then rapidly decrease to 250 nM. There are three major ways in which extracellular DA is decreased. First, DA is decreased through rapid diffusion from the synapse, second, through re-uptake by DAT and third through inhibition of further DA released signaled by DA autoreceptors. Reuptake by DAT, in particular, plays a prominent role in decreasing extracellular DA. In normally functioning mice, DA clearance form the synapse takes approximately 1 s; clearance takes 100 s in mice lacking DAT (Giros et al., 1996). This suggests that DAT is the primary mechanism for DA inactivation.

Although low doses of stimulants increase extracellular levels of DA by blocking DAT (e.g., Hernandez & Hoebel, 1988; Kalivas and Duffy, 1990; Gratton & Wise, 1994; Wise Newton, Leeb, Burnette, Pocock & Justice, 1995; Tolliver, Newman, Katz, Ho, Fox, Hsu et al., 1999), they may also simultaneously lower its pulsatile release, (relative to basal levels), resulting in a net decrease of DA. This decrease in pulsatile DA release may be due to activation of presynaptic D2 receptors as a direct result of elevated extracellular DA. For instance, following administration of an acute dose of stimulant such as cocaine, the DA transporter is blocked and the resting level of synaptic DA rises approximately 6-fold. Due to this elevation, presynaptic D2 receptors are activated and reduce the relative rise in pulsatile release of additional DA into the synapse to only about 2-fold. This would explain how acute doses of stimulants decrease impulsivity in persons with Attention Deficit Hyperactivity Disorder, who are hypothesized to have heightened levels of baseline DA. However, it does not explain how chronically administered cocaine increases impulsivity for long periods of time after the cocaine is no longer present.

As mentioned above, stimulant drugs, including cocaine, have biphasic effects on behavior. At low doses, they may show beneficial effects on behavior, and at high doses create detriments. It is suggested that the later occurs due to over-stimulation of the DA system (Seeman & Madras, 2005). Following administration of chronic doses of stimulants, extracellular DA is dramatically increased approximately 35-fold above baseline levels, which leads to widespread stimulation if post-synaptic DA receptors. This substantial rise in DA negates the presynaptic inhibition of DA release seen when low levels of stimulants are administered. In this case, pulsatile release is increased 7-fold, resulting in an increase in synaptic DA above baseline levels. In some cases, this extracellular increase may lead to a down-regulation of D2-like receptors (Seeman & Madras, 2002). There is research to suggest that these biological effects, in particular the down-regulation of D2 auto-receptors, may be one mechanism behind the manifestation of impulsive behavior following chronic cocaine administration.

D2 Receptor Involvement in the Manifestation of Impulsivity. Research has shown that decreased D2-like receptor binding sites in the NAc cause animals to decrease the value of delayed reinforcers, thus increasing impulsivity (Wade et al., 2000). These results are consistent with more recent findings from van Gaalen et al. (2005) that rats that were administered the D2 receptor antagonist eticlopride prior to performance of a delay-discounting task had no alterations in impulsivity. However, when eticlopride was administered in conjunction with low doses of amphetamine, the effects of amphetamine were attenuated, and impulsivity was increased. These findings support the hypothesis that D2 receptors play an intricate role in mediating impulsivity by regulating the pulsatile release of DA following nerve impulses (see above).

Positron emission tomography (PET) revealed that impulsive human drug addicts had decreased D2 binding sites relative to non-addicts (Volkow, Fowler, Wang, Hitzemann, Logan, & Schlyer et al., 1993). In a later study, Kalivas et al. (2005) found that these decreases are prominent in the striatum. Consistent with these findings is work from Dalley, Fryer, Brichard, Robinson, Theobald & Lane et al. (2007) who assessed how trait impulsiveness may lead to drug using or seeking behavior. It was shown that rats that were impulsive on delay-discounting tasks have significantly reduced D2/D3 receptors in the ventral striatum than do rats that were less impulsive. Interestingly, impulsive rats were also more likely to self-administer cocaine than rats that were not characterized as impulsive. These results are in accord with findings from Anderson and Woolverton (2005) showing differences in impulsive behavior between Lewis and Fischer 344 rats. Past work has shown that Lewis rats have lower DAT levels in the NAc compared to Fischer rats (Flores, Wood, Barbeau, Quirion & Srivastava, 1998). Additionally, Lewis rats have lower levels of D2-like and D3 receptors in the NAc relative to Fischer rats (Flores et al., 1998). Using the same delay-discounting procedure as used by Evenden and Ryan (1996), Anderson and Woolverton (2005) found more impulsive behavior in the Lewis rats than in the Fischer rats. Overall, these results imply that decreases in D2 autoreceptors and DA receptor binding sites lead to increases in impulsive behavior. However, most of the above studies only assessed the influences that genetic or *pre*-drug exposure variables played on the D2 receptors mediation of impulsive behavior (Anderson & Woolverton, 2005, Dallery et al., 2007). To date, no studies have assessed the effects of cocaine on D2 receptor regulation in relation to impulsivity.

Purpose

Cocaine increases impulsive behavior in the laboratory in both human and non-human animals (e.g. Logue et al., 1992; Coffey, et al., 2003; Roesch et al., 2007). However, few of these studies have assessed impulsive behavior using a delay-discounting procedure (e.g., Logue et al., 1992). Of the studies that have assessed impulsive behavior using a delay-discounting procedure, only one of them assessed the effects of cocaine on impulsive behavior during the procedure; all other studies assessed impulsive behavior preceding or following cocaine administration. Therefore, more work needs to be done assessing how choice behavior is affected during cocaine intoxication since choice situations do not arise only after a drug has already exerted its acute biological and behavioral effects. Additionally, there is evidence to suggest that the DA system plays a role in mediating the effects of cocaine on impulsive behavior (e.g., Chen, Paredes, Van Praag, Lowinson & Gardner, 1992; Dalley et al., 2007). However, more work needs to assess exactly how this system mediates choice behavior.

Therefore, the purpose of the proposed study was threefold. First, the degree to which chronic cocaine administration affected impulsivity using a delay-discounting procedure was assessed. Second, the role that the DA system played in mediating impulsive behavior was assessed. Third, the data was explained by comparing it to predictions made by two choice theories. Rats were trained to perform a discrete trials delay-discounting procedure (as seen in Anderson & Woolverton, 2005), whereby they chose between one pellet of food immediately or three pellets of food following an adjusted delay (0, 10, 20, 40, 60 s) after receiving chronic administration of deionized water (DI; 1 mg/kg) or cocaine (3, 7.5, 15 mg/kg). Following performance on the delay-discounting task, the brains of the rats were extracted, and levels of D2-like receptors were assessed by means of western blotting. Data from the delay-discounting

task was then compared against predictions made by the matching law and Mazur's hyperbolic discount function. It was expected that as delay to the larger reinforcer increased, impulsivity would increase in all rats. In particular, rats receiving DI were expected to tolerate longer delays on the task than those receiving cocaine. In addition, rats that received cocaine were expected to have lower levels of D2 receptors than rats that received DI.

Method

Subjects

Subjects in the study were twenty-four, 90-day day old, experimentally naïve male Sprague-Dawley rats. Subjects had free access to water and restricted access to food during testing. Specifically, rats were maintained at approximately 85% of their free-feeding weight over the course of the study, housed individually, and exposed to a 12:12 light-dark cycle. Rats were tested 5-7 days a week.

Behavioral Apparatus

Rats were tested in four similar operant testing chambers manufactured by MED Associates Inc. (Model #203 1.3). The chambers were constructed out of Plexiglas and metal and were approximately 30 cm wide, 24 cm deep and 29 cm high. Each chamber was equipped with two flat response levers (5 cm x 2 cm) mounted side by side on the front panel. The levers were located 2.5 cm above the floor and 0.7 cm from each side of the chamber on the middle of the front wall of the chamber. White response lights (2.5 cm in diameter) were mounted above each response lever. The chamber was also equipped with a food hopper to provide food pellets containing sucrose (Bio-Serv™ 45mg purified rodent tablets, F0021). Rats received the pellets through a 5cm x 5cm x 8.5 cm opening located beneath the response levers, in the center of the front panel of the chamber. A house light mounted on the back wall (top) illuminated the

chamber. Each chamber was enclosed in a sound attenuating apparatus, and a fan was mounted on each chamber to provide ventilation and reduce extraneous noise. In the same room as the testing area, an IBM-compatible computer was used to run a MED-PC program, which controlled all experimental events and recorded all lever responses made by each rat.

Drugs

Cocaine HCl (Sigma-Aldrich, St. Louis, MO) was dissolved in deionized water (DI). Intraperitoneal (i.p.) injections of cocaine (3, 7.5, or 15 mg/kg) or DI (1 mg/kg) was administered to all subjects.

Delay-Discounting Task

Rats were trained to press the lever by means of successive approximations. Following shaping, rats were exposed to a delay-discounting procedure whereby a single lever press to one lever lead to one pellet of food immediately, whereas a single lever press to the other lever lead to three pellets after an adjusted delay. The procedure from Anderson and Woolverton (2005) was followed, which is a modified version of the adjusted delay-discounting procedure originally created by Evenden and Ryan (1996).

Rats completed one session daily of five sets of choice-trials. Each set consisted of eight trials containing both *forced-choice* and *free-choice* trials (for a total of 40 trials per session). The first two trials in every set were forced-choice trials, whereby only the small or large food reinforcer was available. During a forced-choice trial, the house light was turned on, and food reinforcement from only one of the levers was made available (e.g., from the lever associated with the smaller reinforcer), signaled by the light turning on above that lever. The house light was turned off after a choice was made and food was delivered. If a rat did not press the lever after 30 s, the reinforcer corresponding to that lever was automatically delivered. For the second

forced-choice trial, reinforcement from the other lever (e.g., the larger reinforcer) was made available. The order of lever presentation during the forced-choice trials was randomized. Forced-choice trials were designed to ensure rats experience both the larger reinforcer and smaller reinforcer equally before exposure to a trial where both sources of reinforcement were available concurrently.

Following the two forced-choice trials at the start of every set, the rat was exposed to six free-choice trials. Free-choice trials were identical to forced-choice trials except that lights above *both* levers were illuminated, giving the rat a choice between simultaneously available larger and smaller reinforcers. Unlike the forced-choice trials, if a rat did not press the lever within 30 s, no reinforcer was delivered, a "null" response was recorded, and the intertrial interval (ITI) was started. The ITIs between all trials (forced and free) were scheduled in such a way that each trial was a total of 90-s long, in order to maintain constant reinforcement frequency across all sessions for all rats.

Training and Baseline Phases. During the first set of trials (out of 5) the delay to the larger reinforcer was set at 0 s. This delay was then increased in the following order: 1, 2, 4, 6 s. Each delay was in effect for a single set of 8 trials. Following the above delay set, delays to the larger reinforcer were then increased to 0, 2, 4, 8,16 s, followed by 0, 5, 10, 20, 40 s, ending with the terminal values (baseline) of 0, 10, 20, 40, 60 s. Rats were exposed to each delay set for at least 5 sessions and until behavior was stable. Stability was defined as all rats finishing each session with the number choices for the larger reinforcer during the equal-delay condition (0 s) at 80% or more for three consecutive sessions, with less than 20% variation between the number of choices made for the larger reinforcer across these three days.

Following training, rats were exposed to a baseline phase (0, 10, 20, 40, 60 s). Rats were exposed to this phase for at least 5 more consecutive days, and until behavior was stable. To control for possible lever bias, 12 of the rats were assigned to a condition in which the right lever always provided the larger reinforcer and the left lever the smaller reinforcer. The other 12 rats were assigned to the left lever condition, whereby the left lever always delivered the larger reinforcer and the right lever the smaller reinforcer.

Drug Phase. Immediately following the last day of baseline testing, subjects were given a daily injection of cocaine (3, 7.5, 15 mg/kg) or DI (1 mg/kg) five minutes preceding testing. Drug administration was scheduled to occur for 14 consecutive days. However, due to discovery of a bad shipment of cocaine, drug was only administered for 9 consecutive days. Rats were randomly assigned to four groups (six rats per group), whereby each rat received one of the cocaine doses or DI.

Withdrawal Phase. Following the last day of the drug phase, subjects continued testing in the delay-discounting task for 14 consecutive days to assess the effects of cocaine withdrawal on impulsive behavior.

Analysis. Consistent with past work (e.g., Evenden & Ryan, 1996; Paine et al., 2003; Anderson & Woolverton, 2005), to assess the effects of cocaine on impulsive behavior, two dependent variables were used in the analyses: the percentage of choices made for the *larger* reinforcer as a function of delay and rats' indifference points. Both measures are advantageous for assessing different aspects of impulsivity. Indifference points provide a succinct measure of rats' sensitivity to delay, and percentage of choices made for the larger reinforcer gives more detailed information about what choices were made and when (at what delays) they were made.

Across all phases of the study, choice for the larger reinforcer was calculated for each rat during free-choice trials by dividing the total number of larger reinforcer choices by the number of larger and smaller reinforcer choices, and multiplying the proportion by 100. Indifference points, or the point at which rats chose each reinforcer 50% of the time, was obtained by means of regression analysis. The pattern of choices made by several of the rats during the drug and withdrawal phases did not lend itself to the calculation of an indifference point (e.g., rat only made one choice for the larger reinforcer across all sessions of testing). Therefore, indifference points were calculated for each group (DI, 3 mg/kg, 7.5 mg/kg and 15 mg/kg of cocaine), using the mean percentage of choices made, and not for each individual rat.

To ensure that rats did not differ on performance on the delay-discounting task prior to drug administration, a two-way repeated measures analysis of variance (RM ANOVA) was performed on the last 3 days of baseline testing, with cocaine dose (dose) as the between-subjects variable and delay to the larger reinforcer (delay) as the within-subjects variable.

To assess the effects cocaine had on rats' choice for the larger reinforcer, as well as to ascertain differences in performance between days when cocaine was administered and days it was not, a three-way repeated measures (RM) ANOVA was performed with dose (DI, 3, 7.5, 15 mg/kg) as a between-subjects variable and delay (0-60 s) and day (2-23) as within-subjects variables. To separate the effects found during the drug and withdrawal phases, separate three-way RM ANOVAs were run for the drug phase (days 2-9) and withdrawal phase (day 10-23). For all within-subject variables, Mauchly's test of sphericity was used, and when appropriate, degrees of freedom were adjusted with the Greenhouse-Geisser epsilom. All significant interactions were assessed for simple effects using individual ANOVAs. When appropriate, interactions were assessed by means of Bonferroni post-hoc comparisons. To assess the effects

cocaine had on rats' indifference points, one-way RM ANOVAs were performed with treatment group (DI, 3, 7.5, 15 mg/kg) as the between-subjects variable and day (2-23) as a within-subjects variable for both the drug and withdrawal phases.

In addition, the choice patterns of rats during each session of drug exposure was assessed in order to ascertain if rats that received cocaine differed in their pattern of responding relative to rats that did not receive cocaine. To do this, a one-way ANOVA was performed, with omitted responses (when rats did not press the lever) as a between subjects variable.

Western Blots

Western blots were performed in order to detect levels of D2-like receptors in rats' NAc. Following completion of behavioral testing, brains were harvested so the NAc could be isolated from each rat. Rats were euthanized immediately following the last day of testing, by means of CO2, and decapitated. Brains were sliced into 1mm sections, 2.20mm from bregma, and 0.75 mm tissue punches were extracted from the core and shell of the NAc; tissue samples were immediately placed on dry ice and frozen at -80 degrees Celsius until the tissues samples were ready to be sonicated.

The tissue samples were removed from the freezer, placed on dry ice, and sonicated at 50 htz for approximately 20 s in 100 micro liters of tris lysis buffer. The buffer contained protease inhibitor tablets to protect against degradation of proteins. Following sonication, samples were spun-down in a centrifuge for 15 minutes at 10000 rev. The resulting supernatant was collected, stored in clean tubes, and SDS dye (sodium dodecyl sulfate) was added. SDS is a detergent which denatures proteins and helps to promote their separation by molecular weight. The samples were boiled for 5 minutes at 90 degrees Celsius and frozen.

A Bradford Protein Assay was performed to determine how much of each sample would be needed to perform the western blot. Equal sample sizes were required to obtain an accurate measurement of the desired protein of interest (D2 receptor). Once the amount of each sample was assessed, they were loaded at the appropriate volumes into wells on top of stacking and separating gels. Because SDS negatively charged the proteins upon electrically stimulation, the proteins migrated towards the positive end of the gel. It is important to note that both the stacking and separating gels contain acrylamide, which helps promote the separation of proteins. However, the staking gel has a lower density of acrylamide than the separating gel. Therefore, proteins moved relatively fast through the stacking gel, stopping once they reached the separating gel, allowing proteins to begin migrating from the same point.

The gel was run for approximately one hour at 100 volts, then transferred to a nitrocellulose membrane. The transfer took approximately 1 hour. Following the transfer, the membrane soaked in PBS (phosphate-buffered saline) for several minutes before letting it rock in a 3% BSA-TBST (Bovine Serum Albumin–Tris Buffered Saline in Tween 20) solution for 1 hour. This was done to inhibit non-specific binding of the antibodies directly to the membrane. In order to identify the D2-like receptors, membranes were then rocked in primary antibody, Anti-Human Dopamine Receptor D2 (Millipore Co., Billerica, MA). The membrane was left to rock in the solution for approximately 1 hour at room temperature, to allow the anti-body to bind to D2-like receptors. For some of the samples, the membrane rocked in the primary anti-body for 2 hours, and for others it sat overnight.

Following initial binding of the primary antibody (1:1,000 concentration), the membrane was rinsed to remove all unbound proteins. To do this, the membrane was rocked in 3% BSA-TBST three times for 10 minutes each. Membranes were then exposed to a 3% BSA-TBST

solution containing the secondary antibody (anti-rabbit; 1:10,000 concentration). The membrane was rocked slowly in this solution for approximately 1 hour at room temperature. The membrane was rinsed again, 3 times for 10 minutes each, in 3% BSA-TBST. In order to detect secondary antibody binding, a 33ul NBT/66ul BCIP substrate was poured on the membrane, which caused the antibodies to become stained, thus leading to detection of D2 receptor proteins. After approximately 10-15 minutes, the membrane was rinsed with DI, air-dried and stored in a dark place.

Analysis. A quantitative measure of D2 receptor concentrations was obtained by measuring the density of each band of the western blot using Kodak Gel-Logic 200 software. The blots were scanned and the bands of interest identified. Density of D2 receptor protein was calculated relative to values obtained from bands labeled for α-tubulin (e.g., D2 receptor density /tubulin density). A one-way ANOVA was performed, with dose as the between-groups factor, to assess the differences between band intensities.

Curve Fitting

Several methods have been developed to describe choice behavior. Two widely used models are Herrnstein's Matching Law (1961) and Mazur's Hyperbolic Discount Function (1987). While the two models describe choice behavior in different ways, they are similar in that each account for the role that delay plays in altering choice behavior.

The Matching Law. The matching law is a theory of choice behavior. Specifically, it is a theory which predicts that, over time, relative rates of responding will match relative rates of reinforcement in a given situation (Herrnstein, 1961). The matching law does not predict *that* a choice will be made (e.g. whether you get up in the morning or stay in bed); rather it predicts the fraction of time in which a certain choice *will* occur (Herrnstein, 1997). Simply stated, the

matching law predicts that when human or non-human animals are placed in a situation whereby behavior is free to vary across different activities, animals will allocate their behaviors to each activity in exact proportion to the value of reinforcement obtained from each activity (Herrnstein, 1961). Generally, studies assessing the matching law do so using concurrent variable-interval or variable-ratio schedules of reinforcement. It will be beneficial to assess how this equation predicts choice behavior under the current response situation since many real life choice situations fall under a fixed-ratio schedule of reinforcement (e.g., taking the drug now or not taking the drug).

There are four main properties of matching. These factors include: 1) the amount of the reinforcer 2) the quality of the reinforcer 3) the rate at which the reinforcer is delivered and 4) the delay which is endured to attain the reinforcer. Since each factor has been shown to play an integral role in matching, each property has been factored into the generalized matching equation. The current study focused on how delay affects impulsivity using the following modified equation of the matching law:

$$V = A/D$$

whereby 'V' represents value of a reinforcer, 'A' represents amount of the reinforcer and 'D' is the delay to each reinforcer.

Mazur's Hyperbolic Discount Function. Another way in which choice behavior can be described is by Mazur's hyperbolic discount function (Mazur, 1987). This theory suggests that a hyperbolic relationship between reinforcer value and delay underlies choice behavior. In other words, it predicts that the delay to a given reinforcer is inversely related to reinforcer value. Therefore, if the delay to a reinforcer is long, the value of that reinforcer is smaller than if the delay to the reinforcer is short (Domjan, 2003; Anderson & Woolverton, 2005). Multiple studies

have assessed how this model describes choice behavior during a standard delay-discounting procedure (e.g., Mazur, 1987). In the current study, the following hyperbolic discount function was used in order to assess how delay affects the value of the smaller-sooner and larger-later reinforcers on the delay-discounting task:

$$V = A / (1 + kD)$$

whereby 'V' represents the value of a given reinforcer, 'A' represents the amount of that reinforcer and 'D' is the delay at which that reinforcer is delivered. '*k*' is a free parameter which represents how sharply the value of a reinforcer (V) decreases following certain delays (D) (Mazur, 2001). Work assessing choice behavior has used *k* as a measure of the degree to which subjects tolerate delay (e.g., Madden, 2008). For instance, work with humans has shown that *k* serves as a predictor for future drug use (e.g., Kollins, 2003). Larger '*k*' values signify greater impulsivity.

Analysis. A goodness-of-fit (chi-square) analysis was used to assess which model best fit the current data. The number of larger reinforcer choices made by rats during baseline, drug and withdrawal phases was analyzed against predictions made by the matching law and the hyperbolic discount models of choice. For the hyperbolic discount function, *k* values were adjusted to acquire the best fitting function, and were recorded to assess how cocaine affected the 'value' of delayed reinforcers.

Results

Delay-Discounting Task

Baseline. Figure 1 shows the mean percentage of choices made for the larger reinforcer across the last 3 days of baseline testing. Choice for the larger reinforcer decreased as delay to reinforcement increased [$F(4, 80) = 241.215$, $p < 0.001$]. As expected, there were no significant

difference between each groups' percentage of choices for the larger reinforcer during baseline testing [F (12, 4) = 1.269, $p = 0.253$].

Drug and Withdrawal Phases. Indifference points from the drug and withdrawal phases are plotted in figure 2 in order to show changes over time. Indifference points for day 1 of testing are not shown due to data loss because of computer malfunction. There was a main effect of dose during the drug administration [F (3, 21) = 6.051, $p = 0.004$] and withdrawal [F (3, 39) = 73.228, $p < 0.001$] phases. Rats that received 15 mg/kg of cocaine had significantly smaller indifference points during drug administration than did rats that received DI ($p = 0.017$). Rats that received 15 mg/kg of cocaine also had smaller indifference points during withdrawal from cocaine than rats that received DI ($p < 0.001$) 3 mg/kg of cocaine ($p < 0.001$) and 7.5 mg/kg of cocaine ($p < 0.001$).

There were significant main effects of delay [F (1.940, 31.045) = 173.315, $p < 0.001$] and day [F (5.631, 90.095) = 3.569, $p = 0.004$] during testing (days 2-23). In addition, there was a delay by day by dose interaction [F (33.329, 177.756) = 1.643, $p = 0.022$] for the percentage of choices made for the larger reinforcer. Separate analyses on the drug and withdrawal phases revealed a main effect of day [F (3.857, 61.714) = 3.568, $p = 0.012$] and delay [F (1.461, 23.384) = 189.014, *p*, 0.001] for the drug phase and a main effect of delay [F 1.935, 38.704) = 122.417, $p < 0.001$] for the withdrawal phase.

Figure 3 shows the mean percentage of choices made for the larger reinforcer by rats in each drug condition as a function of delay, for each day of drug exposure (day 1 is not shown due to computer failure). On day 5, rats that received 7.5 and 15 mg/kg of cocaine made significantly fewer responses for the larger reinforcer when the larger reinforcer was delayed 10 s than did rats that received DI ($p = 0.014$; $p = 0.011$ respectively*).* On day 8, rats that received

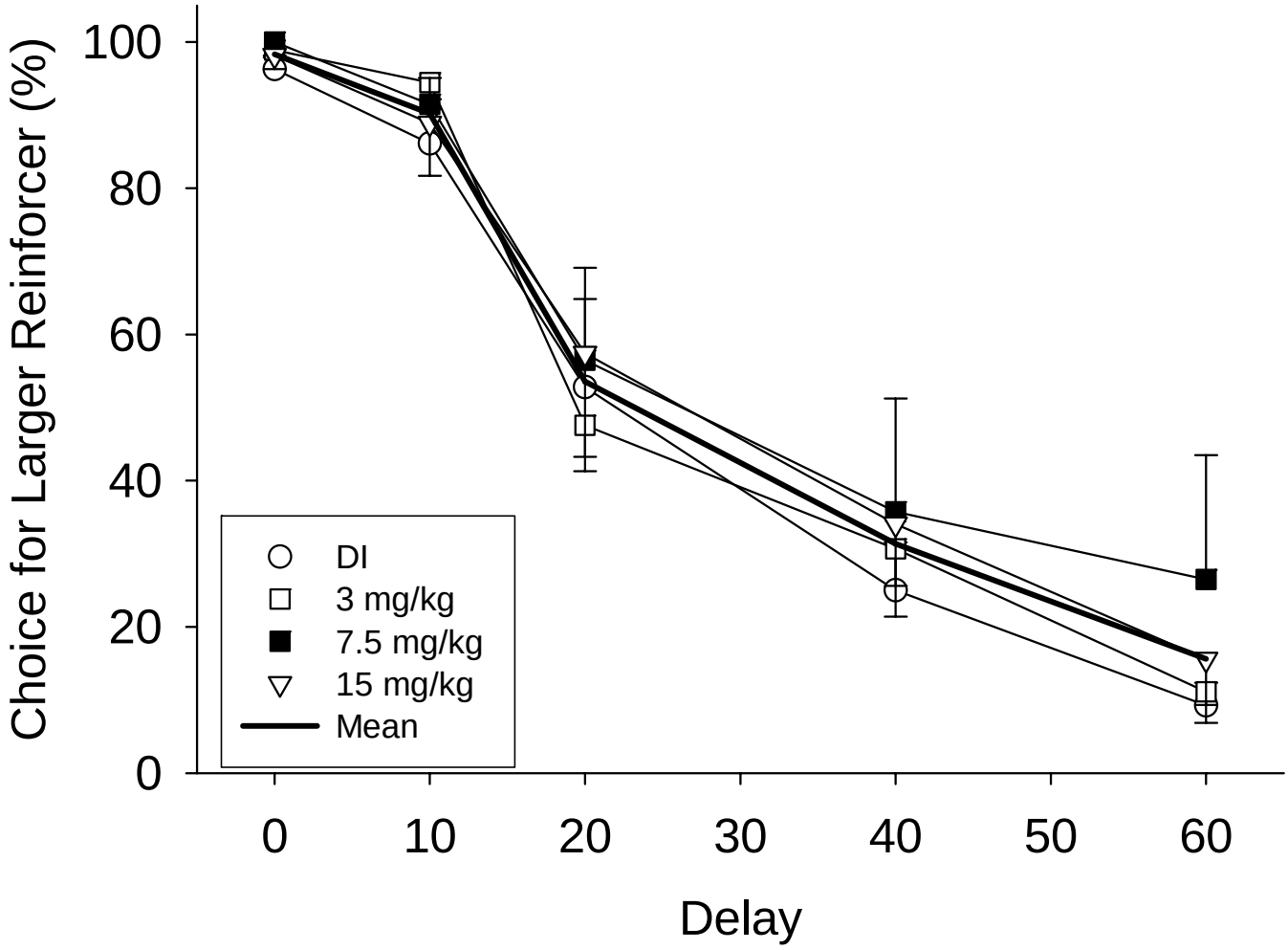

Figure 1. Percentage of choices made for the larger reinforcer during the last three days of baseline testing.

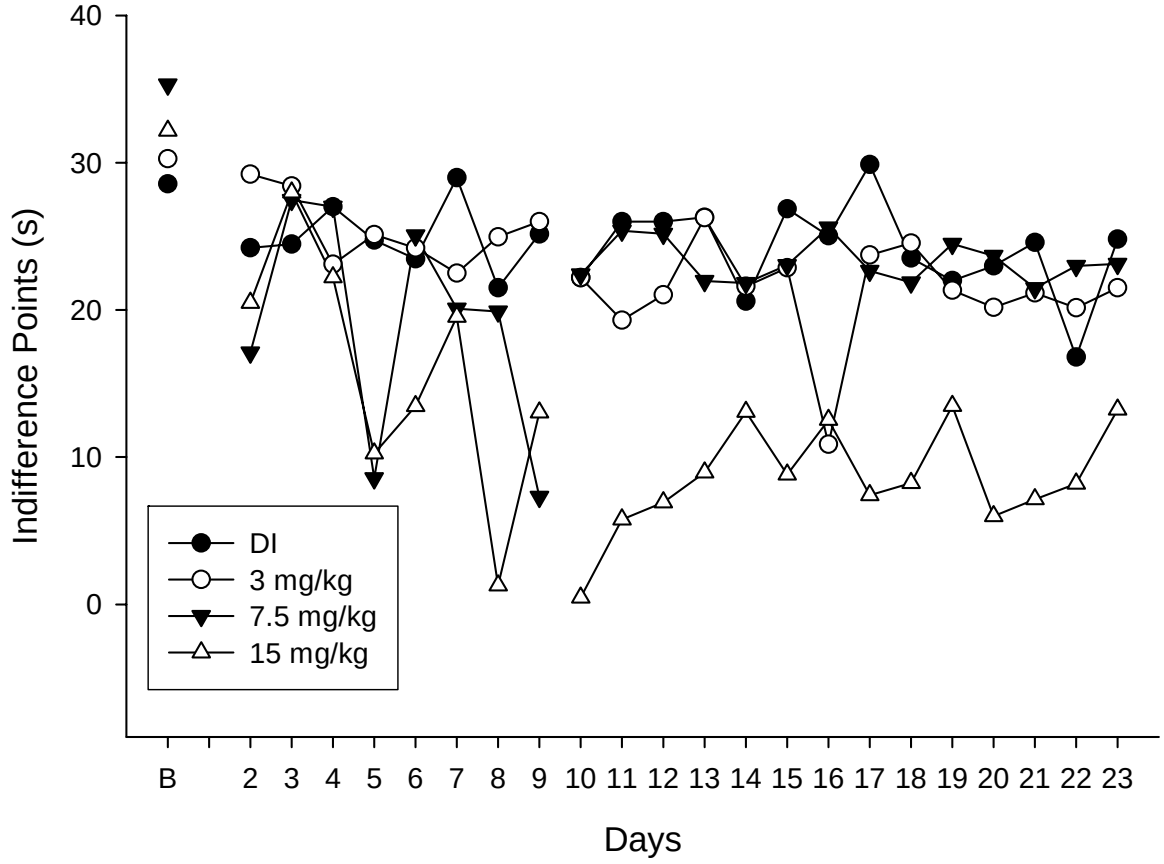

Figure 2. Indifference points across time. Each point represents the mean indifference point for rats in each drug condition (N = 6). 'B' represents baseline performance prior to drug administration, days 2-9 represent the drug administration phase and days 10-23 represent the withdrawal phase.

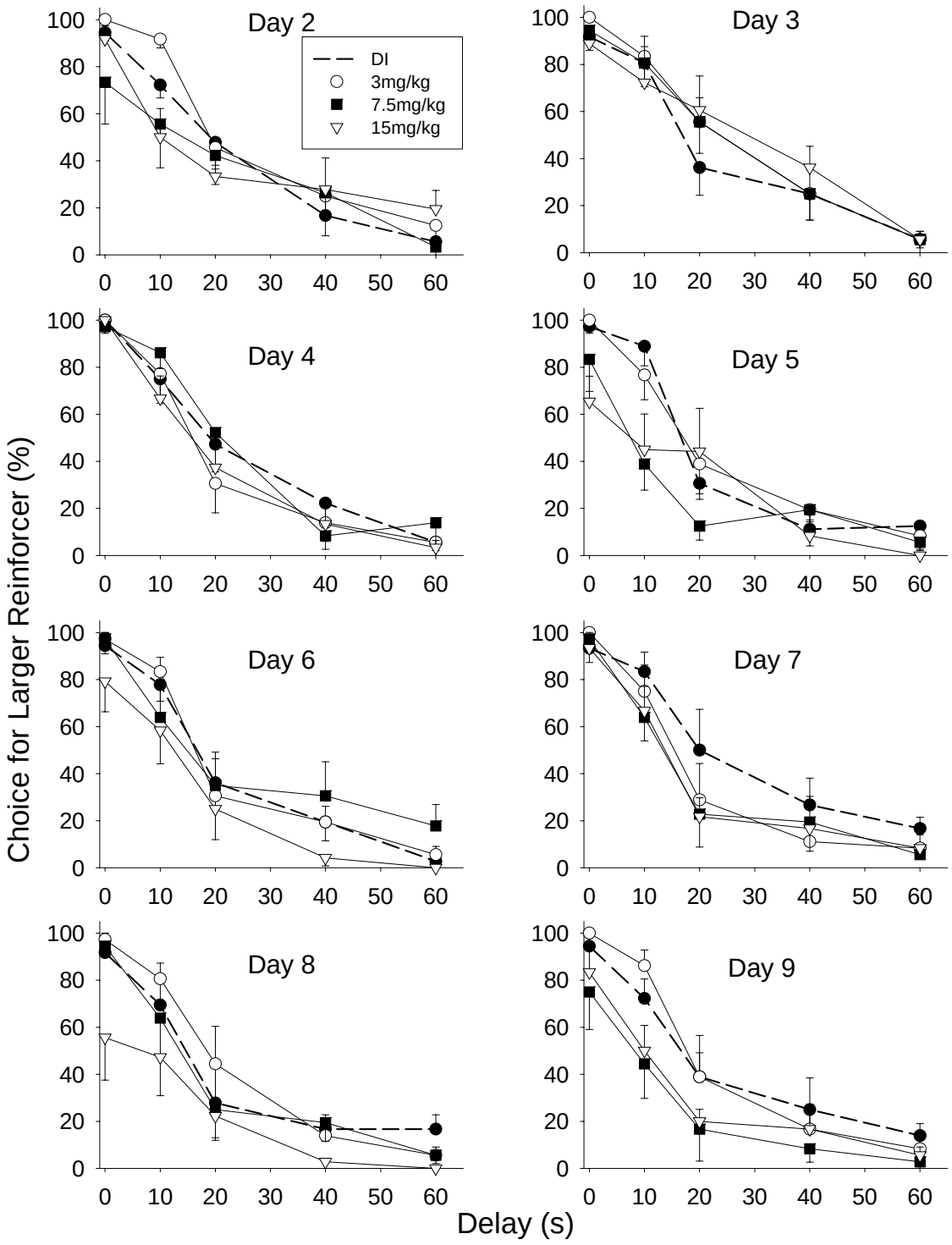

Figure 3. Percentage of choices made for the larger reinforcer across all days of drug administration.

15 mg/kg of cocaine made significantly fewer choices for the larger reinforcer when the larger reinforcer was delayed 0 s than did rats that received 3 mg/kg of cocaine ($p = 0.034$); these rats also made significantly fewer choices for the larger reinforcer when it was delayed 60 s than did rats that received DI ($p = 0.042$). Rats that received 7.5 and 15 mg/kg of cocaine also made significantly fewer choices for the larger reinforcer on day 9 than during baseline ($p = 0.037$; $p = 0.008$).

Figures 4 and 5 show the mean percentage of choices made for the larger reinforcer by rats in each drug condition as a function of delay, across all 14 days of withdrawal from cocaine (days 10-23) . Rats that received 15 mg/kg of cocaine chose the larger reinforcer significantly less during the first day of cocaine withdrawal (day 10) when the larger reinforcer was delayed 0 s than rats that received DI ($p = 0.024$), 3 mg/kg of cocaine ($p = 0.003$) and 7.5 mg/kg of cocaine ($p = 0.009$). As days without cocaine increased, these findings diminished, and by day 16 were no longer present ($p = 0.356$). Rats that received 15 mg/kg of cocaine chose the larger reinforcer significantly less on day 10 than during baseline ($p = 0.038$) and at the start of testing (e.g., day 2; $p = 0.049$). However, no significant differences were found between days 8 or 9 and day 10 (e.g., $p = 0.960$).

Choice Patterns. All rats omitted responses (did not press one of the levers) during forced-choice trials (see figure 6); this behavior was most prominent when delays to the larger reinforcer were high (e.g., 40 & 60 s). There were no significant differences between the number of choices omitted by rats that received cocaine and those that did not [$F (3, 20) = 1.626$; $p = 0.215$]. The larger reinforcer was omitted significantly more than the smaller reinforcer ($t = -2.714$, $p = 0.009$), and omissions were often followed by exclusive preference for the non-

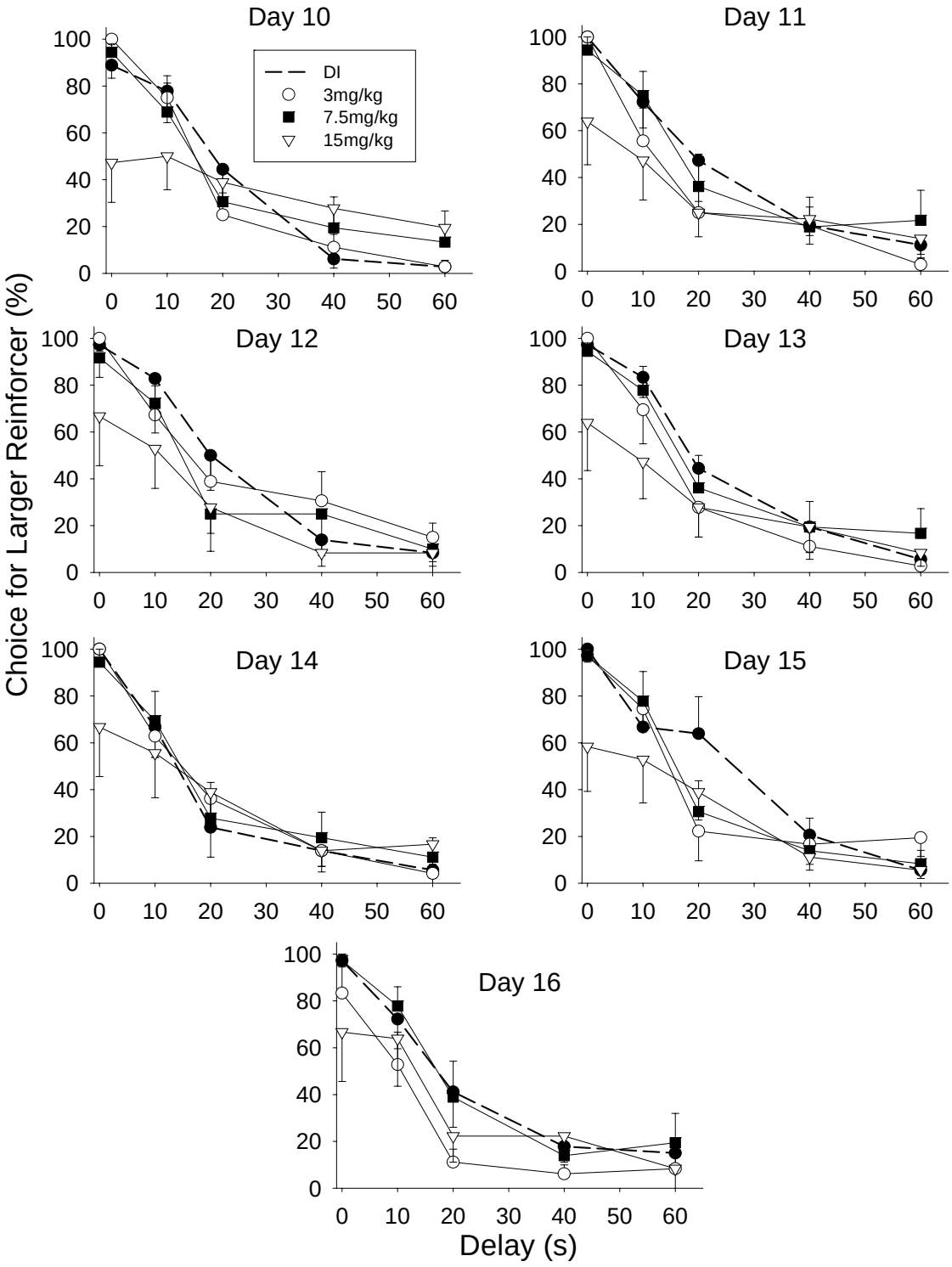

Figure 4. Percentage of choices made for the larger reinforcer across the first 7 days of withdrawal (days 10-16).

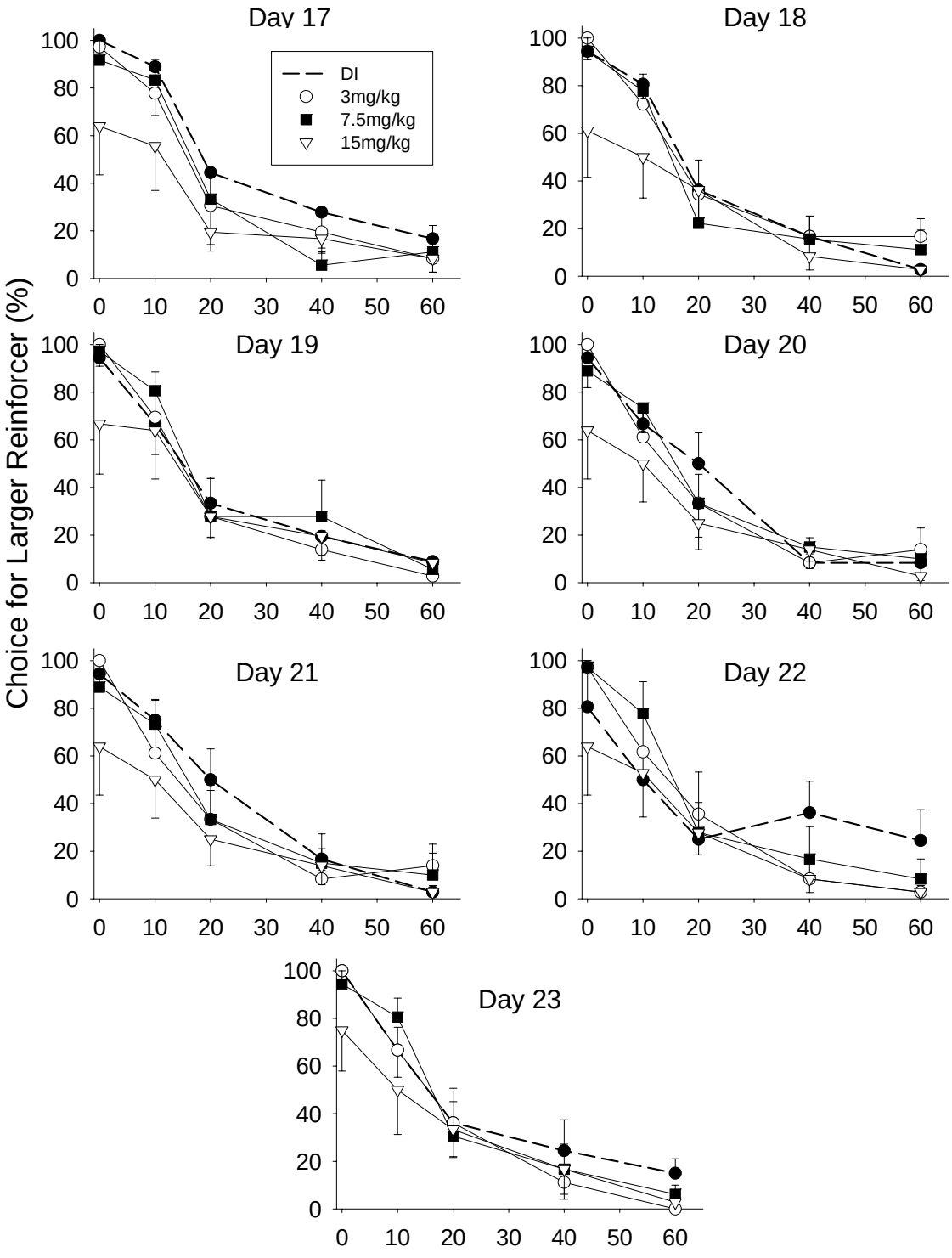

Figure 5. Percentage of choices made for the larger reinforcer across the last 7 days of withdrawal (days 17-23).

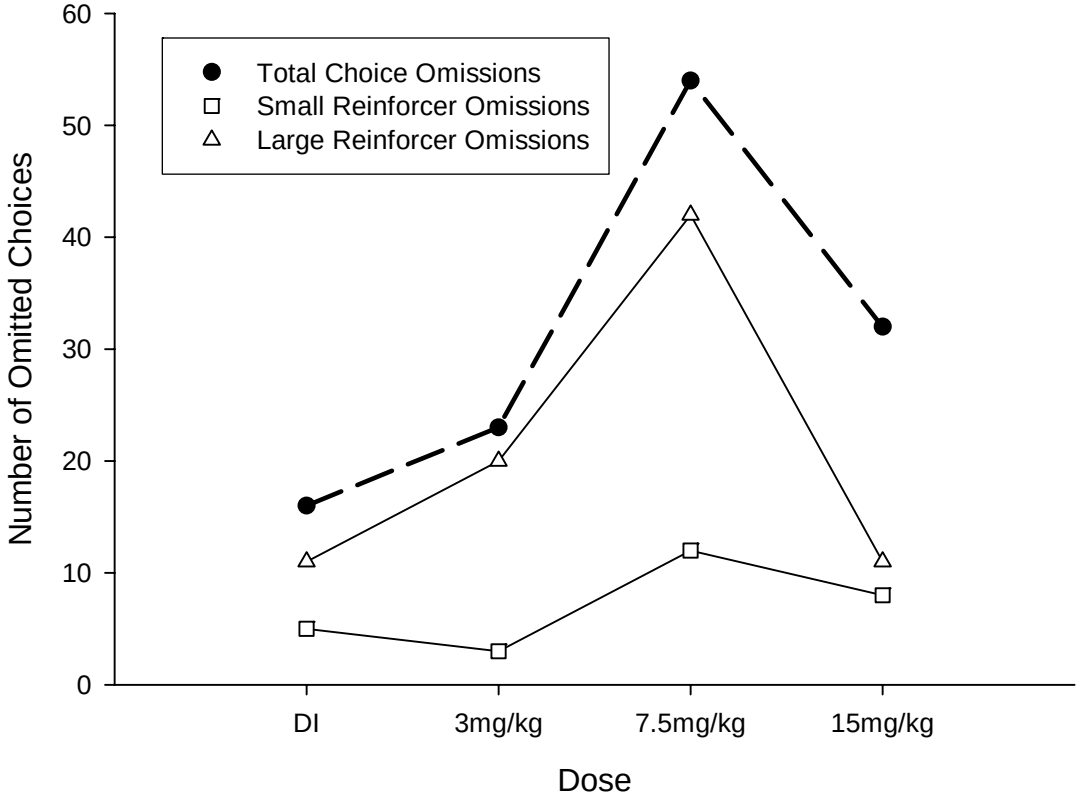

Figure 6. Number of omitted choices made on forced-choice trials during drug administration. omitted reinforcer (85 out of 125 lever omissions) during the proceeding free-choice trials (e.g., if the larger reinforcer was omitted the smaller reinforcer was preferred).

Western Blots

D2 receptor densities for each treatment group are shown in figure 7. Each bar represents data from two rats, with the exception of the 7.5 mg/kg cocaine condition which depicts data from only one rat. There were no significant differences in the number of D2 receptors in the NAc of rats that received cocaine compared to control animals [$F(2, 3) = 0.088396$, $p = 0.91$].

Curve Fitting

The rats' pattern of choice behavior on the delay-discounting task was compared against predictions made by the generalized matching law and the hyperbolic discount function; findings are summarized in tables 1 and 2. It was expected that both choice formulas would depict a hyperbolic function and that animals would show a decrease in preference for the larger reinforcer as a function of delay to that reinforcer. Past work supports the idea that choice behavior resembles a hyperbolic function with respect to delay (e.g., Mazur, 1987; Herrnstein, 1997). Choice for the larger reinforcer decreases in a negatively accelerating curve, whereby a dramatic decrease in preference for the larger reinforcer is seen at shorter delays and at larger delays decreases in preference reaches a plateau.

Chi-square goodness-of-fit analyses revealed that both the generalized matching law and hyperbolic discount function were a good fit for the current data. In particular, the matching law was a better fit for data when no drug was administered (e.g., baseline phase and rats administered DI; e.g., $\chi^2 = 0.237$) than was the hyperbolic discount function (e.g., $\chi^2 = 0.716$; see figure 8). This was the case even when the best fitting 'k' value for the hyperbolic discount function was obtained. On the other hand, figures 9 and 10 show that the hyperbolic discount

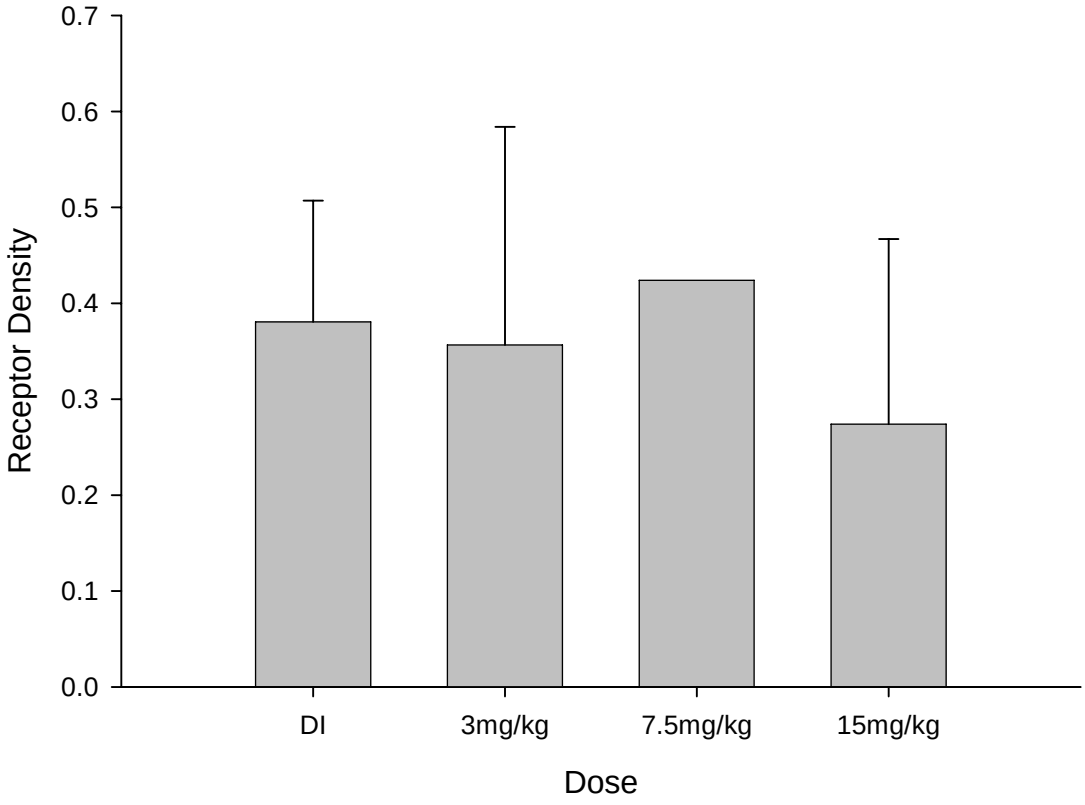

Figure 7. D2 receptor densities for rats in each drug condition.

Chi-Square: Goodness-of-Fit						
	Baseline		**Drug**		**Withdrawal**	
	HDF	ML	HDF	ML	HDF	ML
DI	1.056	0.323	0.769	0.718	0.634	0.427
3	1.177	0.214	1.045	0.661	0.684	1.809
7.5	0.354	0.718	0.362	0.999	0.779	1.005
15	0.667	0.342	0.591	1.914	1.296	3.139
Mean	0.716	0.237	0.582	0.992	0.582	1.353

Table 1. Chi-square (goodness-of-fit) values for data from baseline, drug and withdrawal phases for the hyperbolic discount function (HDF) and the matching law (ML) across all drug conditions.

Hyperbolic Discount Function: 'K' Values			
	Baseline	**Drug**	**Withdrawal**
DI	0.055	0.075	0.063
3	0.049	0.07	0.1
7.5	0.037	0.08	0.082
15	0.039	0.1	0.15
Mean	0.0461	0.093	0.093

Table 2. 'K' values for the best fitting hyperbolic discount function curve.

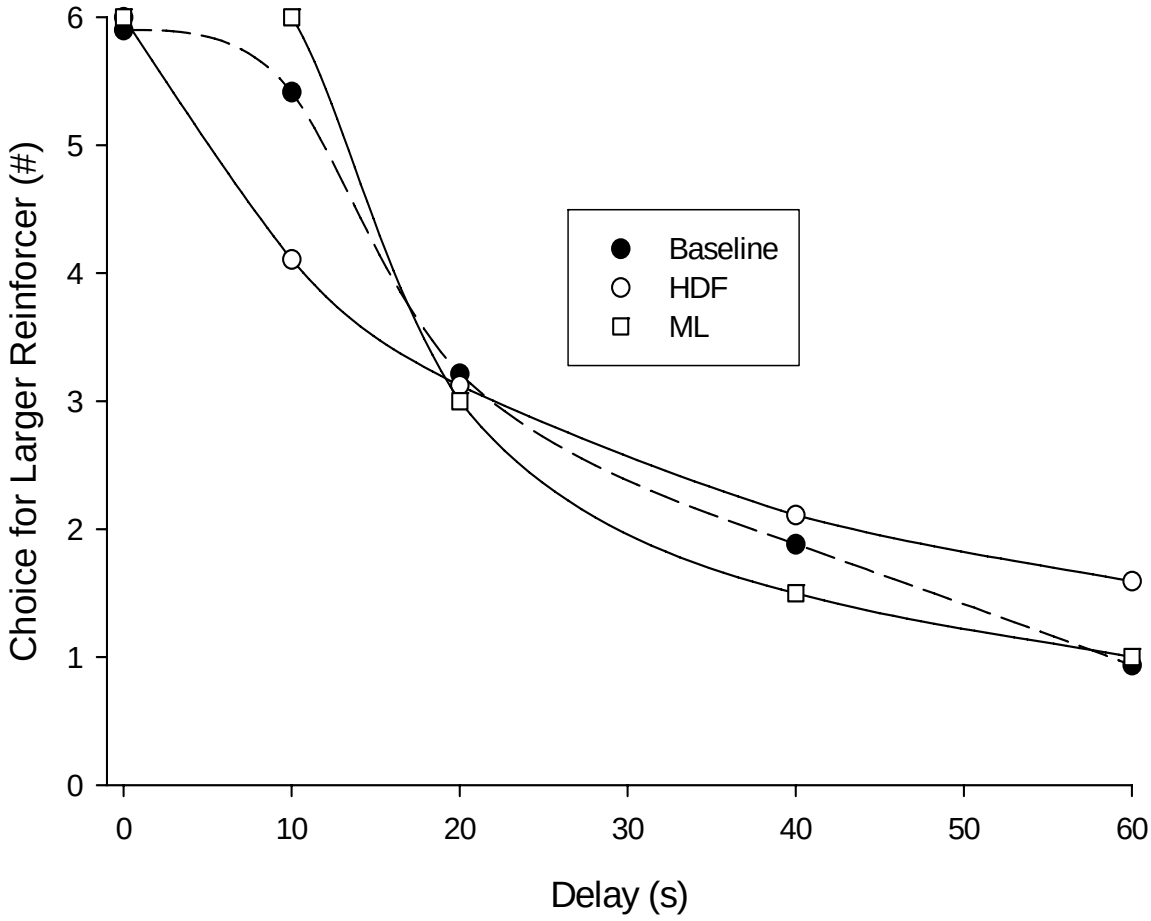

Figure 8. Best fitting hyperbolic discount function (HDF) and matching law (ML) functions for rats during baseline testing.

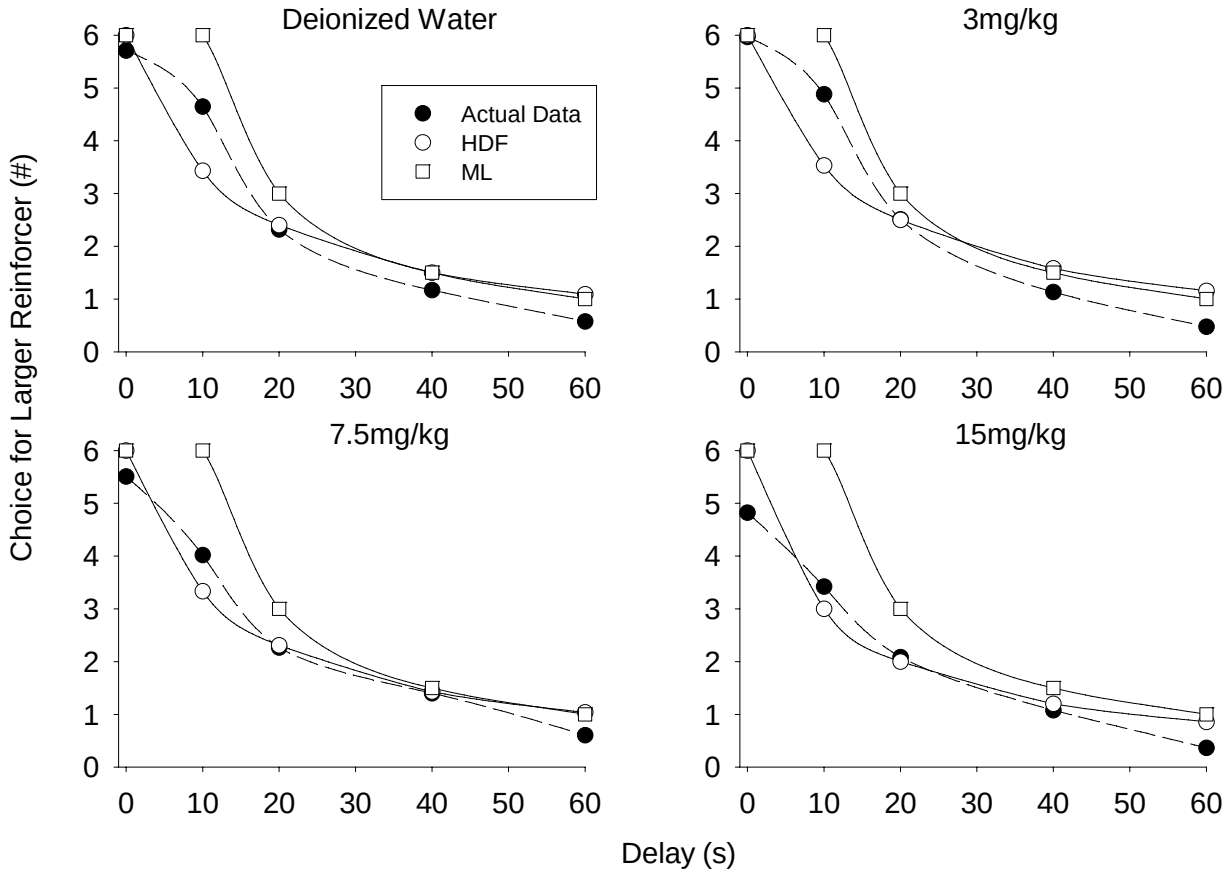

Figure 9. Best fitting hyperbolic discount function (HDF) and matching law (ML) functions for rats during the drug administration phase.

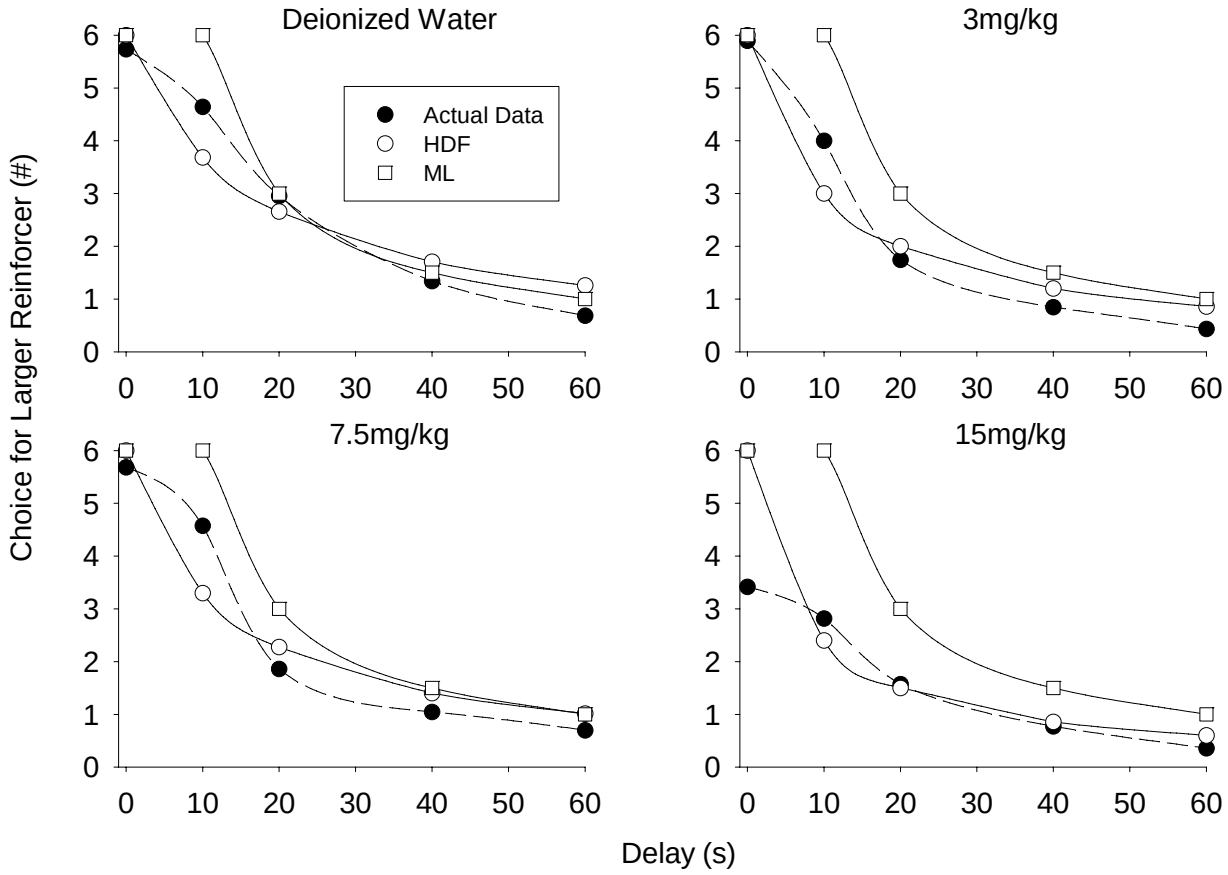

Figure 10. Best fitting hyperbolic discount function (HDF) and matching law (ML) functions for rats during the withdrawal phase.

function provided a better fit for data from rats that received cocaine across drug and withdrawal phases of the study (e.g., $\chi^2 = 0.582$) than did the matching law (e.g., $\chi^2 = 0.992$; see table 1). In particular, the hyperbolic discount function provided a better fit for data for rats that received the highest doses of cocaine (7.5 and 15 mg/kg) during the drug administration phase ($\chi^2 = 0.362$ and 0.591 respectively) and during withdrawal provided a better fit for data across all doses of cocaine ($\chi^2 = 0.684$, 0.779 and 1.296).

As expected, 'k' values from the hyperbolic discount function were higher (indicating a reduced preference for the larger reinforcer) for rats that received cocaine than rats that received DI (see table 2). In particular, the best fitting hyperbolic discount curve for rats that received DI during the drug administration phase had a 'k' of 0.075, whereby the best fitting curve for rats that received 7.5 mg/kg and 15 mg/kg of cocaine had 'k' values of 0.08 and 0.10 respectively. Similar results were obtained during withdrawal, whereby the 'k' values for the best fitting curve for rats that received DI and 3 mg/kg of cocaine were 0.063 and 0.10 respectively, and for rats that received 7.5 and 15 mg/kg of cocaine were 0.082 and 0.15 respectively. 'K' values for rats that received 7.5 and 15 mg/kg of cocaine also increased across phases (from baseline to drug administration and from drug administration to withdrawal; see table 2).

Discussion

The purpose of the current study was three-fold: (1) to assess changes in impulsive behavior on a delay-discounting task during and immediately following chronic cocaine exposure (2) to assess the potential effects that chronic cocaine exposure has on the DA system and (3) to assess how these findings are best predicted by two prominent choice theories. Past work shows that not only is the choice to use cocaine an act of impulsivity (Logue et al., 1992),

but the use of cocaine itself has been shown to increases impulsivity in human and non-human animals (Logue et al., 1992; Coffey et al., 2003; Paine et al., 2003; Roche et al, 2007). This increase in impulsivity has been suggested to manifest, in part, due to alterations in DA neurotransmission; namely, decreases in levels of dopamine D2 auto-receptors in rats NAc (Anderson & Woolverton, 2005; Dalley et al., 2007).

Based on past work (e.g., Paine et al., 2003; Roesch et al., 2007), it was predicted that impulsive behavior would increase as a function of increasing delay, and that cocaine would exacerbate this in a dose-dependent manner. It was also expected that increased impulsivity would negatively correlate with D2 receptor levels in rats' NAc, whereby rats that received cocaine would have decreased levels of D2 receptors relative to control animals. In addition, it was expected that choice behavior on the delay-discounting task would be hyperbolic, and best fit by Mazur's Hyperbolic Discount Function (Mazur, 1987). Results of the present study were consistent with some, but not all, of these predictions. Chronic cocaine exposure did increase impulsivity, this was described by both the matching law and hyperbolic discount function. However, D2 receptor levels were not correlated with increased impulsivity.

Delay-Discounting Task

This is the first study to report how impulsivity changes over time when cocaine is present during testing. Most studies that have assessed the effects of cocaine on impulsivity have done so either hours (Paine et al., 2003) or weeks (Roesch et al., 2007) following cocaine exposure. Only one study to date has assessed delay-discounting when cocaine was present during testing (Logue et al., 1992); but that study did not assess a time-course of drug action (effects of cocaine across each day of testing). In addition, most studies have only tested a single dose of cocaine (e.g., Logue et al., 1992; Paine et al., 2003).

In the current study, impulsive behavior was assessed preceding, during and for two-weeks following chronic exposure to cocaine (3, 7.5, 15 mg/kg) or DI (1 mg/kg). As expected, prior to cocaine administration rats chose the larger reinforcer less as delay to its presentation increased. Cocaine exacerbated this effect. Rats that received 15 mg/kg of cocaine had significantly smaller indifference points (indicating heightened impulsivity) and chose the larger reinforcer significantly less on the delay-discounting task relative to baseline and control animals during the drug administration and withdrawal phases. As days with cocaine exposure increased, a gradual decrease in rats' indifference points occurred, followed by a gradual increase in indifference points following cessation of cocaine. These findings are in accord with past research showing that chronic cocaine administration increases impulsive behavior on delay-discounting tasks (e.g., Logue et al., 1992; Paine et al., 2003; Roesch et al., 2007). Impulsivity increases when cocaine is present (e.g., Logue et al., 1992) and remains altered even after discontinued use (e.g., Roesch et al., 2007). However, some discrepancies do exist between past work and current findings.

First, Logue et al. (1992) reported an increase in impulsivity during cocaine administration, with a full recovery to baseline when cocaine (15 mg/kg) administration ceased. As in Logue et al. (1992), the current study reported an increase in impulsive behavior during cocaine exposure, but only a partial recovery to baseline following 15 mg/kg of cocaine (see figure 3). These differences may be the result of the *duration* of cocaine exposure as well as differences in how the findings of each study were analyzed. Rats in Logue et al. (1992) achieved stability on the discounting task at different rates, which altered the number of days each rat was exposed to cocaine (10-36 days). The duration of cocaine exposure may play a role in the long-term effects cocaine has on behavior.

In the current study, all rats received cocaine for nine consecutive days. It may be the case that rats in Logue et al. (1992) that were exposed to cocaine for shorter periods of time had fewer alterations in impulsive behavior following the cessation of cocaine than rats exposed to cocaine for prolonged periods of time. The measures of impulsivity in that study were collapsed across rats, and derived from the last five stable days of testing during baseline and cocaine administration, therefore this cannot be assessed. Current findings analyzed behavior on individual days of testing, showing how behavior changed across time, and not just the end-result of cocaine treatment. Past work (Logue et al., 1992) tell us how repeated exposure to cocaine alters behavior while cocaine is present, but does not give a time-course of how behavior is altered during and immediately following cocaine use.

Second, as in the present study, Paine et al. (2003) assessed the time-course of cocaine's effects on impulsive behavior, but reported only a transient increase in impulsivity (on day 7 of 14) following chronic exposure to cocaine with a return to baseline performance by day 14. Current findings showed a gradual increase in impulsive behavior with no return to baseline performance. These discrepancies may be due to differences in the *timing* of cocaine administration. Paine et al. (2003) administered cocaine (15 mg/kg) *following* completion of the delay-discounting task. In the current study, cocaine (3, 7.5, 15 mg/kg) was administered five minutes *preceding* the task. These findings suggest that the effects of cocaine on impulsivity are time dependent. That is, there is a more gradual increase in impulsive behavior when cocaine is present during testing, but only temporary alterations in impulsivity when cocaine is absent during testing.

Lastly, when cocaine administration ceased, indifference points for rats that received 7.5 mg/kg of cocaine recovered to baseline immediately, and rats that received 15 mg/kg of cocaine

partially recovered. Past work (Roesch et al., 2007) reported significant increases in impulsive behavior six weeks following chronic exposure to cocaine (30 mg/kg); this is four weeks longer than reported in the current study. Discrepancies in the length of time impulsive behavior persisted may be the result of the *dose* of cocaine administered. Lower doses of cocaine were used in the current study relative to Roesch et al. (2007). Taken together, these findings suggest that the effects of cocaine on impulsive behavior are dose-dependent, such that at low doses (7.5 mg/kg) no long lasting effects on impulsivity were seen following cessation of cocaine, and at moderate doses (15 mg/kg) gradual decreases in impulsivity were seen as days without cocaine increased. At higher doses (30 mg/kg), impulsive behavior remained significantly heightened up to six weeks following cocaine cessation (Roesch et al., 2007).

Overall, findings are in agreement with past work that chronic cocaine leads to an increase in impulsive behavior on delay-discounting tasks (Logue et al., 1992). The present findings show that impulsive behavior gradually increases following exposure to cocaine and that recovery is rapid after low doses of cocaine, but occurs slowly, if at all, after higher doses of cocaine (15 mg/kg). This study extends past work showing that the effects of cocaine on impulsivity are both dose and time dependent.

However, it could be argued that the preference rats show for a reinforcer during this task may actually be the manifestation of the animals' inability to discriminate between reinforcers due to drug effects. Is cocaine increasing rats' rate of discounting for delayed reinforcers, or is cocaine simply disrupting the animals' ability to distinguish between reinforcers? To investigate this, the choice patterns of rats were assessed during each session of drug exposure. This was done in order to ascertain if rats that received cocaine differed in their pattern of responding relative to rats that did not receive cocaine. There were no indications that rats' choice behavior

was the result of an inability to discriminate between reinforcers. The choice patterns of rats that received cocaine did not differ from rats that received DI. In fact, all rats exhibited similar behavior with respect to forced-choice trials. At the beginning of each set, forced-choice trials were utilized in order to ensure that rats experienced both the larger and smaller reinforcers prior to free-choice trials. Interestingly, all rats omitted responses during these trials.

This behavior occurred regardless of what lever reinforcement was made available, indicating that behavior was not due to a lever bias. These findings are similar to past work (Roesch et al., 2007) which found that rats that were chronically exposed to cocaine had an increased sensitivity to delay, exhibited less accurate responding (responding for the wrong reinforcer) and increased latencies to respond during forced-choice trials. Taken together, these findings may indicate a new aspect of impulsivity not yet assessed by researchers. As delay to reinforcement is increased, not only will rats show preference for the smaller-sooner reinforcer, but they will show this preference for the smaller reinforcer (not pressing the lever) even when the non-preferred option (delayed reinforcer) is the only available option (e.g., during forced-choice trials).

Western Blots

This is the first study to assess the effects of cocaine on D2 receptor levels and its relation to impulsive behavior. Most research that has assessed the role of the D2 receptor on impulsive behavior has generally assessed genetic, or non-drug related variables (e.g., Wade et al., 2000; Anderson & Woolverton, 2005; Dalley et al., 2007). In the current study, D2 receptor levels were assessed in rats that received cocaine or DI, and it was expected that increases in impulsivity would negatively correlate with D2-receptor binding sites in rats' NAc. Western blot analyses revealed no significant differences in D2 receptor binding sites in rats that received cocaine when

compared to rats that received DI. These findings may be the result of a small sample size and correspondingly high variance. Only two rats from the DI, 3 mg/kg and 15 mg/kg groups and one rat from the 7.5 mg/kg group were used in the western blot analyses. Variance between groups was high; therefore, it is possible that with additional rats, differences in D2 receptor levels would emerge. The current findings do not show that D2 receptors play a role in mediating the effects of cocaine on impulsive behavior.

Curve-Fitting

In the current study, choice behavior (percentage of choices made for the larger reinforcer) during baseline, cocaine exposure and withdrawal was compared to predictions made by the generalized matching law and hyperbolic discount function. Past work (Mazur, 2001) suggests that the generalized matching law is a better fit for concurrent schedules of reinforcement, and that the hyperbolic discount function is a better fit for discrete-trial schedules of reinforcement. However, both the matching law and hyperbolic discount function provided a good fit for the current data. The matching law was a better fit for rats' behavior in the absence of cocaine (baseline and control animals) and the hyperbolic discount function was a better fit for rats' behavior when cocaine was administered at higher doses (7.5 and 15 mg/kg).

Typically, concurrent variable interval (VI) schedules of reinforcement are used to assess the relationship between choice and non-drug reinforcement (e.g., see Davison & McCarthy, 1988 for review; Herrnstein, 1997). In these cases, the matching law is often a good predictor of choice (e,g, Davison & McCarthy, 1988; Anderson, Velkey & Woolverton, 2002). However, less work has assessed how the matching law fits patterns of behavior derived from fixed-ratio (FR) discrete-trial schedules of reinforcement. Current findings using an FR schedule revealed that in the absence of cocaine, rats' relative rates of responding matched relative rates of reinforcement

but when cocaine was on board rats appeared to undermatch, or choose the larger reinforcer less than predicted by the matching law. Undermatching is common in situations that use VI schedules of reinforcement (e.g., Meyers & Meyers, 1977; Anderson et al., 2002). Therefore, it may be concluded that under certain situations the matching law explains behavior derived from FR schedules in a similar manner as behavior derived from VI schedules. Cocaine alters this in such a way that larger-delayed reinforcers become preferred less than smaller-sooner reinforcers. In other words, relative rates of responding (choice preference) no longer matched relative rates of reinforcement (reinforcer amount).

When cocaine was present during testing, the hyperbolic discount function served as a better model for choice (when the best fitting k values were obtained), suggesting that cocaine altered the value of delayed reinforcers in a hyperbolic manner. Past work (Critchfield & Kollins, 2001; Kollins, 2003) shows that the 'k' parameter functions as a measure of impulsivity, whereby larger 'k' values represent higher rates of discounting (increased impulsivity) and lower 'k' values represent lower rates of discounting (decreased impulsivity). Drug users often generate larger 'k' values than do non-drug users (Kollins, 2003) and discount delayed reinforcers at higher rates than non-drug users (e.g., Kirby & Petry., 2004). Current findings support this work; during drug administration and withdrawal, rats that received larger doses of cocaine (15 mg/kg) were more impulsive and had correspondingly larger 'k' values than rats that received lower doses of cocaine (3 and 7.5 mg/kg) or DI and were less impulsive. These findings show that 'k' is positively correlated with impulsivity. Additionally, higher 'k' values obtained during drug exposure correlated with higher 'k' values during withdrawal, supporting past work that 'k' can serve as a predictive measure of future impulsivity (Kollins, 2003).

Overall, current findings show that behavior on the delay-discounting task was hyperbolic, and that in the absence of cocaine relative rates of responding matched relative rates of reinforcement. When cocaine was administered, rats no longer exhibited matching behavior and the value of the larger reinforcer decreased in a dose-dependent manner.

Limitations

The current study has several limitations that should be accounted for in future work. First, cocaine was only administered for 9 days due to a bad shipment of the drug. Future work could replicate this study with all 14 days of cocaine exposure as originally planned. Extended exposure to cocaine may alter changes in impulsivity during withdrawal from the drug. Second, due to the nature of the delay-discounting task, the pattern of choices made by several of the rats during cocaine administration did not lend itself to the calculation of an indifference point. Using a titrating procedure may be more advantageous when assessing indifference points than the adjusting delay-discounting procedure used the in the current study. A titrating procedure would allow subjects to alter reinforcer delay based on their own choices, thus obtaining individual indifference points. Lastly, a small sample size was used to derive measures of D2 receptor density. Future work should increase the number of animals used to assess D2 receptor levels following chronic cocaine exposure in order to better represent the sample of animals tested.

Future Work

The results of the current study raise several important points that should be considered in future research. First, the rats' behavior remained altered during withdrawal from cocaine, indicating that long-term changes had taken place following chronic cocaine exposure. Past research (Roesch et al., 2007) reported changes in impulsive behavior up to six weeks following cocaine exposure, yet no work has assessed how long these changes persist. Future work should

assess a time-course of behavior to ascertain how long these changes persist and their corresponding biological mechanisms. There is evidence to suggest that the behavioral and biological changes that occur following chronic cocaine exposure are permanent (e.g.,Volkow et al., 1993). Even after four months of abstinence, cocaine addicts still exhibit decrements in brain functioning relative to normal controls (Volkow et al., 1993).

Second, current findings may suggest that chronic, but not acute, cocaine increases impulsive behavior. This is implied from findings that show a significant reduction in preference for the larger reinforcer near the end of drug treatment (days 8 and 9) and during withdrawal (day 10) but not on earlier days of treatment (e.g., day 2). To assess this, future work should replicate the current study using acute (single injections) cocaine administration and compare results to current findings.

Third, in relation to the biological underpinning of impulsivity, further investigation should continue to assess the role of the D2 receptor in mediating this behavior. Western blots can tell us how many D2-like receptors are located in areas like the NAc, however, it is not a fully quantitative measure and does not show the binding affinity for each receptor, as would be shown using techniques such as radio-ligand binding assays. Therefore, further investigation with more quantitative techniques should be conducted to further assess the role this receptor plays in mediating the effects of cocaine on impulsive behavior.

Fourth, in assessing how to relate these findings to the matching law and hyperbolic discount function, future work should assess modified versions of the matching law. One version of this equation employs factor 'I.' This factor, much like 'k' used in the hyperbolic discount function, is a free parameter which acts as a scaling factor for delay. Animals that sharply discount delayed reinforcers have higher values of 'I' than animals that gradually discount

delayed reinforcers (Herrnstein, 1997). It may be the case that this modified equation would better fit behavior exhibited during cocaine administration. Additionally, the hyperbolic discount function is a steady-state function that shows that cocaine increases impulsive behavior by devaluing delayed reinforcement, but it does not tell us how. Future work should assess alterations to the hyperbolic discount function to create a more dynamic function, so it can predict not only *if* changes in behavior will occur but *how* these changes will occur.

Lastly, future work should assess if pre-commitment procedures can alter impulsivity following cocaine exposure. Pre-commitment procedures create situations that allow animals to make a choice at an earlier point in time that will later inhibit their ability to choose a smaller reinforcer, over a larger reinforcer, at a later point in time. Rachlin and Green (1972) utilized a pre-commitment procedure to inhibit pigeons from switching preferences from a larger to a smaller reinforcer as delay to the larger reinforcer increased. Future work should assess if impulsivity due to cocaine exposure can be reversed using this procedure.

Applications

Taken together, findings from this study have several applications with regards to the effects cocaine has on impulsive behavior. First, if researchers can identify the patterns of behavior associated with illicit drug use, they can better treat those suffering from drug dependence. The current findings show a gradual decrease in indifference points over time during cocaine exposure (7.5 and 15 mg/kg). This pattern of behavior was best explained by the hyperbolic discount function, whereby at shorter delays dramatic increases in impulsivity were seen and reached a plateau at higher delays.

Second, by identifying the times at which individuals are most vulnerable for relapse (e.g., use cocaine or stay sober) researchers can better target when and how therapeutic

interventions are used. The current study showed that following low doses of cocaine (7.5 mg/kg) recovery of indifference points is rapid, and following high doses of cocaine recovery occurs slowly, if at all. These findings suggest that the period of time immediately following cocaine cessation is when individuals are most likely to make decisions that are impulsive and possibly lead to relapse (e.g., use cocaine or go to work).

Lastly, by identifying possible biological mechanisms mediating the effects of cocaine on choice behavior, researchers can develop effective pharmacotherapies for combating cocaine dependence. The current study did not find a role for the D2 receptor in mediating impulsivity following cocaine exposure. However, past work (e.g., Dalley et al., 2007; Pattij et al., 2008) did show a role for this receptor, as well as several other brain areas (e.g., orbitofrontal cortex and infralimbic region). These brain areas, along with the D2 receptor, should be investigated concerning the role they play in mediating impulsive behavior.

Summary and Conclusions

Chronic exposure to cocaine (7.5 and 15 mg/kg) gradually decreased indifference points (increased impulsivity) on a delay-discounting task. Following cessation of cocaine, recovery for rats that received lower doses (7.5 mg/kg) of cocaine was rapid. Recovery occurred slowly in rats that received 15 mg/kg of cocaine, suggesting that the effects of cocaine on impulsivity are both time and dose-dependent. Contrary to past work (e.g., Anderson & Woolverton, 2005; Dalley et al., 2007) D2 receptor levels did not differ between rats that received cocaine and those that received DI, suggesting other biological mechanisms may account for cocaine's effects on impulsivity. Current findings were best explained by the matching law when cocaine was absent and by the hyperbolic discount function when cocaine (7.5 and 15 mg/kg) was present. 'K'

increased as a function of cocaine dose, suggesting that cocaine dose-dependently increased impulsivity by decreasing the value of delayed reinforcers.

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ABSTRACT

THE EFFECTS OF CHRONIC COCAINE ON DELAY-DISCOUNTING IN RATS AND THE POTENTIAL ROLE OF THE D2 RECEPTOR

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The current study assessed changes in impulsive behavior as a result of chronic cocaine exposure and the potential role the D2 receptor played in mediating these effects. Findings were compared to predictions made by the matching law and the hyperbolic discount function. Twenty-four male Sprague-Dawley rats were exposed to a discrete-trials delay-discounting task in which they chose between a small reinforcer of 1 food pellet immediately and a large reinforcer of 3 food pellets after an adjusted delay (0, 10, 20, 40 60 s). Rats received daily injections of deionized water (DI) or cocaine (3, 7.5, 15 mg/kg) 5 min prior to the delay-discounting task for 9 consecutive days, followed by 14 consecutive days of testing in the absence of cocaine. Following testing, rats were euthanized and their brains removed in order to assess levels of D2 receptors in the nucleus accumbens (NAc) by means of a western blot analysis. All rats showed a decreased preference for the larger reinforcer as delay to the larger reinforcer increased. Repeated exposure to cocaine (7.5 and 15 mg/kg) further decreased preference for the larger reinforcer. When cocaine administration was discontinued, preference for the larger reinforcer returned to baseline levels in the 7.5 mg/kg group, but remained depressed in the 15 mg/kg group. Findings did not indicate a role of the D2 receptor in mediating these effects. Both the matching law and hyperbolic discount function provided a good fit for the data. These findings indicate that repeated exposure to cocaine dose-dependently alters impulsive behavior over time.

Impulsivity remains when cocaine is no longer administered and recovery after high doses of cocaine occurs slowly, if at all. The D2 receptor is not involved in mediating these effects, suggesting that other biological mechanisms may account for changes in behavior.