THE ACUTE EFFECTS OF COCAINE ON 5-HT_3 RECEPTOR ACTIVATION AND SELF-CONTROL IN RATS

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THE ACUTE EFFECTS OF COCAINE ON 5-HT$_3$ RECEPTOR ACTIVATION AND SELF-CONTROL IN RATS

Self-control can be defined as the selection of a larger but more delayed reinforcer, over a smaller but more immediate reinforcer. *Impulsivity* is the opposite of self-control, whereby a smaller more immediate reinforcer is chosen over a larger but more delayed reinforcer (Rachlin & Green, 1972; Ainslie, 1974; Grosch & Neuringer, 1981; Eisenberger, Masterson & Lowman, 1982; King & Logue, 1987; Logue, 1988). An interesting feature of the self-control literature, as it applies to animal learning, is its implications for understanding drugs of abuse. For example, Logue, Tobin, Chelonis, Wang, Geary and Schachter (1992) suggest that drug abuse, such as cocaine use, can be considered 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). Interestingly, cocaine has been shown to decrease self-control and increase impulsive behavior in the lab (e.g. Logue et al., 1992; Anderson & Woolverton, 2003; Coffey, Gudleski, Saladin, & Brady, 2003). By understanding the way in which drugs of abuse, such as cocaine, affect self-control behavior, we may gain a better understanding of the relationship between behavior and the corresponding pharmacological mechanisms.

The basis of cocaine's pharmacological effects on self-control and impulsive behavior are unclear, but it has been suggested that part of this effect is mediated by dopamine (DA) and serotonin (5-HT) neurotransmitter systems (e.g. Logue et al., 1992; Wade, de Witt & Richards, 2000; Cardinal, Pennicott, Sugathapala, Ribbins & Everitt, 2001; van Heering, 2001; van Gaalen, Reinhild, Bronius, Schoffelmeer, & Vanderschuren, 2006). Past research suggests that cocaine administration inhibits 5-HT reuptake, thus leading to an increase in synaptic 5-HT levels (Carey

& Damianopoulos, 1994; Walsh & Cunningham, 1997; Repetto & Gold, 2005). This increase in synaptic 5-HT activates the 5-HT_3 receptor, which is involved in presynaptic functioning, modulating neurotransmitter release (e.g. Jiang, Ashby, Kasser & Wang, 1989; Chen, Paredes, Van Praag, Lowinson & Gardner, 1992; Carta, Allan, Partridge, & Valenzuela, 2003). Specifically, research shows that 5-HT_3 receptor activation influences dopamine release directly (e.g.,Chen et al., 1992)

Systemically administered cocaine acts on all brain areas that have monoamines, including the nucleus accumbens (NAc) (e.g. Gratton & Wise, 1994). The NAc is one of the projections of the mesolimbic dopamine pathway, which is heavily associated with behavioral reinforcement, chronic drug abuse, and dependency of psychostimulant drugs (Julien, 1999). Lesions to this area have been shown to impair self-control behavior (e.g., Cardinal, et al., 2001). Specifically, Cardinal et al. (2001) showed that when rats were faced with the choice of a small and immediately available food reinforcer over a large but delayed reinforcer, those rats that received lesions to the NAc chose the smaller reinforcer more often; this decrease in self-control behavior is thought to be due to a reduction in extracellular DA. DA depletion has been suggested to prevent rats from being able to exert effort or sustain delays to a more preferred reinforcer (Salamone, Cousins & Bucher, 1994). However, contrary to the above research suggesting that decreases in self-control may be due to a decrease in DA, it has been shown that increases in extracellular DA are also associated with increases in impulsive behavior (van Gaalen, et al., 2006). Taken together, past research agrees that DA mediates self-control behavior; however, these studies have conflicting views as to its exact mechanism (e.g., Cardinal et al., 2001; van Gaalen et al., 2006).

In light of these past findings, it may be the case that cocaine causes a decrease in self-control behavior due, in part, to its ability to indirectly activate the 5-HT_3 receptor. The present study assessed the effects of intraperitoneal (IP) cocaine administration on self-control behavior in rats. Past research studying the effects of DA on self-control is conflicting, in that studies have found that both increases and decrease in extracellular DA can decrease self-control (Cardinal et al., 2001; Wade et al., 2000). However, based on research which suggest that increases in extracellular DA leads to decreases in self-control behavior (e.g., Wade et al., 2000), we expect that because higher doses of cocaine lead to higher levels of DA, administration of high doses of cocaine will lead to lower rates of self-control choices on a discrete trials self-control procedure, whereby subjects choose between a small and immediately available reinforcer and a larger but delayed reinforcer. We also expect that this decrease in self-control behavior will be partially mediated by 5-HT_3 receptor activation. This mediation will be assessed by co-administering the 5-HT_3 receptor antagonist Ly-278, 584 in combination with cocaine.

Cocaine and Self-Control

In addition to its pharmacological affects, cocaine effects self-control and increases impulsivity in both human and animal subjects (e.g., Logue et al., 1992; Conrod, Pihl, Stewart & Dongier, 2000; Anderson & Woolverton, 2003; Paine et al., 2003). In order to understand how this stimulant of abuse affects self-control behavior, it is necessary to first explain how self-control behavior is studied in the laboratory.

The study of self-control is part of a broader area of learning that examines choice behavior and the rules by which human and non-human animals adjust to reward and punishment (Staddon, 2001). Many factors play a role in whether an animal makes a self-control or impulsive choice. These factors include, but are not limited to, the magnitude of a reinforcer

(Tobin, Chelonis & Logue, 1993) and delay of a reinforcer (Bradshaw & Szabadi, 1992; Peters, Hunt & Harper, 2004). Additionally, it has been suggested that there are even species differences associated with self-control behavior; specific differences have been shown between pigeons and rats, (van Haaren, van Hest & van de Poll, 1988).

A common procedure used to study self-control is a *discrete-trials concurrent schedule of reinforcement*. During such a procedure, subjects are required to choose between two simultaneously available schedules of reinforcement (Ainslie, 1974). For instance, when rats are used, two levers in a standard operant chamber may be presented simultaneously; emitting a single lever-press to one lever would lead to a small but immediately delivered reinforcer (e.g., 2 pellets of food following no delay) and a lever-press to the other lever would leads to a larger but more delayed reinforcer (e.g., 4 pellets of food following a 4 s delay). In this type of situation, subjects tend to choose the more immediate reinforcer (e.g., Ainslie, 1974). However, when the delay between the availability of each reinforcer is increased, preferences begin to shift and subjects will typically choose the more self-control choice; whereas, if the delay is decreased, subjects will more likely chose the impulsive option.

For example, Bradshaw and Szabadi (1992) exposed rats to a concurrent discrete-trials procedure, as described above, whereby one lever provided 50 µl of a 0.05 M sucrose solution immediately and the other lever provided 50µl of a 0.32 M sucrose solution following varying delays. Results revealed that increasing the delay to the larger more delayed reinforcer, while holding "delay" for the smaller reward constant at 0 s, increased preference for the smaller more immediate reinforcer. In essence, rats became more impulsive. When delays for the smaller reinforcer were increased (past 9 s), and the delay to the larger reinforcer was fixed at 9 s, preference for the larger reward increased, leading to more self-control behavior. Numerous

other studies have also revealed ways in which delays to a reinforcer can be altered to increase self-control behavior (e.g., Rachlin & Green, 1972; Ainslie, 1974).

In a variation of the concurrent schedule described above, Rachlin and Green (1972) presented pigeons a choice between 2 s access to grain immediately or 4 s access to grain following a 4 s delay, in a concurrent schedule procedure. In order to receive access to either reinforcer, pigeons had to distribute 25 key pecks between two different keys. At the start of the study, pigeons' key pecks could be distributed on either of the 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 followed by a 6 s blackout (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 concurrent schedule procedure, the pigeons' twenty-fifth peck was make on the left key, only the left key was re-illuminated during the second phase of the study. This additional requirement is a form of pre-commitment because a key is chosen at the beginning of the trial and the animal must complete the following schedule before the next trial begins. Overall, the results of Rachlin and Green (1972) reported that whenever subjects were presented with 2 s immediate access to grain and the 4 s delayed access to grain choices, the 2 s access to grain was usually chosen. However, as T increased, the key, which would only lead to the larger-later reward, was chosen more often (Rachlin & Green, 1972). This study illustrates the importance of an added delay both between initial reinforcer choice and delivery as well as between the end of one trial and the start of the next.

Ainslie (1974) conducted a similar study to illustrate the propensity pigeons have for seeking a smaller less delayed reward over a larger more delayed reward. Pigeons had to choose between pecking a green key for 4 s access to grain following a 15 s delay, or a red to gain access to 2 s of grain immediately. Result reported that that pigeons would choose the smaller reward continually for up to 20,000 trials (Ainslie, 1974).

Together, studies show that choice behavior relies not only on the magnitude of the reinforcer, but also the delay to which that reinforcer is available. When given the choice, most studies show that subjects will pick the smaller more immediate reward, over the larger more delayed reward in a concurrent schedule paradigm unless delay to both reinforcers are increased (e.g., Rachlin & Green,1972; Ainslie 1974).

More recently, research has also assessed how a variety of stimulants of abuse, such as amphetamines, affects self-control and impulsive behavior in the lab (e.g., Evenden & Ryan, 1996). In particular, several studies have assessed the role cocaine abuse plays in decreasing self-control in human and animal subjects (Conrod et al., 2000; Anderson & Woolverton, 2002; Paine, Dringenberg, & Olmstead, 2003). Research suggests that cocaine decreases self-control in a number of operant tasks (Logue et al., 1992; Conrod et al., 2000; Anderson & Woolverton, 2002 & Pain et al., 2003) including discrete trials choice procedures (e.g., Logue et al., 1992; Evenden & Ryan, 1996).

One of the first studies investigating the effects of chronic cocaine use on self-control in rats was performed by Logue et al. (1992). They exposed rats to daily IP injections of saline (1ml/kg) or cocaine (15mg/kg). Specifically, rats were injected with saline preceding cocaine administration and following cocaine administration. Following each cocaine injection, rats were tested on a self-control 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 adjusted delay. Sessions were comprised of 40 trials, which were organized into 10 blocks of 4 trials each. The first two trials were forced-choice trials whereby only one of the two levers (i.e., the smaller-sooner lever or larger-later lever) was active; forced-choice trials assured that all rats would experience each reinforcer condition. The last two trials in a block were free-choice trials, whereby rats could choose to press either lever. Delay to the larger-later reward was adjusted depending on choices made in the preceding free-choice trials. If rats chose the larger reinforcer in both free-choice trials in a given block, delay to the reinforcer would increase by 0.5 s. However, if the larger reinforcer was chosen only once, the delay would not increase, and if the smaller reinforcer was chosen in both free-choice trials delay to the larger reinforcer would decrease by 0.5 s. Logue et al. (1992) reported that chronic cocaine injections significantly reduced self-control choices, leading to smaller adjusted delays to the larger reward as days with cocaine treatment increased. Self-control increased when cocaine injections stopped.

In a more recent study, Anderson and Woolverton (2002) assessed how self-control behavior is affected when the reinforcers are two differing doses of cocaine. Specifically, the study assessed how cocaine dose and delay to each dose affected the self-administration of cocaine in rhesus monkeys. Five male rhesus monkeys were implanted with an intravenous (i.v.) catheter into a major vein to allow for self-administration of cocaine. In order for subjects to receive reinforcement, a single response was required. Experimenters exposed rats in experimental sessions seven days a week. Each session was comprised of two blocks of ten-discrete-choice trials, for a total of 20 trials. Each block consisted of two forced-choice trials followed by eight free-choice trials. Delay to reinforcement was varied on each lever, but doses were always presented in a 3:1 ratio, as were delay-to-reinforcement times.

When cocaine doses and delay times were equal, choice for each reinforcer was divided equally among alternatives. Likewise, when doses were unequal and delay was held constant, the larger dose was almost exclusively preferred among subjects. In addition, results revealed that when different doses of cocaine were injected after differing 3:1 delays, choice for the larger later dose decreased as choice for the smaller sooner dose increased. This effect was also found when higher doses of cocaine were used. Overall, results suggested that impulsivity increases when subjects are faced with a situation in which high doses of cocaine are available after long delays versus low doses of cocaine after short delays (Anderson & Woolverton, 2002; see also Paine et al., 2003).

Together, results of the above studies support the idea that cocaine decreases self-control behavior. It has been suggested by some researchers that this decrease is partially mediated by increases in extracellular DA (van Gaalen et al., 2006), thus decreasing self-control behavior. In addition, 5-HT receptors have been found to play a role in mediating DA release in the NAc (e.g., Chen et al., 1992), thus possibly contributing to the decreases we see in self-control following cocaine administration.

Neuropharmacological Mechanisms of Self-Control

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 IP 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).

While it is suggested that no single neurotransmitter is responsible for all behavioral and biological effects of cocaine, 5-HT and DA receptors have been shown to play an important role in self-control behavior (Logue et al., 1992; Wade et al., 2000; Cardinal et al., 2001; van Heering, 2001; van Galen, 2006). Historically it has been thought that decreases in 5-HT are responsible for the emergence of decreases in self-control behavior (Mobini, Chiang, Ho & Bradshaw, 2000). Reasoning for this theory stems from work studying suicide victims and attempters (e.g., van Heering, 2001) as well as rats with lesions to their serotonergic systems (e.g., Mobini et al., 2000). However, cocaine's inhibiting effects on self-control could be attributed, in part, to an *increase* in both synaptic 5-HT and DA (Hernandez & Hoebel, 1988; Logue et al., 1992; Gratton & Wise, 1994; van Gaalen et al., 2006).

It is well established that cocaine administration increases extracellular DA levels in the NAc of rats (e.g. Hernandez & Hoebel, 1988; Gratton & Wise, 1994; Tolliver et al., 1999). For instance, Hernandez and Hoebel (1988) assessed the effects that amphetamine, cocaine, electrical brain stimulation, and food had on DA levels in the NAc of freely moving rats. Using an in vivo intracerebral microdialysis procedure, DA and dihydroxyphenylacetic acid (DOPAC) samples were extracted from the NAc of rats preceding, during and immediately following self-administration of cocaine. Specifically, Hernandez and Hoebel (1988) found that DA levels increased five-fold above baseline levels when administered the stimulant drug. Similar results were found by Kalivas and Duffy (1990) as well as Wise, Newton, Leeb, Burnette, Pocock and Justice (1995), who both found an increase in extracellular DA levels in the NAc of rats following cocaine administration. Specifically, Wise et al. (1995) found that regardless of dose regime, DA levels increased 200-800% over baseline levels following acute self-administration of the drug.

Cocaine administration not only affects the dopaminergic system, but also the 5-HT system (Holman, 1994; Walsh & Cunningham, 1997; Julien, 1999 Repetto & Gold, 2005). Much like the DA system, cocaine also increases synaptic 5-HT levels by inhibiting its reuptake e.g., Walsh & Cunningham, 1997). Studies have shown that 5-HT elevation can aid in modulating DA release in the NAc (Benloucif, Keegan & Galloway, 1993). This further activation of the DA system stems from activation of the 5-HT_3 receptor (e.g. Chen et al., 1992; Carey & Damianopoulos, 1994; Repetto & Gold, 2005).

Andrews and Lucki (2001) performed one study that assessed the effects of cocaine on the 5-HT system. Similar to Hernandez and Hoebel (1988) they investigated the effects of cocaine administration on extracellular 5-HT and DA levels in the NAc of freely moving rats.

Microdialysis probes were implanted into rats' NAc and a baseline measure of 5-HT and DA was obtained before administration of cocaine. Following systemic IP administration of cocaine, 5-HT and DA samples were taken every 20 minutes for 3 hours. Likewise, 5-HT and DA samples were collected following infusion of 0, 3, and 10μM of cocaine into the NAc. Andrews and Lucki reported a dose-dependent increase in extracellular levels of both 5-HT and DA in the NAc. At lower doses, the levels of DA were higher than that of 5-HT, however when both were infused with 10mM of cocaine in the NAc, no significant differences existed in the extracellular levels of the two neurotransmitters. Andrews and Lucki suggested that this difference in neurotransmitter levels may not be due to the difference in affinity cocaine has for each receptor type, but perhaps was due to the larger number of DA receptors found in the NAc. Thus, cocaine not only increases DA levels in the NAc, but 5-HT levels as well (see also Carey & Damianopoulos, 1994; Walsh & Cunningham, 1997; Duvauchelle, Ikegami, & Castaneda, 2000).

Furthermore, activation of the 5-HT and DA systems do not occur independently of one another, but rather in conjunction with one another (e.g., Jiang et al., 1990; Logue et al., 1992; Benloucif et al., 1993; Walsh & Cunningham, 1997). As stated above, the 5-HT_3 receptor plays a role in mediating the abuse potential effects of cocaine by modulating DA release (e.g., Chen et al., 1992; Walsh & Cunningham, 1997; Carta et al., 2003). In contrast to most serotonin receptors, 5-HT_3 receptors are ligand-gated ion channels belonging to the nicotinic acetylcholine receptor superfamily (Fozard, 1992) and, as shown in Figure 1, are permeable to Na^+ and K^+ ions (Wolf, 2000). Research shows that 5-HT_3 receptor agonists influence DA release (e.g., Jiang et al., 1990; Chen et al., 1992; Walsh & Cunningham, 1997), and can increases the self-administration of drugs, such as cocaine, in rats (e.g., Farber, Haus, Spath, & Drechsler, 2004). It has been shown that while large concentrations of 5-HT_3 receptors are found in the cortex, there are also some found in the VTA and NAc that are key areas believed in modulating DA release and further affecting self-control behavior (Cardinal et al., 2001).

Summarizing, past research suggests that an increase of synaptic serotonin levels activates the $5HT_3$ receptor, which in turn, increases synaptic dopamine levels (e.g., Chen et al., 1992). This activation of the $5HT_3$ receptor modulates the release of dopamine, resulting in an additional increase in synaptic dopamine in the NAc (e.g., Abi-Dargham, Laruelle, Wong, Robertson, Weinberger & Kleinman, 1993; Matell & King, 1997; Herges & Taylor, 2000). Increased levels of dopamine have been associated with, and increase, the motivation to perform impulsive acts (van Gaalen, 2006).

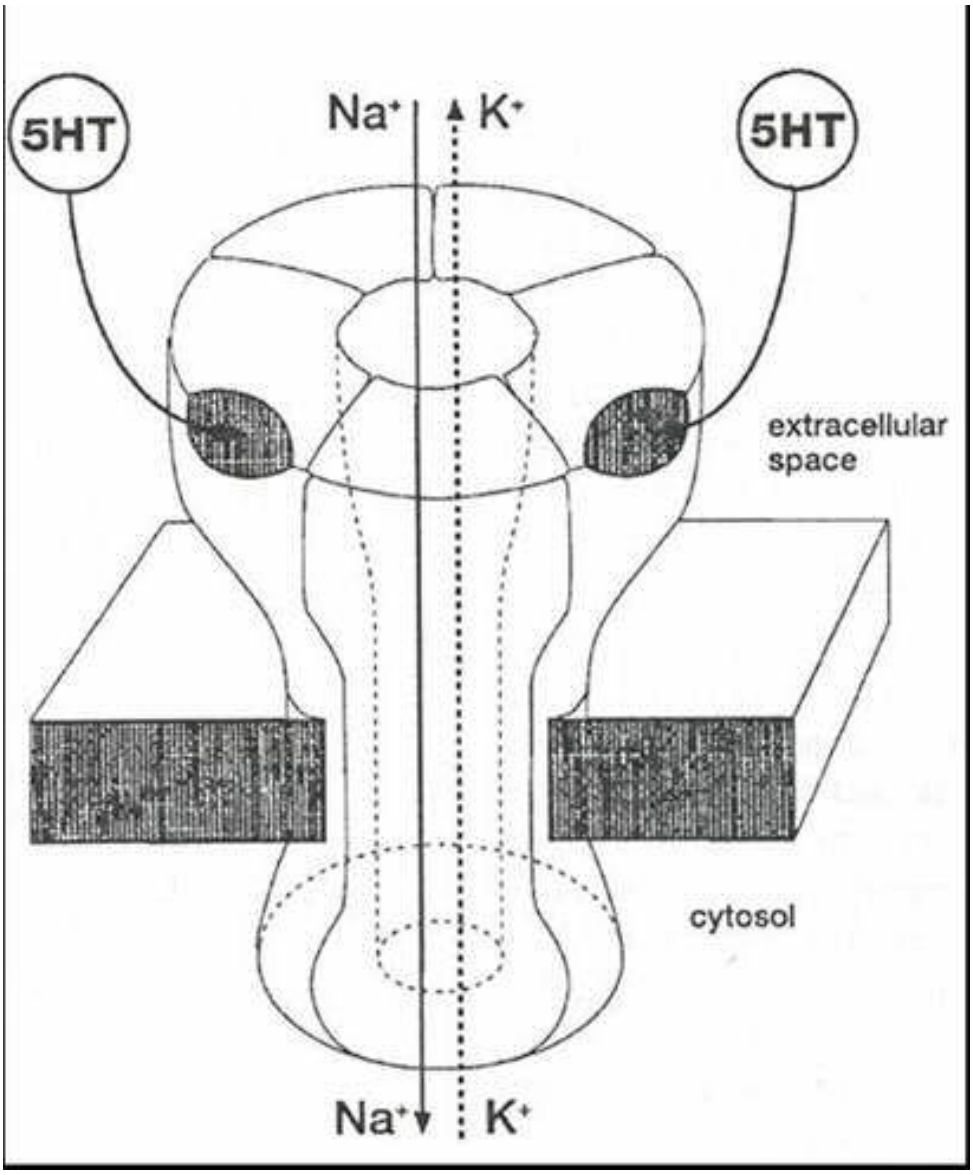

Figure 1. The 5-HT_3 receptor as depicted by Wolf (2000).

Proposed Study

Research indicates that, along with the DA system, the 5-HT system plays a critical role in mediating self-control behavior (e.g., Logue et al., 1992). Specifically, cocaine has been shown to inhibit the reuptake of both neurotransmitters, increasing their synaptic levels (e.g. Holman, 1994, Carey & Damianopoulos, 1994; Walsh & Cunningham, 1997; Duvauchelle, et al., 2000; Farber, et al., 2004). Increasing synaptic 5-HT concentrations activates the 5-HT_3 receptor that further increases DA release in the NAc (Chen et al., 1992). Increases in DA may lead to decreases in self-control behavior (e.g., van Gaalen et al., 2006).

To date, a paucity of research as been performed assessing the affects of acute cocaine exposure on self-control and impulsive behavior in rats. The purpose of the present study is to assess the effects of acute cocaine administration on choice behavior in rats, replicating past research, which has shown that cocaine decreases self-control. The study adds to the literature by examining how the 5-HT system is involved in mediating this self-control behavior. It is expected that as cocaine dose increases, preference for a smaller, more immediate reinforcer, over a larger later more delayed reinforcer, on the self-control task will emerge. Furthermore, it is predicted that when a 5-HT_3 antagonist, LY-278,584, is administered to rats in combination with cocaine, activation of the 5-HT_3 receptor will be inhibited, and an increase in self-control behavior will be seen.

Method

Subjects

Subjects in the study were eight, 90-day day old, 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,

and were housed individually and were exposed to a 12:12 light-dark cycle. The rats were run six to seven days a week. During the drug phase of the study, the rats were run daily.

Apparatus

The 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) on the middle of the front wall of the chamber. White response lights (2.5 cm in diameter) were mounted above each response lever which were mounted side by side on the front panel of the chamber (2.3 cm from the side wall of the chamber and 14 cm from the top of the chamber). The chamber was also equipped with a food hopper to provide food pellets containing sucrose (TestDiet 45mg purified rodent tablets, 5TUL). 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 a separate room, adjacent to 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.

Procedure

Drugs. Cocaine HCl and Ly-278,584 (Ly), from Sigma-Aldrich, were dissolved in distilled water. Cocaine was administered to all subjects in 0 mg/kg, 7.5 mg/kg, 15 mg/kg and 30 mg/kg doses and Ly-278,584 was administered to all subjects in 0 mg/kg, 0.01 mg/kg, 0.10 mg/kg and 1.0 mg/kg doses.

Pre-training. We trained rats to press the left lever by using a modified autoshaping program. Each trial began with the presentation of the light above the lever for 15 s, followed by a single food pellet. Separating each trial was a 60 s intertrial interval (ITI) during which the lever light was turned off. If a rat pressed the lever during the light presentation, a pellet was immediately given, and the next trial ensued. Each session consisted of 20 trials. Rats were trained on this procedure until they reached a criterion of emitting at least 19 responses in a session. Two of the rats did not lever press reliably, and we switched to a shaping by approximations (handshaping) procedure to teach them to press the lever, and then moved the rats to the autoshaping program. All rats began on the left lever and after reaching the criterion were trained to press the right lever.

Training: Phase 1 (Baseline, 30 sessions). Rats were exposed to 10 sets of choice-trials. Specifically, each set consisted of two *forced-choice* and two *free-choice* trials (for a total of 40 trials per session). Each trial provided reinforcement according to a discrete-trials schedule of reinforcement (following Logue et al., 1992; Tobin et al., 1993). For all choice trials ("forced" or "free"), a single lever press to one lever (called the "impulsive choice") led to one pellet after a one-second delay, whereas a single lever press to the other lever (called the "self-control choice") produced three pellets after a three second delay. All trials were separated by an ITI with a duration randomly selected from a list of possible values whose mean was 15 s (3 s, 6 s, 9 s, 12 s, 15 s, 17 s, 19 s, 21 s, 23 s, 25 s).

Figure 2 illustrates events taking place during the forced choice and free choice trials. During a forced-choice trial, the houselight turned on, and reinforcement from only one of the levers was available (e.g., from the lever associated with the "impulsive" reinforcer), signaled by the light turning on above that lever. The houselight was turned off after a choice was made and

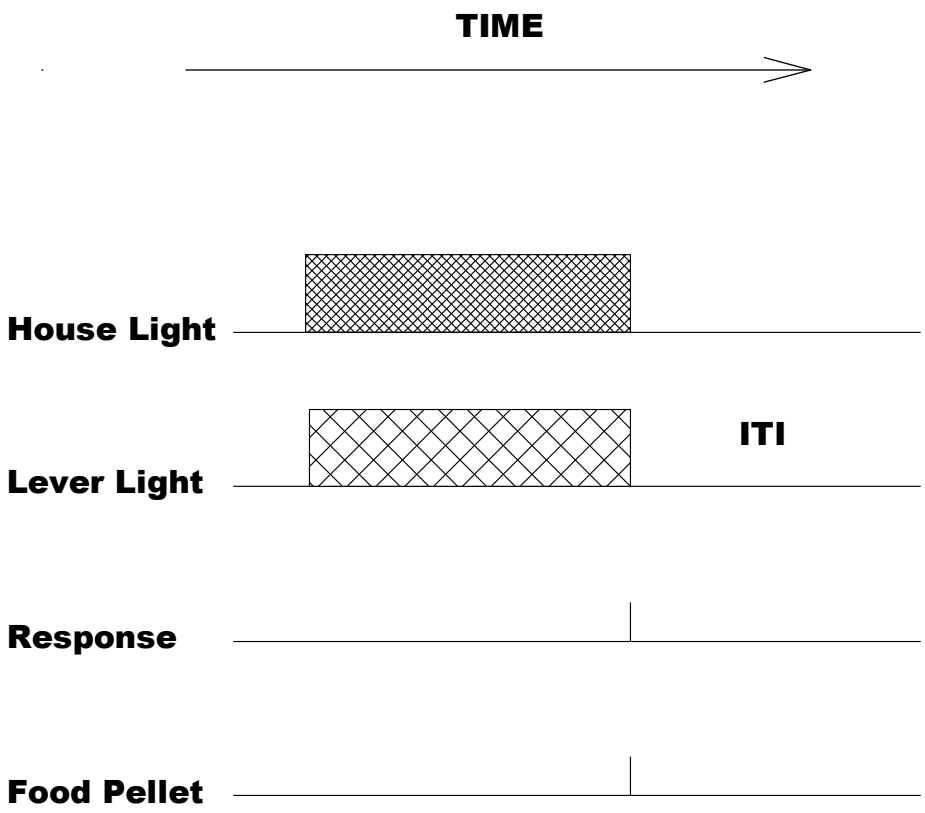

Figure 2. Example of an impulsive choice trial.

food was delivered. If a rat did not press the lever after 120 s, the reinforcer corresponding to the lever was automatically delivered. For the second forced-choice trial, reinforcement from the other lever (e.g., the self-control reinforcer) was available. The order of lever presentation during the forced-choice trials was randomized. Forced-choice trials were designed to ensure rats experienced both the larger-later reward and smaller-sooner reward equally before exposure to a trial where both sources of reinforcement were available concurrently.

Following the two forced-choice trials, the program provided two free-choice trials during which lights above both levers were illuminated. Unlike the forced-choice trials, if a rat did not press the lever within 120 s, no reinforcer was delivered, and the response was counted as a "null" response.

To control for lever bias, we assigned the first four rats (R21–R24) to a condition in which the right lever always provided the larger-more delayed reinforcer and the left lever the smaller-more immediate reinforcer. The second four rats ran in the left lever condition (R25–R28), whereby the left lever always served as the self-control lever.

Training: Phase 2 (Drug Challenge, 51 sessions).

Across sessions, subjects were given an injection of cocaine alone, LY-278,584 alone, or a combination of cocaine and LY-278,584. Table 1 represents the different cocaine and Ly-278,584 combinations used. For cocaine, the doses were 7.5mg/kg, 15 mg/kg and 30mg/kg. For LY-278-584, the doses were .01 mg/kg, .10 mg/kg and 1.0 mg/kg. Rats were run on the self-control task every day but only received a drug treatment every third day, for a total of 16 treatments. However, due to experimenter error, rats were given 30 mg/kg of cocaine paired with .01 mg/kg of Ly-278,584 twice. As a result, a seventeenth treatment day was conducted whereby

	0mg/kg Ly (control)	**.01mg/kg Ly**	**.10mg/kg Ly**	**1.0mg/kg Ly**
0mg/kg cocaine (control)	0mg/kg cocaine 0mg/kg Ly	0mg/kg cocaine .01mg/kg Ly	0mg/kg cocaine .10mg/kg Ly	0mg/kg cocaine 1.0mg/kg Ly
7.5mg/kg cocaine	7.5mg/kg cocaine 0mg/kg Ly	7.5mg/kg cocaine .01mg/kg Ly	7.5mg/kg cocaine .10mg/kg Ly	7.5mg/kg cocaine 1.0mg/kg Ly
15mg/kg cocaine	15mg/kg cocaine 0mg/kg Ly	15mg/kg cocaine .01mg/kg Ly	15mg/kg cocaine .10mg/kg Ly	15mg/kg cocaine 1.0mg/kg Ly
30mg/kg cocaine	30mg/kg cocaine 0mg/kg Ly	30mg/kg cocaine .01mg/kg Ly	30mg/kg cocaine .10mg/kg Ly	30mg/kg cocaine 1.0mg/kg Ly

Table 1. Cocaine and Ly-278,584 doses.

rats received 30 mg/kg of cocaine and .10 mg/kg of Ly-278,584. Five minutes following each drug administration, subjects were tested. The order of conditions was such that rats were given injections of cocaine alone, followed by Ly-278,584 alone and finally combinations of cocaine and Ly-278,584. Within each drug condition doses were given in randomized order. For one injection day in the combination phase, rats were given an injection of saline. All injections were given according to individual body weight. During combo days, Ly-278,584 was also administered five minutes preceding cocaine administration.

Training: Phase 3 (Baseline, 10 sessions). Following the experimental drug phase of the study, rats were tested on a second baseline phase to assess changes in behavior after initial exposure to a drug.

Training: Phase 4 (Baseline, Reversal 10 sessions). Immediately following the second baseline phase, the self-control conditions for each rat were switched. The first set of four rats (R21–R24) that were originally run on the right-lever condition, whereby the right lever was the self-control lever, were run on the left-lever program, whereby the left-lever was now the self-control lever. The second set of four rats (R25–R28) that were originally run on the left-lever program, whereby the left lever was the self-control lever, were run on the right-lever program, which was now the self-control lever.

Results

Across all phases, we calculated the percentage of self-control responses during the free-choice trials by dividing the total number of self-control responses by the number of self-control, impulsive and null responses, and the proportion was multiplied by 100. Similarly, we calculated the percentage of impulsive responses by dividing the total number of impulsive responses by the number of impulsive, self-control and null responses and multiplying the proportion by 100. We

analyzed latency of the responses by calculating a frequency distribution using 1-s bins, then normalized the frequencies. The normalized frequencies for self-control choices were calculated by dividing the number of self-control choices made in each bin and dividing it by the maximum number of choices made in a single bin for each individual rat. The normalized latency frequencies for impulsive choices were calculated in the same manner.

Phase 1 (Baseline)

Figure 3 shows the percentage of self-control (top) and impulsive (bottom) choices across all sessions in Phase 1. All subjects, regardless of which condition they were run in (left vs. right self-control lever), learned the self-control task and were responding in a stable manner by the last 10 days of the baseline phase, maintaining high levels of self-control behavior and low levels of impulsive behavior. Specifically, by the last session, subjects R21–R24 made an average of 87.25% self-control responses and 12.6% impulsive responses and subjects R25–R28 made an average of 94.25% self-control responses and 5.75% impulsive responses on the last 10 days of baseline. However, there were different patterns of acquisition. Rats R21–R24 showed a more gradual increase in self-control responses across the first five to six sessions than did R25–R28. Correspondingly, impulsive behavior for rats R21-R24 decrease more gradually than it did for R25-R28. Results of an independent samples *t*-test revealed no significant difference in self-control ($t = 2.152$, $p = .075$) or impulsive behavior ($t = 2.152$, $p = .075$) between the performance of each group in the last 10 sessions of Phase1. We therefore collapsed data from all rats across all rats for subsequent analyses.

Figure 4 shows the mean latency of all rats to make a self-control or impulsive response during the first 10 (top) and last 10 (bottom) sessions, respectively. To assess possible differences, we conducted a two-way repeated measures analysis of variance (RM ANOVA) on

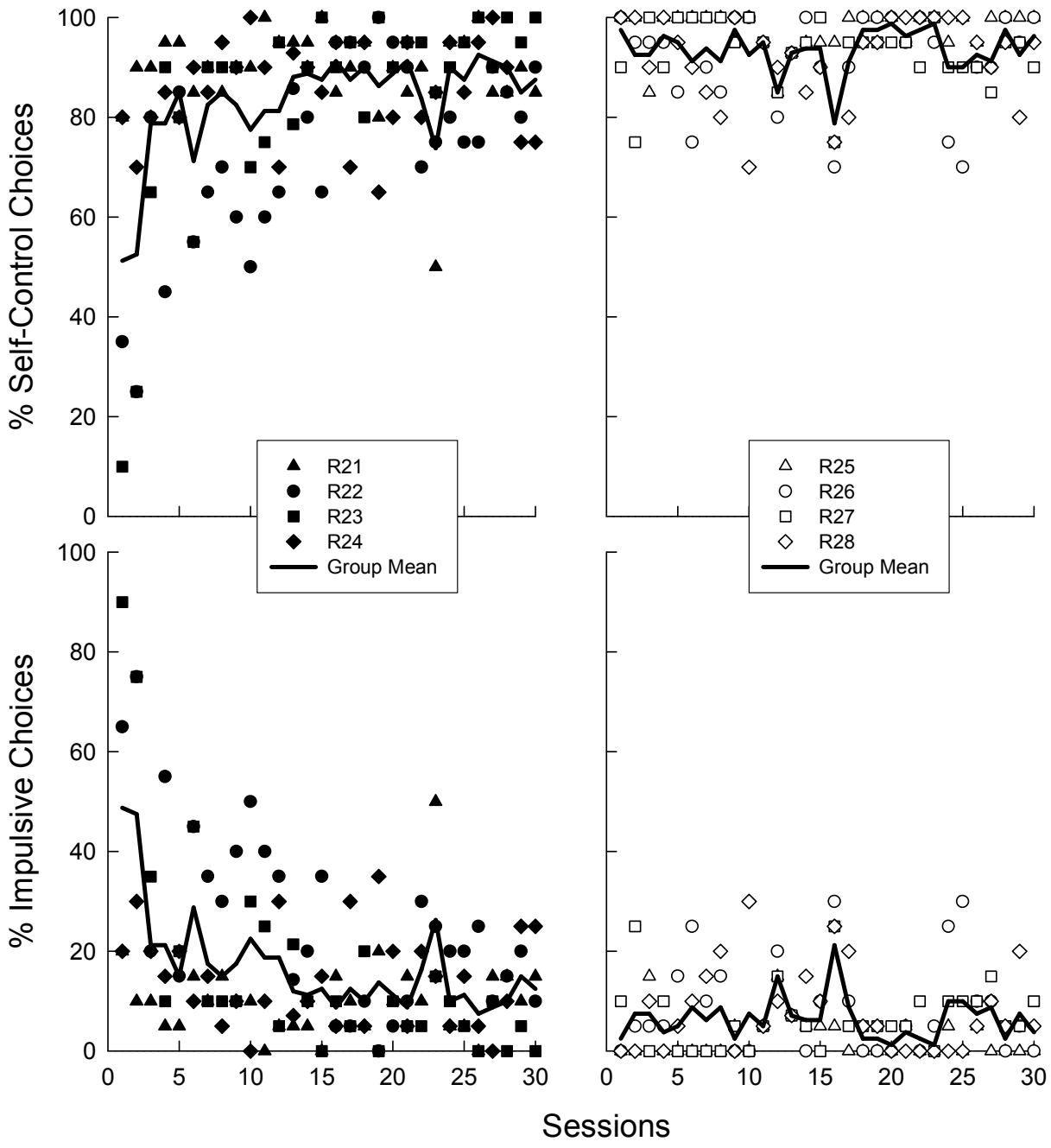

Figure 3. Percentage of self-control (top) and impulsive (bottom) choices across all sessions from Phase 1 of the study.

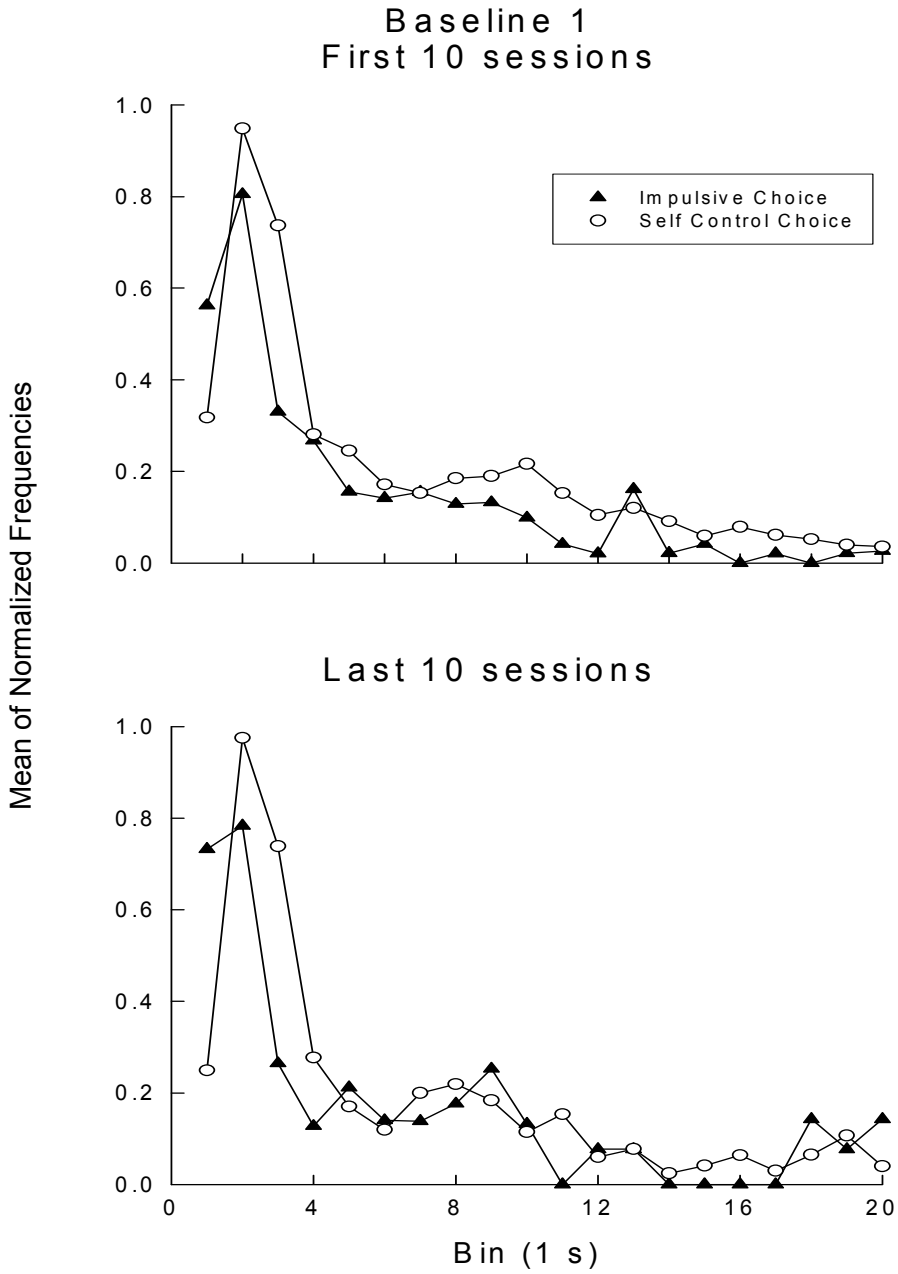

Figure 4. The group mean latency to make a self-control or impulsive response during the first 10 (top) and last 10 (bottom) sessions in Phase 1.

the first four bins by choice. The RM ANOVA revealed a main effect of bins in the first 10 sessions $F(7,21) = 15.875$, $p \leq .001$. Student-Newman-Keuls (SNK) post-hoc comparisons revealed that significantly more choices were made in bin 2 than were made in all other bins ($q = 9.447$, $p = < .001$). A RM ANOVA was also conducted on the last 10 days, and, as in the first 10 sessions, a significant main effect emerged for bins, $F(7,21) = 29.856$, $p \leq .001$. Again, more choices, overall, were made in bin 2 than were made in all other bins ($q = 13.269$, $p < .001$). A main effect was also found for choice type $F(7,21) = 9.762$, $p = .017$. Significantly, more self-control choices than impulsive choices were made in bins 1-4 than all other bins. Lastly, an interaction between bin and choice type emerged, $F(7,21) = 10.556$, $p \leq .0001$. Specifically, as suggested in Figure 4, SNK post-hoc comparisons found that more impulsive choices were made in bin 1 than were self-control choices in the last 10 sessions of baseline ($q = 5.097$, $p = .001$).

Drug Phase

Performance during exposure to drugs was compared to that during saline to assess relative changes in behavior. The difference between the saline and each drug treatment score was calculated and then plotted using a semi-log scale. Figures 5 and 6 show the percentage of self-control (top), impulsive (middle) and null (bottom) choices made across all sessions in the drug phase when administered cocaine alone or Ly-278,584 alone, respectively. Additionally, a *t*-test for paired samples was calculated to determine if Phase 1: Baseline scores differed from scores obtained in the saline condition. Results revealed that the mean differences between self-control choices in Phase1 were significantly lower from saline scores ($t = 2.60$, $p = .035$), as were impulsive scores ($t = 2.44$, $p = .045$).

Cocaine Only Condition. Rats appeared to emit fewer self-control responses as cocaine doses increased. Specifically, a decrease in the mean number of self-control choices was seen

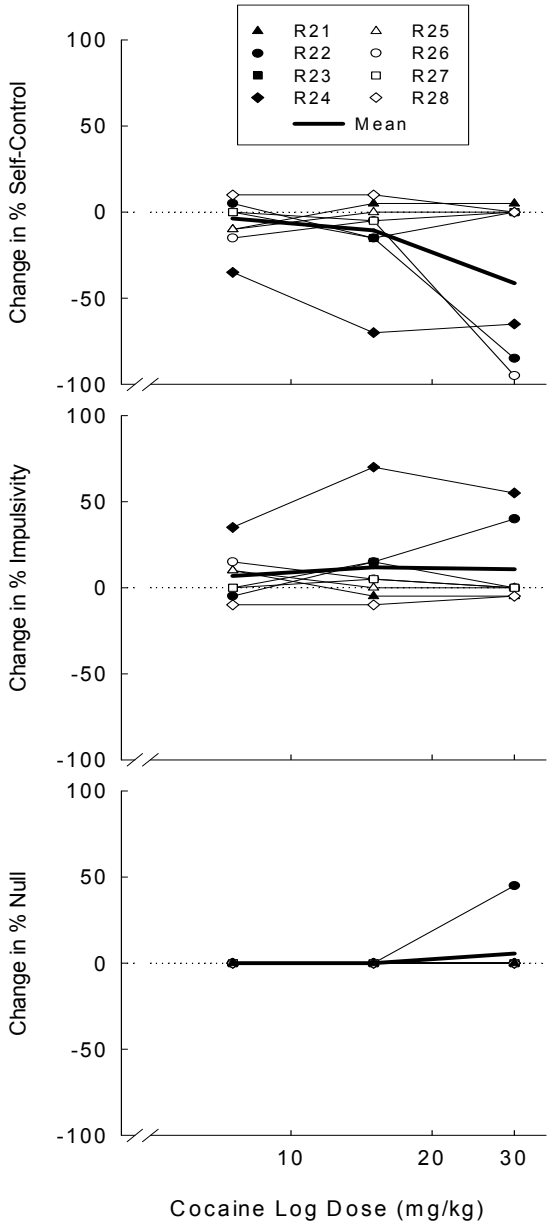

Figure 5. Percentage of self-control (top), impulsive (middle) and null (bottom) responses emitted during the cocaine alone condition.

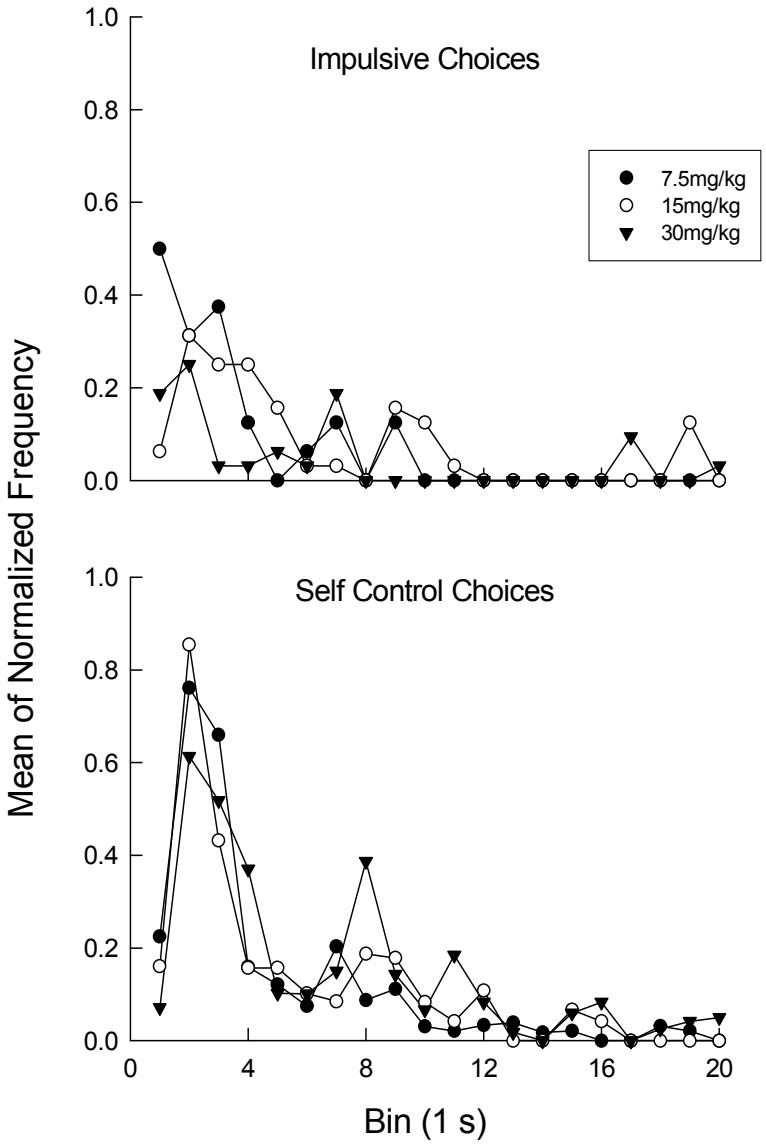

Figure 6. The group mean latency to make an impulsive response (top) or self-control response (bottom) during the first 4 bins of the cocaine only condition.

following administration of the 30mg/kg dose of cocaine. However, results of a RM ANOVA revealed no significant differences in self-control choices across all cocaine levels, $F(7,14) = 2.247$, $p = .142$. Figure 5 also shows the change of impulsive choices (middle) emitted during the cocaine alone condition. Again, no significant differences were found, $F(7,14) = 1.713$, $p = .216$. The top of Figure 6 shows the mean latency to make an impulsive response during the cocaine only condition, whereas the lower panel shows the average latency to make a self-control response. There were no consistent differences between the latency to make an impulsive choice and bin number. However, the RM ANOVA did reveal a significant main effect of bins when making a self-control response, $F(7,42) = 16.110$, $p < .001$. Specifically, a SNK post-hoc comparison revealed that more self-control responses were made in bin 2 than all other bins regardless of drug condition (7.5mg/kg, 15mg/kg and 30mg/kg), and that most self-control choices were made approximately one to two seconds after the start of a trial ($q = 8.638$, $p < .001$).

Ly-278,584 Only Condition. In Figure 7, we plotted the percentage of self-control (top) and impulsive (middle) responses emitted during the Ly-278,584 alone condition in order to assess how the drug, in the absence of cocaine, affected self-control and impulsive behavior. As Figure 7 shows, with the possible exception of subject R24, rats did not perform consistently different from saline across all levels of the drug.

Figure 8 shows the mean latency to make impulsive (top) and self-control (bottom) choices in each Ly-278,584 condition in order to assess the effects that Ly-278,584, in the absence of cocaine, had on the latency of emitting self-control or impulsive responses. Results of a RM ANOVA revealed no consistent differences in the time it took to make an impulsive response on the task, when differences were measured relative to that during saline. Significant

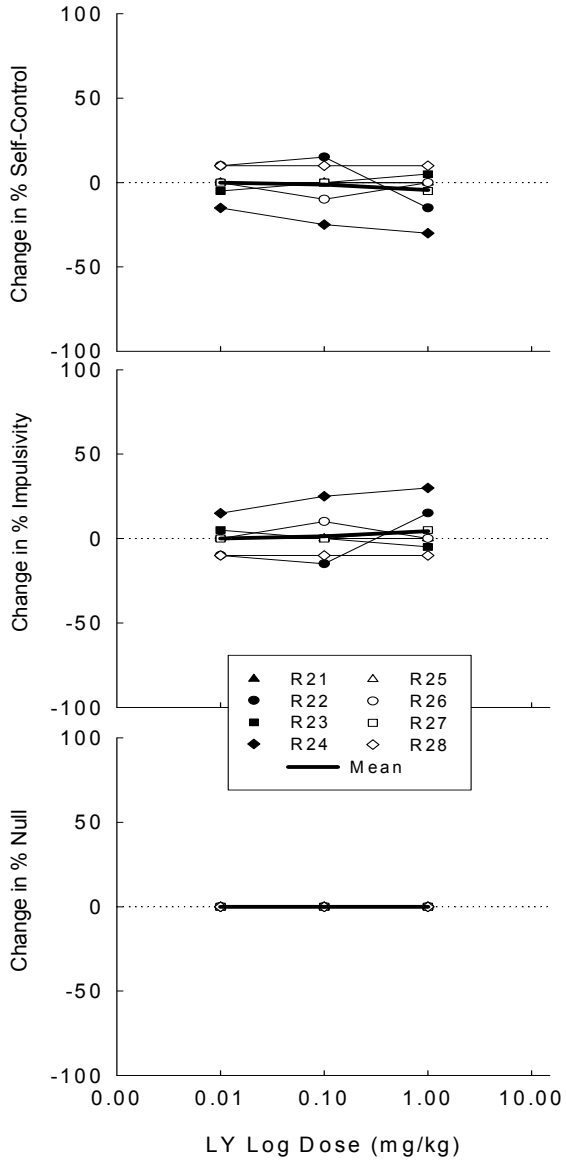

Figure 7. The percentage of self-control (top) and impulsive (middle) and null (bottom) responses emitted during the Ly-278,584 alone condition.

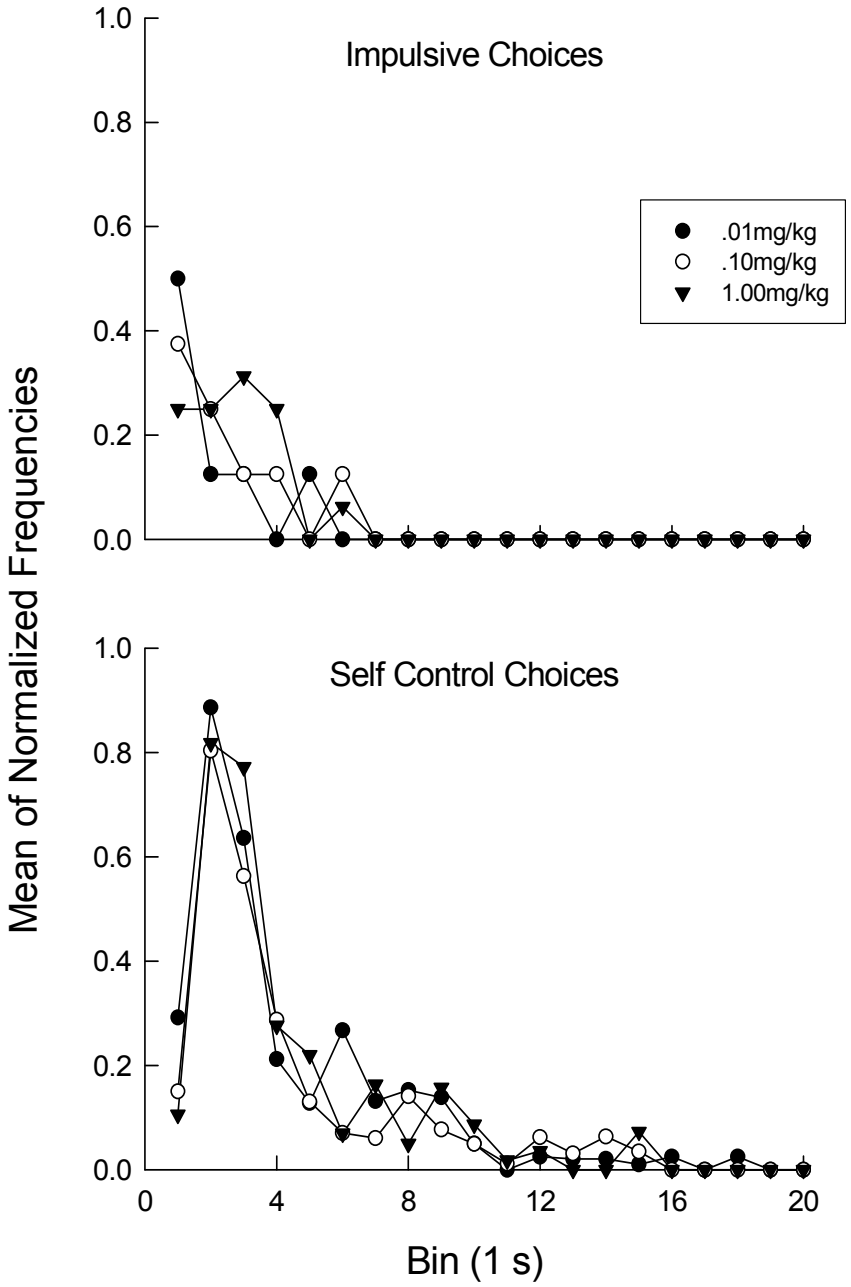

Figure 8. The latency to make an impulsive (top) and self-control (bottom) choice in each Ly-278,584 condition.

main effects for bins, however, were found for self-control responses $F(7,42) = 23.869$ $p < .001$. Specifically, most self-control choices were made in bin 2. Post-hoc comparisons revealed that within each condition, most self-control choices were made in bins 2 and 3 across all Ly conditions ($q = 10.171$, $p < .001$).

Ly and Cocaine Combination Condition. Figure 9 (top) shows the mean change in self-control, from saline, as a function of cocaine dose, while Figure 10 (top) shows the mean change in self-control, from saline, as a function of Ly-278,584 dose. A paired-sample *t*-test was performed to assess if there were significant differences between scores on the task in the two 30mg/kg cocaine and .01mg/kg Ly-278,584 conditions. No significant differences in self-control behavior ($t = 55.500$, $p \geq .05$) or impulsive behavior ($t = 78.000$, $p \geq .05$) were revealed, therefore the mean of the two conditions was calculated and served as the data point for that condition. Results of a RM ANOVA revealed a significant main effect for cocaine dose, $F(7,28) = 9.832$, $p = .002$, and an interaction between cocaine dose and Ly-278,584 dose had a trend towards significance, $F(7,28) = 2.675$ $p = .052$. Specifically, a SNK post-hoc comparison showed that across all Ly-278,584 conditions, rats emitted significantly more self-control responses when administered 7.5mg/kg or 15mg/kg of cocaine than when administered 30mg/kg of cocaine ($q = 5.848$, $p = .003$) for bin 2. Rats did not perform consistently different from saline across all doses of cocaine when administered 1.0mg/kg of Ly-278,584.

Figures 11, 12 and 13 show the mean normalized frequencies of impulsive (top) and self-control (bottom) responses made on the self-control task in the 0.01mg/kg, 0.10mg/kg and 1.0mg/kg Ly-278,584 and cocaine combination conditions, respectively. In the .01mg/kg Ly-278,584 condition, no consistent differences were found for the latency of impulsive choices; however, a RM ANOVA did reveal a main effect for bin for self-control choices, $F(7,42) =$

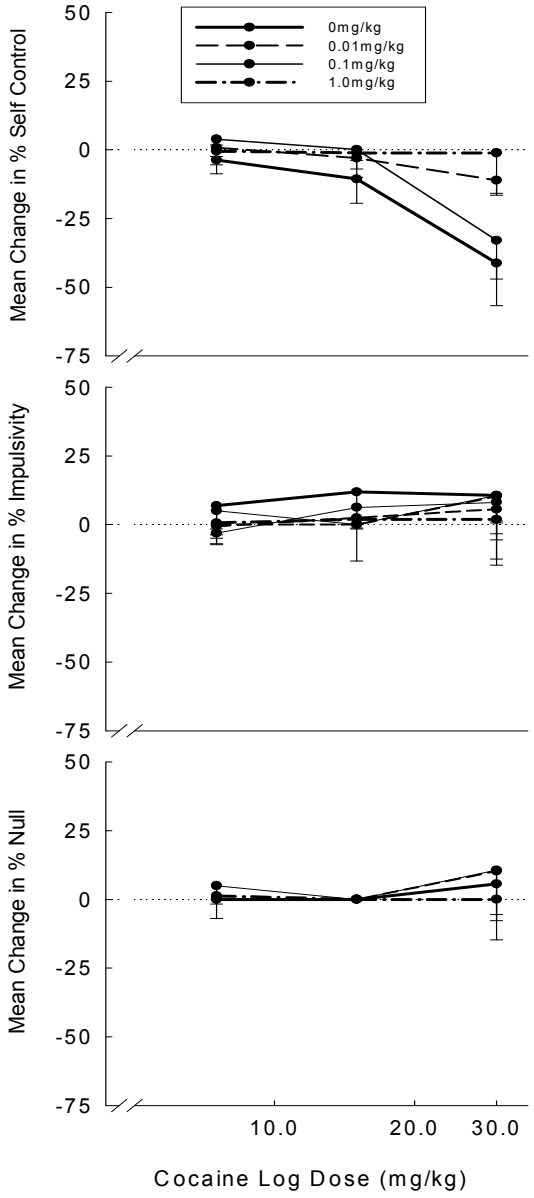

Figure 9. The mean change in self-control (top), impulsive (middle) and null (bottom) responding, from saline, as a function of cocaine dose.

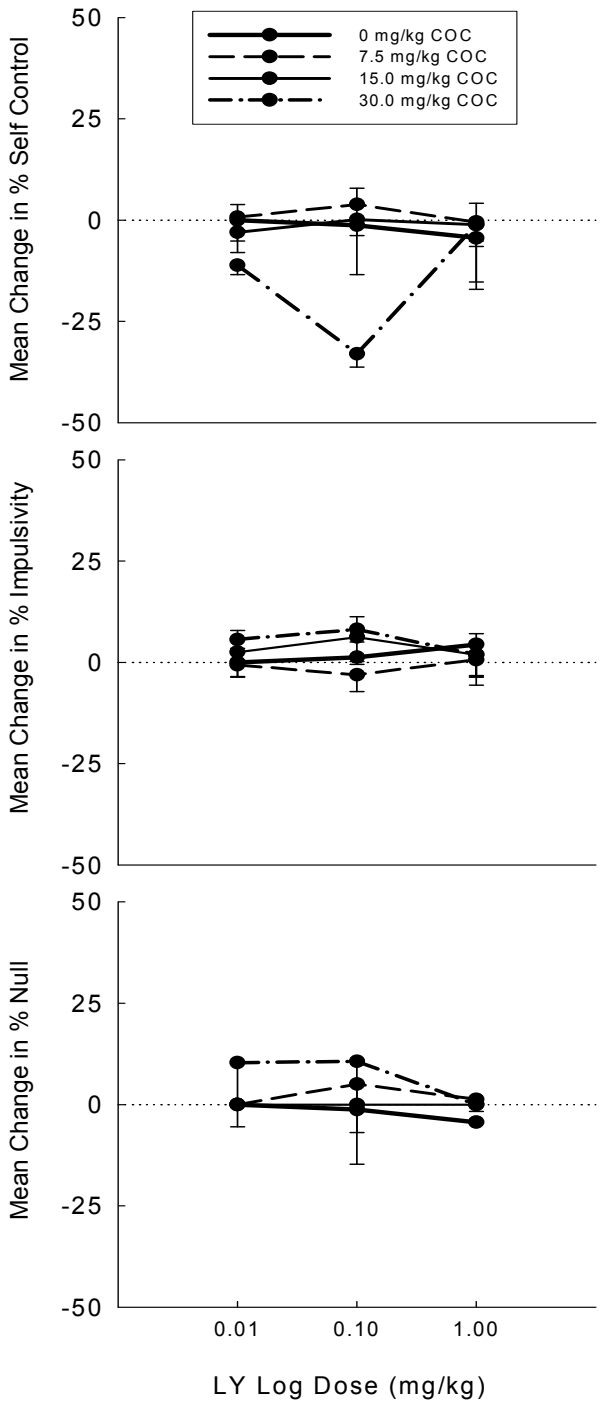

Figure 10. The mean change in self-control (top), impulsive (middle) and null (bottom) responding, from saline, as a function of Ly-278,584 dose.

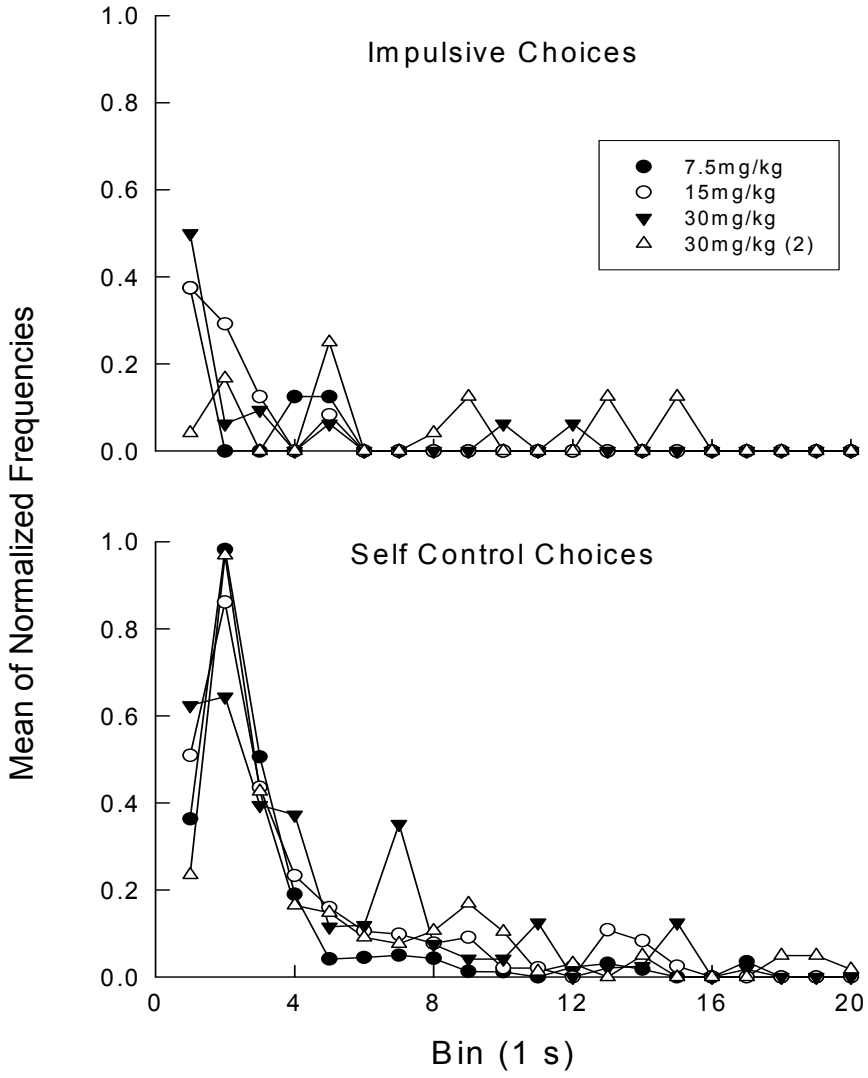

Figure 11. The normalized frequencies of impulsive (top) and self-control (bottom) responses made in the 0.01mg/kg Ly-278,584 condition.

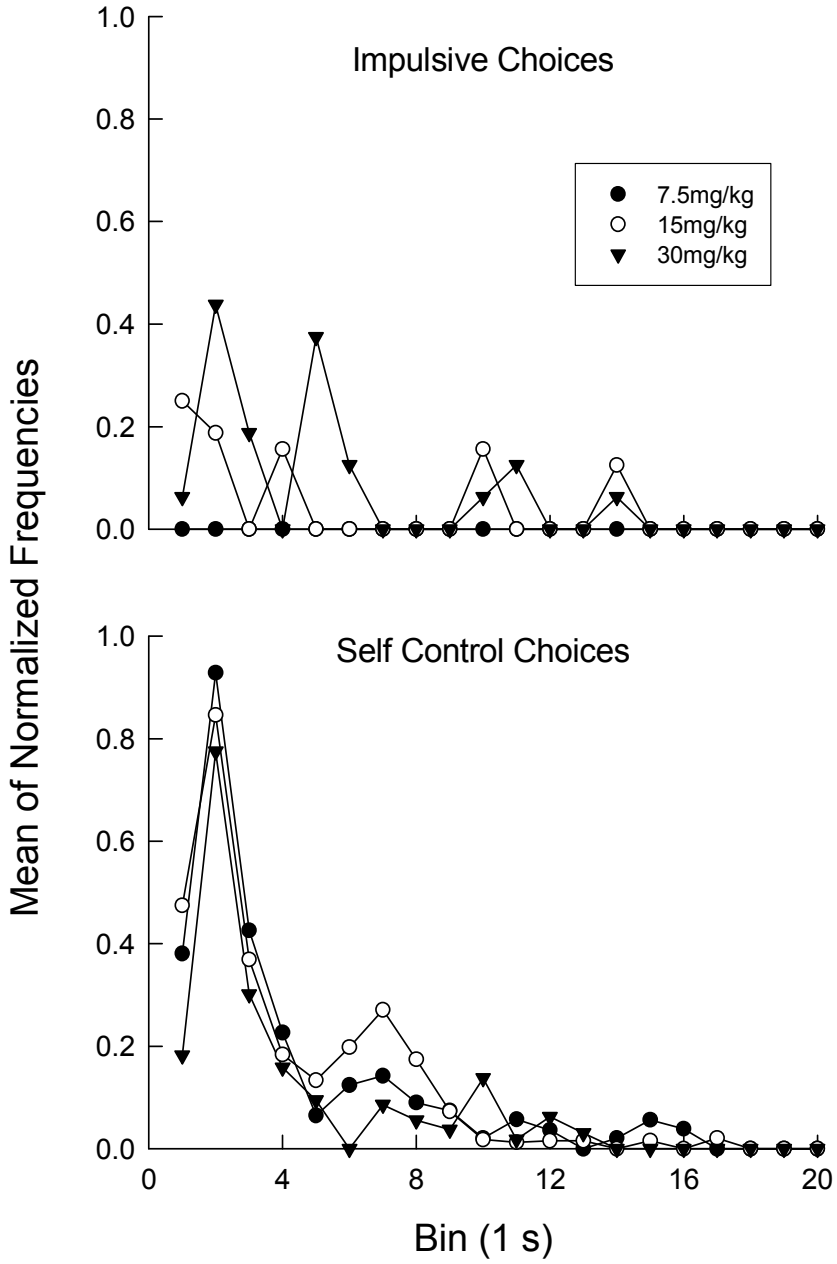

Figure 12. .The normalized frequencies of impulsive (top) and self-control (bottom) responses made in the 0.10mg/kg Ly-278,584 condition.

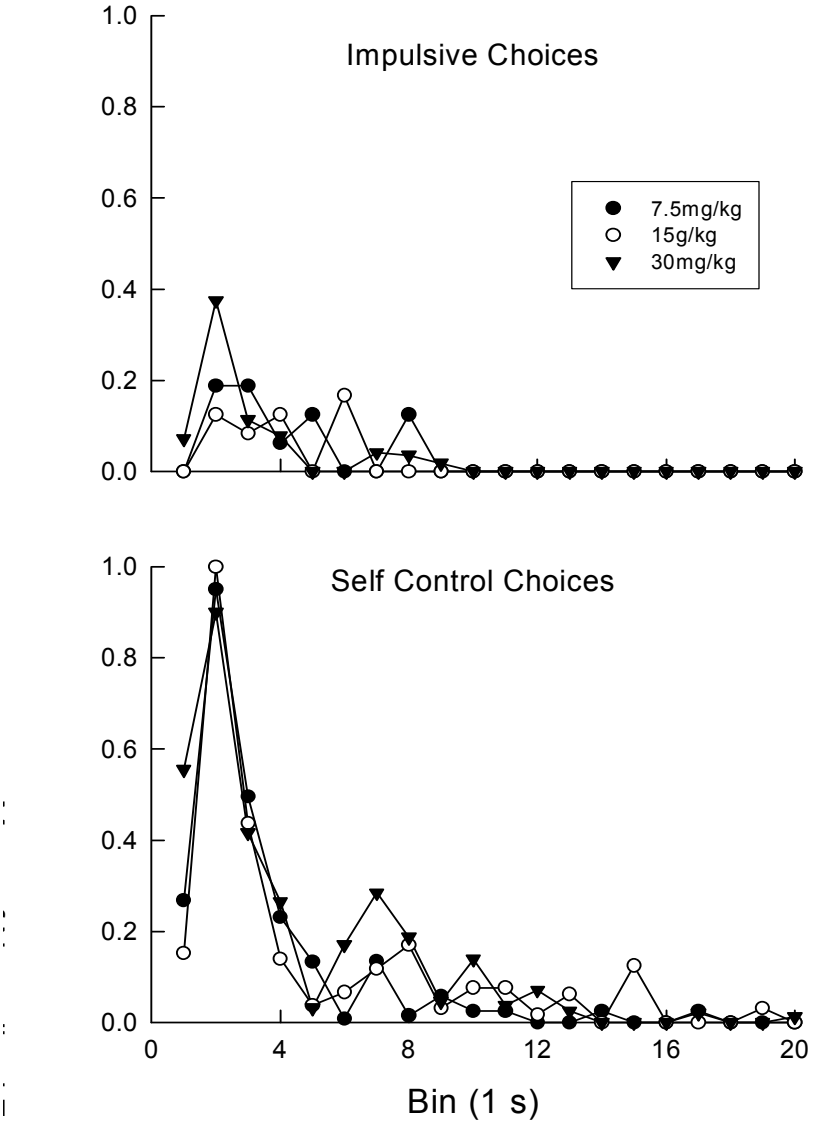

Figure 13. The normalized frequencies of impulsive (top) and self-control (bottom) responses made in the 1.00mg/kg Ly-278,584 condition.

13.963, $p < .001$. Specifically, SNK post-hoc comparisons revealed that more self-control choices were emitted in bin 2 than bin 4 ($q = 8.880$, $p < .001$).

In the .10mg/kg Ly-278,584 condition, a bin by cocaine dose interaction was revealed for impulsive choices, $F(7,42) = 0.134$, $p = .008$. Specifically, more impulsive choices were emitted in bin 2 following a 30mg/kg dose of cocaine than when administered 7.5mg/kg of cocaine ($q = 4.826$, $p = .004$). In addition, rats emitted significantly more impulsive responses in bin 2 then in all other bins. Results also revealed a significant main effect for bin, $F(7,42) = 15.829$, $p < .001$, whereby more self-control responses were made in bin 2, regardless of cocaine dose, than were made in all other bins.

Lastly, in the 1.00mg/kg Ly-278,584 condition, a main effect for bins was found for impulsive choices, $F(7,42) = 3.159$, $p = .046$. A main effect of bins was also found for self-control choices $F(7,42) = 41.708$, $p < .001$, whereby post-hoc comparisons revealed that more impulsive and self-control choices were made in bin 2 than all other bins (e.g., $q = 14.649$, $p < .001$; as compared to bin 4).

Post-Injection Days. In order to assess the effects drug administration had on choice behavior on days immediately following and preceding drug administration, the percentage of self-control and impulsive choices were calculated for those days. Figure 14 shows the mean number of self-control (top) and impulsive (bottom) choices made on the self-control task on days immediately following a drug treatment (post-injection session 1) and days immediately preceding a drug treatment (post-injection session 2). Results of a RM ANOVA revealed that significantly more self-control choices were emitted in the post injection 2 session than in the post injection 1 session $F(7,105) = 7.367$, $p = .030$. Conversely, significantly more impulsive choices were emitted in the post-injection 1 session than in the post-injection 2 session F(7,105)

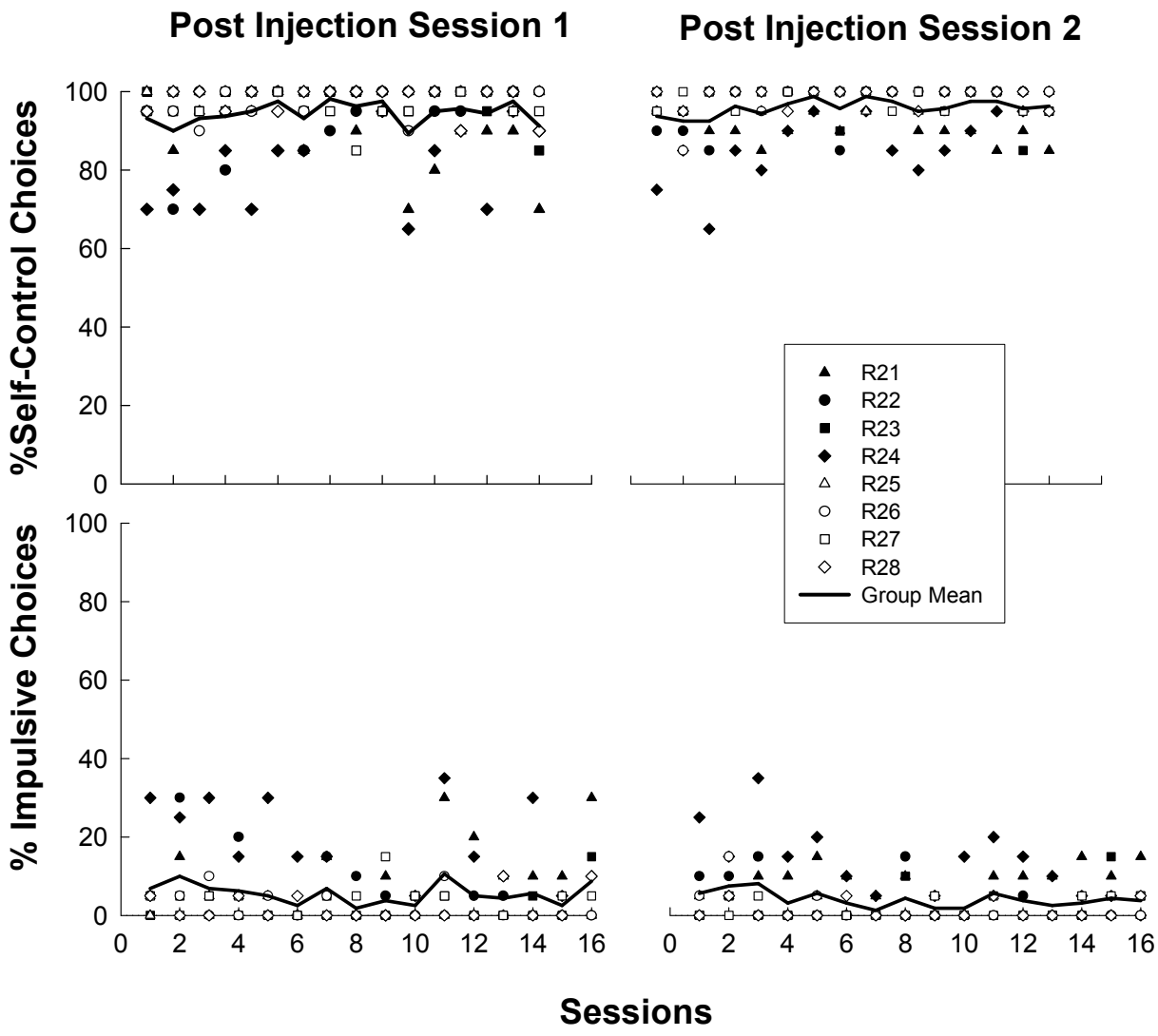

Figure 14. The mean number of self-control (top) and impulsive (bottom) choices made on the self-control task on days immediately following drug treatment (Post Injection Session 1) and days immediately preceding drug treatment (Post Injection Session 2).

= 7.367, p = .030. In order to assess how long it took subjects to make self-control or impulsive choices following and preceding drug injection days, the latencies of each choice were calculated and plotted in Figure 15. Specifically, Figure 15 shows the latencies of self-control (top) and impulsive (bottom) choices on post injection session 1 and post injection session 2. A significant main effect for drug session was found for self-control choices made in the post injection sessions 1 and 2. As shown above, results of a RM ANOVA revealed that significantly more self-control choices were emitted in post injection session 2 then in post injection session 1, F(7, 105) = 2.685, p = .002. No consistent differences were found for the latency of impulsive choices on post injection sessions 1 or 2.

Phase 3: Baseline

Figure 16 shows the percentage of self-control (top) and impulsive (middle) responses across all sessions in phase 3. All rats returned to the same level of performance as seen in Phase 1 (Figure 3) after 10 days. No consistent differences from Phase 1 (Baseline) were seen for impulsive or self-control choices. Specifically, subjects made an average of 96% self-control responses and 3.51% impulsive responses. The mean normalized frequencies were plotted in Figure 16 (bottom), and a RM ANOVA revealed a significant main effect for bins, F(7, 21) = 16.523, p < .001, and a bin x choice type interaction, F(7, 21) = 4.337, p = .016. Specifically, SNK post-hoc comparison revealed that most choices were made in the 2 second bin, and that these choices were generally self-control choices (e.g., q = 4.769, p = .002) as compared to bin 1.

Phase 4: Baseline Reversal

In order to assess if preference for the self-control choice were due to lever bias, the percentage of self-control and impulsive choices were plotted when rats' self-control levers were switched. Figure 17 shows the percentage of self-control (top) and impulsive (middle) choices

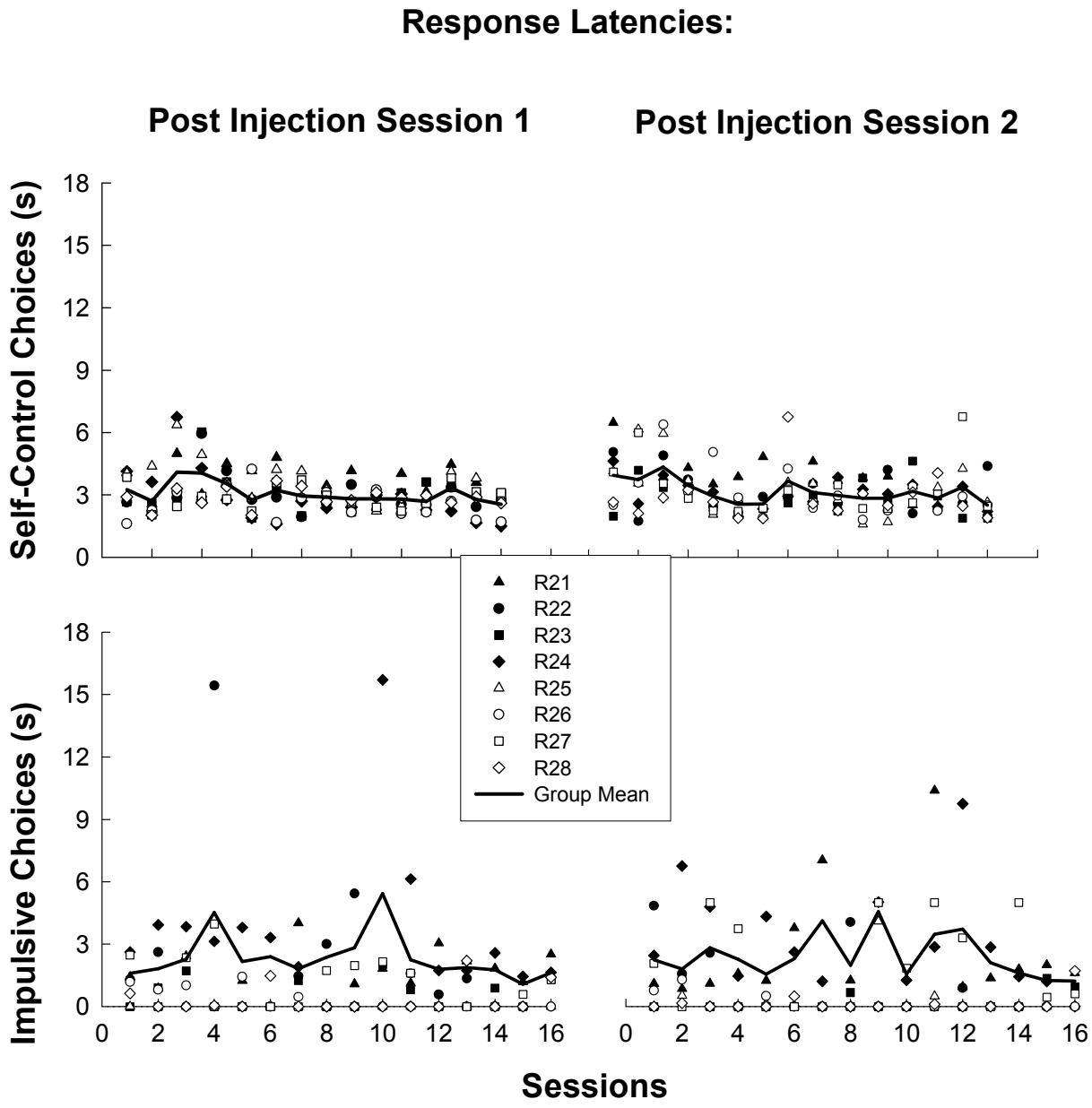

Figure 15. The latencies of self-control (top) and impulsive (bottom) choices on Post Injection Session 1 and Post Injection Session 2.

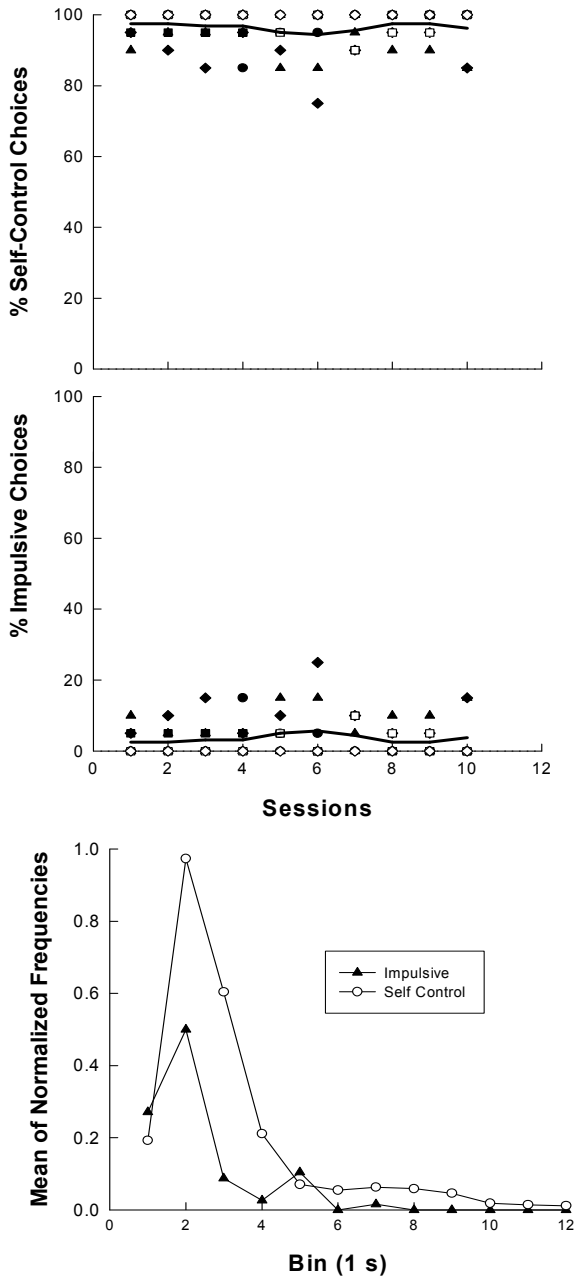

Figure 16. The percentage of self-control (top) and impulsive (middle) responses across all sessions in Phase 3. The mean normalized frequencies for self-control and impulsive choices made during Phase 3 are plotted at the bottom.

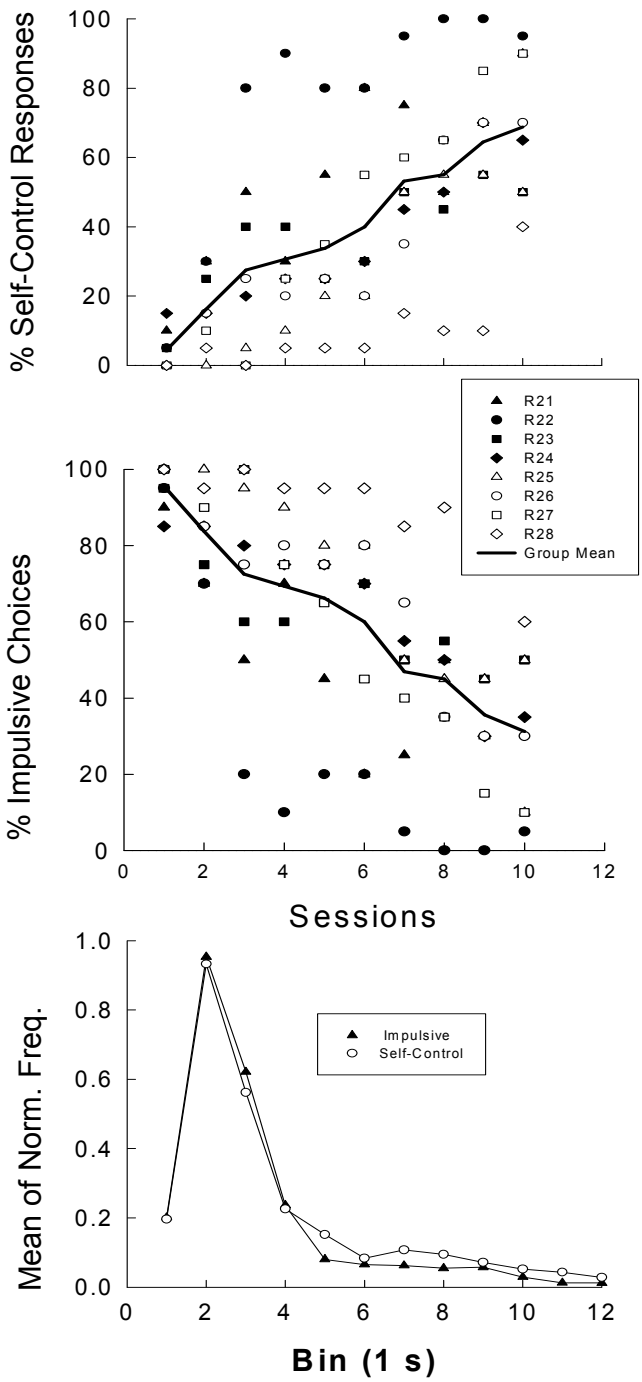

Figure 17. The percentage of self-control (top) and impulsive (middle) responses across all sessions in Phase 4. The mean normalized frequencies for self-control and impulsive choices made during Phase 4 are plotted at the bottom.

made during Phase 4. A steady acquisition curve is shown; and over 10 trials, we again see that rats made more self-control responses than impulsive responses. A paired sample *t*-test revealed significant differences between the two groups' scores ($t = 1.96$, $p < .05$). Figure 17 (bottom) shows the mean normalized frequencies of self-control and impulsive choices in phase 4. No consistent differences exist between the latency to make a self-control choice or an impulsive choice.

Discussion

The purpose of the present study was to investigate the mechanisms mediating cocaine's effects on self-control behavior in rats. Past research shows that cocaine decreases self-control and increases impulsivity in rats (e.g., Conrod et al. 2000; Paine et al., 2003). Effects of self-control may occur because cocaine increases synaptic levels of 5-HT and DA by inhibiting their reuptake (e.g., Holman, 1994, Carey & Damianopoulos, 1994; Walsh & Cunningham, 1997; Duvauchelle, et al., 2000; Farber, et al., 2004), and this increases in synaptic DA has been shown to lead to decreases in self-control behavior (e.g., van Gaalen et al., 2006). In addition, increasing synaptic 5-HT activates the 5-HT_3 receptor which further increases synaptic DA levels (Chen et al., 1992; Walsh & Cunningham, 1997).

In the present study, we expected that administration of a 5-HT_3 receptor antagonist, in conjunction with cocaine, would block the effects of cocaine, thus leading to an increase in self-control behavior. Results of the present study were consistent with some, but not all predictions. Under certain conditions, when paired with Ly-278,584, cocaine did decrease self-control behavior. However, contrary to our predictions, this decrease was not seen when cocaine was administered alone. We conclude three major findings of the current study.

First, prior to any drug administration, rats exhibited high levels of self-control. Preference for the larger, more delayed, reinforcer was also evident during post-injection days, and Phase 3 (Baseline). These results run counter to past research, which suggests that when given the choice between rewards of different amounts and delays, animal subjects tend to act impulsively, preferring the smaller, less delayed, reward (Rachlin & Green, 1972; Ainslie, 1974). Furthermore, it is suggested by some researchers that when faced with two or more alternative reinforcers, animals will distribute their choices according to the value of each source, measured in terms of amount divided by delay (Logue et al., 1992). Thus, in the present study, the choice of receiving 1 pellet of food following a 1 s delay or receiving 3 pellets of food following a 3 s delay, should lead subjects to be indifferent in their choice (i.e., will choice each reinforcer 50% of the time) because the ratio of amount to delay is one in both cases.

Several factors may account for why our rats showed a strong preference for the self-control option. These factors include lever bias, species differences, and the quality and quantity of the reinforcer used. To begin, it is unlikely that the reason for the heightened preference for the self-control reinforcer was due to lever bias. In Phase 4, rats' lever conditions on the self-control task were switched, whereby rats that were originally in the condition where the right lever served as the self-control lever were placed in the condition whereby the left-lever served as the self-control lever. A corresponding change occurred for rats that began the study with the left lever initially associated with the self-control reinforcer. As shown in Figure 17, all rats learned, by the 10^{th} session, which lever was the self-control lever and, again, responded more on the self-control lever than the impulsive lever. Moreover, rats were exposed to two forced-choice trials at the start of every set. These trials were designed to force subjects to respond on both levers, experiencing both reinforcer options, and discourage lever bias. Results of the present

study suggest that preferences for the self-control lever was not due to a bias coming from whichever lever happened to signal the self-control reinforcer at the start of the study. Rather, rats were pressing the lever because it of a strong preference to attain the larger reinforcer.

Next, species differences may account for why, in the current study, we found a heightened preference for the self-control choice. Studies such as Rachlin and Green (1972) and Ainslie (1974), suggest that pigeons generally act impulsively on tasks similar to the one used in the present study. However, van Haaren (1988) ran a similar study in which rats were exposed to a concurrent discrete-trials procedure to obtain either 1 food pellet or 6 food pellets following a 6 s delay. Much like the present study, rats were exposed to free-choice and force-choice trials. Not surprisingly, rats preferred the larger more delayed reward on the task. Even when the delay to the smaller reinforcer was held constant at 6 s and delay to the larger reinforcer varied from 9 s to 36 s, rats still preferred the larger reward over the smaller reward. Overall, the present results are similar to those from van Haaren et al.'s (1988), but differ from studies such as Ainslie (1974) with pigeons. That is, Ainslie (1974) found a preference for the impulsive choice, whereas we, like van Haaren (1988), found a preference for the self control choice. Interestingly, similar to the results of the present study, Logue et al. (1996) found high incidences of self-control in human studies as well; these differences in results are perhaps due to differences in the sensitivity of delay between species (see Tobin & Logue, 1994 for review).

Another possible explanation for our results may be related to the quality and quantity of the reinforcers used. For instance, Tobin et al. (1993) tested rats in procedures similar to those used in van Haaren et al. (1988). However, Tobin used liquid reinforcers while van Haaren used food pellets as reinforcers. Contrary to van Haaren et al. (1988), the results of Tobin et al. (1993) revealed that when liquid reinforcers were used, rats exhibit high levels of impulsive behavior on

a standard discrete-trials task. Instead of food pellets as reinforcers, rats chose between 2 s access to sweetened condensed milk after a 1 s delay and 6 s access to sweetened condensed milk after a 6s delay. This procedure differs from our study in that we used food pellets as reinforcers, and the delay to each reinforcer choice was shorter. It may be the case that if we used liquid reinforcers we would have found a decrease in self-control as well. Additionally, the ratio of amount and delay in the present study was equal to one, which is not true for Tobin et al (1993). Differences between Tobin et al. (1993) and the current study could also be due to the differing ratios of amount and delays used.

Second, another main finding of the present study was that, when administered alone, cocaine administration did not lead to a significant decrease in self-control behavior. We expected to find no change in self-control when Ly-278,584 was administered in the absence of cocaine, because the 5-HT_3 receptors are not tonically active (Kilpatrick & Tyers,1992). However, based on past research studying the effects of cocaine on self-control (e.g., Logue et al., 1992; Evenden & Ryan, 1996; Pain et al., 2003) we expected to find a decrease in self-control behavior following cocaine administration.

What was interesting, however, is that contrary to the long held assumption that an increase in self-control behavior implies a decrease in impulsivity (e.g., Rachlin & Green, 1972; Ainslie, 1974; Grosch & Neuringer, 1981; Eisenberger et al., 1982; King & Logue, 1987; Logue, 1988), we found that this is not always the case, and that null responses are also important to consider. For example, Figure 5 shows the change in the percentage of self-control (top), impulsive (middle) and null (bottom) responses made on the self-control task when cocaine was administered alone. As seen in Figure 5, the change in the percentage of self-control choices was not the exact inverse of the change in the percentage of impulsive choices. The data suggests that

this lack in corresponding changes in self-control and impulsive responses may be due to increases in null responses, as opposed to impulsive responses alone.

Past research assessing the effects of cocaine on self-control found that cocaine administration leads to the performance of more impulsive acts (e.g., Logue et al., 1992; Anderson & Woolverton, 2003; Coffey et al., 2003). However, we found that rats would make either a self-control choice or a null response. Additionally, in phases in which no drugs were administered (e.g., during the baseline phases) the percentage of self-control choices was the exact opposite of the percentage of impulsive choices, suggesting that no null responses were made. These results suggest that cocaine administration does have some effect on choice behavior in general.

Specifically, only a few rats exhibited null responses, most of which were exhibited following a 30mg/kg dose of cocaine. The emergence of null responses on the task may be explained by past research showing that cocaine increases stereotypy and hyperlocomotor movements (King, Joyner, Lee & Ellinwood, 1993). As part of the experiment, King et al. (1993) administered 40mg/kg of cocaine to rats, and a significant increase in stereotypies and hyperlocomotor behavior (e.g., jerky, disjunctive and jumping like movements) were seen as a result. It has been suggested by some researchers that administration of high cocaine doses (i.e., 30mg/kg), impairs rats' ability to perform a self-control task, such as the one used in the present study. For example, Logue et al (1992) suggested that administration of cocaine doses over 15mg/kg impaired responding on a discrete-trials self-control task.

Furthermore, the lack of a consistent decrease in self-control behavior following our high dose level of cocaine may be the result of only a single exposure to each cocaine dose. As discussed earlier, much of the research that has studied how cocaine affects self-control behavior

has been assessed using chronic doses of cocaine, as opposed to acute (e.g., Logue et al., 1992; Anderson and Woolverton, 2003). For example, Gratton and Wise (1994) found that following cocaine self-administration in rats, DA levels in the NAc are elevated. However, these levels were higher following repeated exposure to the drug, as opposed to the first injection of the drug. It may be the case, in the present study, that if we repeated each condition in the cocaine alone phase (7.5, 15 and 30mg/kg), we might see a higher reduction in self-control behavior due to higher levels of DA release. Perhaps it is the case that cocaine only decreases self-control behavior following chronic cocaine administration (e.g., Logue et al., 1992) as opposed to acute cocaine administration.

Third, we found a bimodal effect of Ly-278,584 at the highest level of cocaine. This dose response pattern is consistent with Grant's (1995) observation that higher doses of some 5-HT_3 receptor antagonists are less effective than other doses. We found that at higher doses of cocaine, the medium dose of Ly-278,584 had the largest effect in decreasing self-control. Instead of counteracting the effects of cocaine, it appeared to intensify the effect of cocaine, decreasing self-control. Taken together, results of the present study reveal that cocaine, in combination with Ly-278,584, effect self-control; these findings are consistent with past studies which found that the serotonergic and dopaminergic pathways play a role in mediating self-control behavior in rats (e.g., Logue et al., 1992; Winstanley, Theobald, Dalley, & Robbins, 2005). Results suggest that cocaine may play a role in decreasing self-control behavior, but only in combination with a 5-HT_3 receptor antagonist.

Furthermore, we found that Ly-278,584 did block the effects of cocaine on impulsive behavior. At high doses of Ly-278,584, not only were the mean change in the percentage of self-control behavior or impulsive behavior not significantly different from saline levels, but also no

null responses were made when this dose was administered. Taken together, these results support the idea that the 5-HT_3 receptor may play a role in mediating cocaine induced impulsivity. It may be suggested, then, that due to the lack of null responses in the combination condition, at high doses, Ly-274,584 blocks the motor effects of the drug. These results are consistent with past studied, which show that 5-HT_3 antagonists block the locomotor effects of cocaine (King, Joyner & Ellinwood, 1994).

Implications

Taken together, the results of the present study point to several important implications about the effects drugs have on self-control, and how we can better study these effects. First, the fact that the percentage of self-control and impulsive choices were not always exactly an inverse of each other, identifies the need to re-evaluate both the types of procedures used to study the effects of drugs on self-control behavior as well as how we evaluate the results. Future work should take into account that, while conceptually, self-control and impulsivity are inverses in terms of how they are measured, how we test for these behaviors may create a situation in which these choices are not directly related, or inverses of one another. Future research should not assume that the self-control is always the inverse of impulsivity, and instead measure all behaviors, as shown in the present study, instead of only measuring self-control and assuming impulsivity is inversely related.

Additionally, it is unlikely that increased hyperlocomotor movements or stereotypies impaired rats' ability to perform the task. First, not all rats exhibited high levels of null responding on the task. Specifically, five out of eight rats performed null responses during only one or two sessions. Still, each rat only emitted null responses during one or two drug trials (out of 17). Again, these trials were generally preceding administration of 30mg/kg of cocaine, with

the exception of two occasions in which two rats emitted null responses following 7.5mg/kg of cocaine. These results may just illustrate the individual differences that are often associated with cocaine administration (Ma, et al., 1999).

Next, across all phases of the study, the latency analyses indicate that more choices were made between one and two seconds after the start of the trial, suggesting that cocaine did not impair motor movements enough to delay responding. When rats did make a choice, regardless of whether or not it was a self-control or impulsive choice, they responded on a lever in an average of two seconds. Furthermore, these results hold true even in conditions in which cocaine was not administered. Specifically, during Phase 1:Baseline, Reversal Phase, and Phase 3:Baseline, cocaine was not administered, and yet it still took rats an average of two seconds to make a lever choice. Overall, these results suggest that null responses did not occur due to subject's inability to respond on the task, because it took rats relatively the same amount of time to press a lever whether or not cocaine had been administered.

Future Work

Results of the current study raise several important points that should be considered for future research. Unlike past research studying self-control (e.g., Rachlin & Green, 1974), in the present study we did not find that subjects were indifferent between choosing the larger delayed reward and smaller less delayed reward. It could be the case that the delays between lever pressing and reinforcer delivery were not long enough to produce indifference. This strong preference for the self-control choice may have resulted in a ceiling effect. To correct for this, future work should replicate the present study, but extend the delay between lever press and reinforcer delivery, which may produce indifference between self-control and impulsive choices, as seen in Rachlin and Green (1972) and Ainslie (1974). The size of the, reinforcer (e.g., number

of food pellets) may also be systematically varied to create an indifference; however, in a pilot study, we found that increasing the number of pellets over three caused satiety problems. As discussed above, to account for satiety issues, this task should be replicated with liquid reinforcers such as sweetened condensed milk (Tobin et al., 1993). The delay between reinforcer choice and delivery may also be extended to create indifference (Rachlin & Green, 1972).

Perhaps more importantly, future work should explore how responding on the self-control task depends on the repeated exposure to drug conditions. It may be the case that decreases in self-control is predominantly seen following chronic cocaine administration (Logue et al., 1992; Eveden & Ryan, 1996; Paine et al., 2003). Past research has shown that chronic administration of cocaine down-regulates the 5-HT_3 receptor (e.g., King, Pinto, Konen, Castro, Tran & Hilburn, 2002), which may have an affect self-control behavior. Future studies should examine the effects of 5-HT_3 receptor down-regulation on self-control behavior in rats. Instead of administering an acute IP dose of cocaine every three days, as was done in the present study, future work should assess how chronic daily IP injections affect self-control behavior over time.

Conclusions

Results of the present study show that, when administered alone, acute administrations of cocaine did not significantly decrease self-control behavior. However, when paired with a medium dose of Ly-278,584 (.01mg.kg), high doses of cocaine decreased self-control behavior in rats. Apparently, the behavioral and psychomotor affects of cocaine were attenuated by high doses of Ly-278,584 (1.0mg/kg) across all cocaine dose conditions. The current findings give support for the idea that both the DA and 5-HT systems are involved in mediating self-control behavior (e.g., Logue, 1992). Specifically, because Ly-278,584 blocked some of the effects of

cocaine, it is suggested that the 5-HT_3 receptor does play a role in mediating self-control behavior following cocaine administration, due to direct interactions with the DA system.

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ABSTRACT

THE ACUTE EFFECTS OF COCAINE ON 5-HT_3 RECEPTOR ACTIVATION AND SELF-CONTROL IN RATS

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This study investigated the mechanisms that mediate cocaine's effects on self-control and impulsive behavior in rats. Subjects in the study were eight adult male Sprague-Dawley rats. The rats were exposed to a discrete-trials self-control procedure in which a lever press to one lever produced 1 pellet of food following a 1 s delay and a lever press to the opposite lever produced 3 pellets of food following a 3 s delay. Rats were given 0 mg/kg, 7.5 mg/kg, 15 mg/kg and 30 mg/kg of cocaine and 0mg/kg, .01 mg/kg, .10 mg/kg and 1.0 mg/kg of the 5-HT_3 receptor antagonist Ly-278,584 separately and in combination with each other to assess the effects of $5HT_3$ receptor inhibition on cocaine's effects on self-control. Results revealed no decreases in self-control behavior following administration of cocaine in the absence of Ly-278,584, but did reveal a decrease in self-control in some instances when the two drugs were administered together. Therefore, results do support past research suggesting that serotonergic and dopaminergic systems play a role in mediating the behavioral effects of cocaine.