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CONTRIBUTION OF NUCLEUS ACCUMBENS CORE TO IMPULSIVE CHOICE: ROLE OF DOPAMINE AND GLUTAMATE SYSTEMS

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DISSERTATION

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the College of Arts and Sciences at the University of Kentucky

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ABSTRACT OF DISSERTATION

CONTRIBUTION OF NUCLEUS ACCUMBENS CORE TO IMPULSIVE CHOICE: ROLE OF DOPAMINE AND GLUTAMATE SYSTEMS

Impulsive choice refers to the inability to delay gratification and is associated with increased drug abuse vulnerability. Understanding the underlying neural mechanisms linking impulsive choice and drug abuse can contribute to improved treatment options for individuals with substance use disorders. Evidence suggests a major role for nucleus accumbens core (NAcc) in impulsive choice and the reinforcing effects of drugs of abuse. The neurotransmitters glutamate (Glu) and dopamine (DA) are implicated in the neural adaptations observed in drug addiction; however, the role of intra-NAcc Glu and DA in impulsive choice is unclear. Rats were trained in a delay discounting task, in which animals chose between a small, immediate reinforcer and large, delayed reinforcer. Consistently choosing the small, immediate reinforcer was considered to reflect increased impulsivity. Following delay discounting, *in vitro* receptor autoradiography was performed to quantify the number of N-methyl-D-aspartate (NMDA) receptors and dopamine transporters (DAT) in NAcc and nucleus accumbens shell (NAcSh). In a separate experiment, rats were trained in delay discounting and were implanted with guide cannulae into NAcc. Following surgery, rats received microinfusions of either a) the Glu-selective ligands MK-801 (noncompetitive NMDA receptor channel blocker; 0, 0.3, and 1.0 µg), AP-5 (competitive NMDA receptor antagonist; 0, 0.3, and 1.0 µg), ifenprodil (NMDA NR2B subunit antagonist; 0, 0.3, and 1.0 µg), and CNQX (AMPA receptor antagonist; 0, 0.2, and 0.5 µg) or b) the DA-selective ligands SKF 38393 (D1-like receptor agonist; 0, 0.03, and 0.1 µg), SCH 23390 (D1-like receptor antagonist; 0, 0.3, and 1.0 µg), quinpirole (D2-like receptor agonist; 0, 0.3, and 1.0 µg), and eticlopride (D2-like receptor antagonist; 0, 0.3, and 1.0 µg). In NAcc and NAcSh, NMDA receptor and DAT expression did not differ between high and low

impulsive rats. Furthermore, intra-NAcc administration of NDMA and DA receptor ligands did not significantly alter impulsive choice. These results suggest that Glu and DA systems within NAcc do not directly mediate impulsive decision making. Future work is needed to determine the precise role of NAcc in mediating impulsive choice.

KEYWORDS: Impulsive Choice, Nucleus Accumbens Core, Glutamate, Dopamine, Rat

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Chapter 1: Introduction

Impulsivity

Impulsivity is a multifaceted construct that includes lack of inhibitory control, lack of forethought, and inability to delay gratification (see Evenden, 1999; Whiteside & Lynam, 2001 for reviews). The construct of impulsivity can be measured using personality questionnaires and behavioral studies. Numerous personality questionnaires have been developed to measure impulsivity. Some of the most widely used questionnaires include the Barratt Impulsiveness Scale-11 (BIS-11; Patton, Stanford, & Barratt, 1995), which encompasses the subscales attentional impulsiveness, motor impulsiveness, and non-planning impulsiveness; the I-7 Impulsiveness Questionnaire (Eysenck, Pearson, Easting, & Allsopp, 1985), which is composed of the subscales impulsiveness, venturesomeness, and empathy; and the UPPS Impulsive Behavior Scale (Whiteside & Lynam, 2001), which includes urgency, (lack of) premeditation, (lack of) perseverance, and sensation seeking.

Dickman (1990) emphasizes two broad types of impulsivity: functional and dysfunctional. Functional impulsivity is defined as the tendency to act with little forethought when the situation is optimal. In contrast, dysfunctional impulsivity is defined as the tendency to act with less forethought, which can lead to problematic decisions. Distinguishing between functional and dysfunctional impulsivity is important because this distinction illustrates that impulsivity is not always disadvantageous.

One criticism of personality measures is that they can suffer from the "jingle and jangle" fallacies (Block, 1995; see Whiteside and Lynam, 2001 for a discussion). According to Whiteside and Lynam (2001), the jingle fallacy refers to situations in which two different impulsivity constructs are given the same label, and the jangle fallacy refers to situations in which different labels are used to describe the same construct. These fallacies are problematic because they can impede our understanding of the underlying processes involved in impulsivity. One way to avoid the jingle and jangle fallacies is to use behavioral studies to test the various types of impulsivity.

Impulsive Action and Impulsive Choice

Most of the behavioral procedures measuring impulsivity can be fractioned into two broad categories: impulsive action and impulsive choice (see Winstanley, Olausson, Taylor, & Jentsch, 2010 for a full review). Impulsive action is conceptualized as motor impulsivity; humans and animals that fail to inhibit prepotent responses are considered to have higher levels of motor impulsivity. The primary behavioral tasks used to measure impulsive action are the stop signal reaction time (SSRT), the go/no-go, and the five-choice serial reaction time (5CSRT) tasks (see Winstanley et al., 2010). In the SSRT, subjects are required to inhibit responses they have already initiated when presented with a cue (Logan, Cowan, & Davis, 1984). In go/no-go tasks, subjects are required to either initiate a response (go) or inhibit a response (no-go) when presented with different cues (Newman, Widom, & Nathan, 1985). In the 5CSRT task, animals are trained to respond to a stimulus that is presented in

one of five apertures. The animal is required to wait for a period of time before initiating a response (Carli, Robbins, Evenden, & Everitt, 1983).

The SSRT and go/no-go tasks can be used with human (Logan et al., 1984; Newman et al., 1985) and animal subjects (Eagle & Robbins, 2003; Feola, de Wit, & Richards, 2000; Iverson & Mishkin, 1970; Liu, Heitz, & Bradberry, 2009; Terman & Terman, 1973), but the 5CSRT is currently only measured in animals. However, the 5CSRT is considered to be an animal analog of the continuous performance task, in which humans are required to scan a 5-digit sequence and respond when the number matches a target stimulus (Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956; see Winstanley et al., 2010 for a discussion).

Impulsive choice is conceptualized as the inability to delay gratification and is often measured with delay discounting tasks. The term discounting refers to the decrease in subjective value of a reinforcer as a function of the delay to its delivery. In a typical delay discounting procedure, humans and animals choose between a small magnitude reinforcer delivered immediately and a large magnitude reinforcer delivered after a delay. Consistently choosing the smaller, immediate reward over the larger, delayed reward is often considered to reflect impulsive behavior (Ainslie, 1975). Discounting of delayed rewards is observed in various species, including humans (e.g., Rachlin, Raineri, & Cross, 1991), pigeons (e.g., Mazur, 1987), mice (e.g., Mitchell, Reeves, Li, & Phillips, 2006), and rats (e.g., Richards, Mitchell, de Wit, & Seiden, 1997).

Delay Discounting Paradigms

Delay discounting is often measured in humans by asking participants to choose between two hypothetical monetary rewards differing in magnitude (Rachlin et al., 1991). The value of the larger, delayed monetary reward is held constant, whereas the value of the smaller, immediate reward is decreased systematically. The indifference point is the point at which a person switches their preference from the small, immediate reinforcer to the large, delayed reinforcer. While there may be some concern about the validity of delay discounting when hypothetical rewards are used, results indicate similar rates of delay discounting when hypothetical or real rewards are used (Johnson & Bickel, 2002; Madden, Begotka, Raiff, & Kastern, 2003).

Multiple procedures can be used to measure delay discounting in animals. In the T-maze (Bizot, Le Bihan, Puech, Hamon, & Thiebot, 1999; Rudebeck, Walton, Smyth, Bannerman, & Rushworth, 2006), one arm of the maze is associated with a small magnitude reinforcer, whereas one arm is paired with a larger reinforcer. If the rat chooses the arm with the larger reinforcer, a gate is lowered, and the animal is confined to the arm for a fixed delay before receiving reinforcement. Delays to the larger reinforcer are increased across sessions. Because the T-maze paradigm is more labor intense relative to using an automated operant procedure, it is infrequently used (Madden & Johnson, 2010).

Procedures testing delay discounting often rely on the use of operant conditioning procedures. As discussed by Madden and Johnson (2010), there

are several common features among studies measuring delay discounting using an operant procedure. Typically, the animal must perform a response that places the subject equidistant from the two choice alternatives. Without this control, an animal may respond on a manipulandum because it is closer to that manipulandum relative to the alternative manipulandum. Another common feature is the inclusion of forced-choice trials. During these trials, only one alternative is available. These trials are included to expose the animal to both contingencies of reinforcement.

In the adjusting delay procedure, animals are trained to make choices between a large amount of food delivered after an adjusting delay and a smaller amount delivered after a fixed delay (Mazur, 1987). Generally, subjects complete blocks of trials, which consist of two forced-choice trials followed by two free-choice trials. If the subject chooses the smaller reinforcer on both free-choice trials, the delay to the larger reinforcer is decreased (usually by 1 sec). Conversely, if an animal chooses the larger reinforcer on both free-choice trials, the delay to the larger reinforcer is increased. The delay to the larger reinforcer is not altered if the subject chooses each reinforcer during a block of trials. Upon achieving stability, the mean adjusting delay is calculated and it is termed as the "indifference point". This procedure is repeated across several fixed delays to the smaller reinforcer, and adjusting delays are plotted as a function of the fixed delay to the smaller, sooner reinforcer.

The adjusting delay procedure has received some criticism. In one study Cardinal, Daw, Robbins, and Everitt (2002) trained rats to complete thousands of

trials in an adjusting delay task. Despite the extensive training, rats never reached a constrained range of adjusted delays (i.e., adjusted delays never stabilized). Cardinal et al. (2002) concluded that animals are not sensitive to the adjusting delay. It is important to note that Cardinal et al. (2002) adjusted the delay to the large magnitude reinforcer by 20%-30% (range: 0.4 – 9.0 seconds), whereas Mazur (1987) adjusted the delay in 1-second increments. The large adjustments to the delay to the large reward in the Cardinal et al. (2002) study may have resulted in instable indifference points (see Madden & Johnson, 2010).

The adjusting amount procedure developed by Richards et al. (1997) is similar to the adjusting delay procedure. However, delays stay constant within a session, whereas the size of the delayed reinforcer varies depending on the animal's response on the previous trial. Evidence suggest that the rate of discounting in an adjusting amount procedure is similar to the discounting observed in an adjusting delay procedure, suggesting that these tasks share similar underlying processes (Green, Myerson, Shah, Estle, & Holt, 2007).

Evenden and Ryan (1996) developed a discounting procedure that is commonly used to measure impulsive choice in both humans and animals. This task incorporates blocks of trials, in which the delay for obtaining the larger reward increases within a single session (Evenden & Ryan, 1996), although the delay for obtaining the large reinforcer can be manipulated between sessions (Mobini, Chiang, Ho, Bradshaw, & Szabadi, 2000). As the delay of obtaining the large reinforcer increases, animals switch their preference to the smaller, immediate reinforcer (Evenden & Ryan, 1996). Importantly, the increased

discounting observed across a session is not due to satiation, as animals consistently choose a large reinforcer over a small reinforcer when delivery of the larger reinforcer is not delayed (Evenden & Ryan, 1996). One advantage of this procedure is that it provides a measure of sensitivity to delayed reinforcement during each session. Also, a measurement of sensitivity to reinforcer amount can be measured each session by examining choice for the large reinforcer during no-delay trial blocks (i.e., delay = 0 sec).

Although the original study conducted by Evenden and Ryan (1996) increased the delay across blocks of trials, some studies have examined whether increasing or decreasing the delay to the larger reinforcer across trial blocks alters the rate of discounting of that reinforcer. Studies with human participants have generally shown that increasing the delay within session produces greater discounting relative to decreasing the delay within session (Robles & Vargas, 2008; Robles, Vargas, & Bejarano, 2009; Stillwell & Tunney, 2012; but see Robles & Vargas, 2007). Studies with animals have been mixed; Fox, Hand, and Reilly (2008) reported increased discounting using a descending sequence relative to an ascending sequence, whereas Slezak and Anderson (2009) observed no difference in discounting rate using an ascending or a descending sequence.

Mathematical Models of Discounting

Several mathematical models have been proposed to describe the relationship between delay and subjective value of a reinforcer. The exponential

discounting model postulates that the subjective value of a good decreases by a constant percentage per unit time and can be modeled with the following equation:

$$V = Ae^{-kD}$$

In this equation, *V* is the subjective value of the delayed reinforcer, *A* represents the amount of the reinforcer, *D* is the delay to the delivery of the reinforcer, and *k* is a parameter measuring the rate at which delayed reinforcers are discounted (Samuelson, 1937). A higher *k* value indicates a preference for small, immediate reinforcement.

The exponential model assumes that if a reinforcer is preferred over another reinforcer at one point in time, it will be preferred at all other points in time. However, results from studies with humans (Green, Fristoe, & Myerson, 1994) and animals (Ainslie & Hernstein, 1981; Green & Estle, 2003; Green, Fisher, Perlow, & Sherman, 1981) do not support this hypothesis. For example, human participants given a choice between a small hypothetical monetary reward (e.g., $20) delivered immediately and a large hypothetical monetary reward (e.g., $50) delivered in 1 year often choose the small, immediate reward; however, if a delay is added to both rewards (e.g., $20 delivered in 1 year vs. $50 delivered in 2 years), participants often switch their preference to the larger reward (Green et al., 1994). The exponential model of discounting does not predict these preference reversals (see Green & Myerson, 2004; Madden & Johnson, 2010 for reviews).

To account for preference reversals, the hyperbolic discounting model proposed by Mazur (1987) is often used, which is modeled with the equation:

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

The parameters are identical to those described in the exponential function. There is evidence to suggest that the hyperbolic model provides a better fit of discounting data relative to the exponential model in humans (Rachlin et al., 1991; Vuchinich & Simpson, 2000) and animals (Mazur, 1987).

A hyperboloid function can also be used to model discounting of delayed reinforcers (Green, Fry, & Myerson, 1994). This function is similar to the hyperbolic function proposed by Mazur (1987), with the exception that the denominator of the hyperbola is raised to a power of *s*, which is a nonlinear scaling of amount and/or time and is generally equal to or less than 1.0 (see Green & Myerson, 2004 for a review). According to Myerson and Green (1995), the hyperboloid function provides a better fit of delay discounting behavior relative to the hyperbolic, although studies with animals show no reliable difference between hyperbolic and hyperboloid functions (Green et al., 2007; Mazur, 2000; Richards et al., 1997).

Given the debate surrounding the different theoretical discounting functions, Myerson, Green, and Warusawitharana (2001) propose a "theoretically neutral" model of discounting. Instead of using parameter estimates derived from theoretical models of discounting, Myerson et al. (2001) advocate the use of area under the curve (AUC) to determine sensitivity to delayed reinforcement. One

advantage of using AUC is that the distribution of AUC values are normally distributed, whereas parameter estimates derived from discounting functions tend to be positively skewed (Myerson et al., 2001), thus allowing the use of parametric statistical analyses to compare discounting rates in different groups of subjects.

Relationship between Impulsive Choice and Drug Abuse

Clinical cross-sectional studies indicate that drug users are more impulsive compared to nonusers (Moeller et al., 2001; Sher & Trull, 1994). In humans, greater delay discounting is observed in opioid-dependent individuals (Kirby, Petry, & Bickle, 1999; Madden, Petry, Badger, & Bickel, 1997), cocaine users (Coffey, Gudelski, Saladin, & Brady, 2003; Heil, Johnson, Higgins, & Bickel, 2006), methamphetamine-dependent individuals (Hoffman et al., 2006), alcohol abusers (Field, Christiansen, Cole, & Goudie, 2007; Kollins, 2003; Petry, 2001a, Vuchinich & Simpson, 1998), and cigarette smokers (Bickel, Odum, & Madden, 1999; Mitchell, 1999; Ohmura, Takahashi, & Kitamura, 2005; Reynolds, Richards, Horn, & Karraker, 2004). Furthermore, individuals with a history of substance abuse show greater discounting of crack/cocaine, heroin, and cigarettes relative to monetary rewards (Bickel et al., 1999; Coffey et al., 2003; Madden et al., 1997), reflecting the importance of drug reward over monetary rewards in these individuals.

Although individuals with a history of substance abuse are more impulsive relative to matched controls, it is unknown if enhanced impulsivity predisposes an

individual to substance abuse or if prolonged drug use increases impulsivity. Evidence suggests a bidirectional relationship between impulsivity and drug abuse (see de Wit, 2009), and preclinical research has been valuable in this regard. Using a T-maze paradigm to access impulsive choice, Poulos, Le, and Parker (1995) found that high impulsive (HiI) rats consume more ethanol relative to low impulsive (LoI) rats. Since the seminal study conducted by Poulos et al. (1995), others have examined if impulsive choice predicts vulnerability to different stages of drug seeking. HiI rats acquire cocaine self-administration at a faster rate (Perry, Larson, German, Madden, & Carroll, 2005; Perry, Nelson, & Perry, 2008), show greater escalation of cocaine self-administration (Anker, Perry, Gliddon, & Carroll, 2009), and show greater resistance to extinction (i.e., increased responding on a lever in the absence of reinforcement) to cocaine self-administration (Broos, Diergaarde, Schoffelmeer, Pattij, & De Vries, 2012a) relative to LoI rats. Also, HiI rats self-administer more nicotine and methylphenidate relative to LoI rats (Diergaarde et al., 2008; Marusich & Bardo, 2009), and impulsive choice is predictive of reinstatement to nicotine self-administration (Diergaarde et al., 2008). Thus, increased impulsivity is a predictor of increased substance abuse vulnerability.

Some studies have used a behavioral economic approach to measure whether impulsivity is associated with inelastic demand for drugs of abuse. In this approach, total consumption of a reinforcer, rather than response rate, is measured. Consumption is measured at a variety of prices (i.e., response requirements); if an animal continues to respond for the reinforcer as the price

increases, the demand for the reinforcer is considered to be inelastic. Impulsive choice is predictive of inelastic demand for cocaine (Koffarnus & Woods, 2011) and nicotine (Diergaarde, van Mourik, Pattij, Schoffelmeer, & De Vries, 2012). Interestingly, impulsivity does not predict inelastic demand for alcohol (Diergaarde et al., 2012), which contrasts with previous research demonstrating that impulsive choice predicts increased alcohol consumption (Poulos et al., 1995). These inconsistencies demonstrate the importance of using various drug self-administration paradigms to determine the precise relationship between sensitivity to delayed reinforcement and drug abuse vulnerability.

Some caution needs to be taken when interpreting previous studies examining delay discounting and operant drug self-administration. Stephens et al. (2010) present one confound to self-administration paradigms. Self-administration for psychostimulant drugs may not reflect increased motivation to obtain the drug reinforcer; instead, these drugs produce hyperactivity, which may increase the likelihood that an animal responds on the drug-paired manipulandum. Rats that show increased cocaine-induced hyperactivity are more impulsive in a delay discounting task relative to rats that show an attenuated response to cocaine (Stanis, Burns, Sherrill, & Gulley, 2008). Thus, HiI rats may respond more for psychostimulant drugs due to increased drug-induced hyperactivity.

Another potential interpretational problem with previous studies assessing the role of impulsive choice in drug self-administration is that HiI animals may not respond more for drug because of its reinforcing properties; instead, they may be

more sensitive to reward-associated stimuli. For example, HiI rats exhibit more sign-tracking conditioned responses compared to LoI rats (Tomie, Aguado, Pohrecky, & Benjamin, 1998; but see Lovic, Saunders, Yager, & Robinson, 2011). Also, Diergaarde, Pattij, Nawijn, Schoffelmeer, and De Vries (2009) showed that high impulsive rats nose poke more for a discrete cue formerly paired with sucrose delivery.

To avoid these potential confounds, Yates, Marusich, Gipson, Beckmann, and Bardo (2012) used a non-operant conditioned place preference (CPP) paradigm to measure drug reward in HiI and LoI rats. Impulsive choice was predictive of amphetamine CPP; that is, HiI animals spent more time in an environment previously paired with amphetamine relative to LoI animals (Yates et al., 2012). These results demonstrate that the increased drug self-administration of psychostimulants is not simply the result of drug-induced hyperactivity or increased sign-tracking.

Although increased impulsive choice is predictive of different stages of psychostimulant addiction, there is little evidence that delay discounting is associated with opioid self-administration. HiI and LoI rats acquire heroin self-administration at the same rate and self-administer similar amounts of heroin (Schippers, Binnekade, Schoffelmeer, Pattij, & De Vries, 2012). Furthermore, impulsive choice is not predictive of extinction to heroin self-administration or reinstatement to heroin self-administration (Schippers et al., 2012). Although the relationship between drug addiction and impulsive choice is postulated to be

bidirectional (de Wit, 2009), these results suggest that impulsivity is not a determinant of opioid abuse.

Conversely, despite the clear evidence for impulsive choice being a predictor of stimulant abuse, research also has demonstrated that drug exposure affects impulsive decision making. Cocaine administration (systemic and self-administered) increases impulsive choice in rats (Dandy & Gatch, 2009; Hernandez et al., 2014; Mendez et al., 2010; Simon Mendez, & Setlow, 2007; but see Broos et al., 2012a), as does chronic self-administration of amphetamine or heroin (Gipson & Bardo, 2009; Schippers et al., 2012). Finally, withdrawal from phencyclidine increases impulsive choice (Carroll, Kohl, Johnson, & La Nasa, 2013; Carroll, Mach, La Nasa, & Newman, 2009). In conclusion, exposure to drugs of abuse increases impulsive decision making.

Underlying Neuromechanisms Linking Impulsive Choice and Drug Abuse

Understanding the potential underlying neural mechanisms linking impulsive choice and drug reinforcement can help explain why HiI individuals are prone to drug abuse. Such information is important for the development of better treatment options for individuals with substance use disorders.

Neuroanatomical Regions Implicated in Impulsive Choice

To identify the neuroanatomical structures involved in discounting, techniques such as focal excitotoxic or neurochemical lesions and temporary inactivation are often used. Several brain regions have been implicated in impulsive choice, including amygdala (Churchwell, Morris, Heurtelou, & Kesner,

2009; Winstanley, Theobald, Cardinal, & Robbins, 2004b), dorsal striatum (Dunnett, Heuer, Lelos, Brooks, & Rosser, 2012), and hippocampus (Abela & Chudasama, 2013; Cheung & Cardinal, 2005; Mariano et al., 2009). However, structures within the mesocorticolimbic pathway have received particular interest due to the major hypothesis that chronic drug exposure augments stimulus-reward learning and impairs inhibitory control functions, facilitating relapse-like behavior (Jentch & Taylor, 1999; Robinson & Berridge, 2003). This portion of the dissertation will focus on three regions within the mesocorticolimbic pathway: orbitofrontal cortex (OFC), medial prefrontal cortex (mPFC), and nucleus accumbens (NAc).

Orbitofrontal cortex (OFC). OFC is implicated in various forms of decision making, most importantly in updating the value of an expected reward on the basis of past experience (Gallagher, McMahan, & Shoenbaum, 1999; Izquierdo, Suda, & Murray, 2004; Roesch & Olson, 2004; Schoenbaum, Chiba, & Gallagher, 1998; Schoenbaum, Setlow, & Ramus, 2003; see Wallis, 2007 for a review). OFC also is implicated in drug abuse, as hypoactivity within this region is observed in individuals with cocaine addiction (Volkow et al., 1993, 1991) and re-exposure to a drug-paired context activates OFC in nonhuman animals (Hearing, Miller, See, & McGinty, 2008; Neisewander et al., 2000). Lesions to OFC decrease cocaine self-administration in rats (Hutcheson & Everitt, 2003; but see Grakalic, Panlilio, Quiroz, & Schindler, 2010), and inactivation of OFC attenuates cue-induced cocaine seeking behavior (Fuchs, Evans, Parker, & See, 2004).

Studies examining the role of OFC in delay discounting behavior have produced variable results. During performance in an adjusting-delay procedure, an increase in Fos expression in OFC is observed (de Costa Araújo et al., 2010). Also, several studies have found an increase in the rate of discounting following lesions to OFC (Mobini, Chiang, Ho, Bradshaw, & Szabadi, 2002; Kheramin et al., 2002, 2004; Rudebeck et al., 2006). However, other studies have observed either a decrease in discounting (Mar, Walker, Theobald, Eagle, & Robbins, 2011; Winstanley et al., 2004b) or no effect in discounting behavior following temporary inactivation via GABA agonists or permanent lesions (Abela & Chudasama, 2013; Churchwell et al., 2009; Jo, Kim, Lee, & Jung, 2013; Mariano et al., 2009; Stopper, Green, & Floresco, 2014). These discrepancies may result from differential destruction of subregions of OFC, as lesions to medial OFC increase sensitivity to delayed reinforcement, whereas lesions to lateral OFC decrease discounting (Mar et al., 2011).

Other methodological factors that can potentially explain the discrepancies observed across studies include baseline levels of impulsive choice and cues that signal the delay to the larger reinforcer. For example, inactivation of OFC increases impulsive choice in LoI rats when the delay is signaled, but decreases impulsivity in HiI rats when the delay is not signaled (Zeeb, Floresco, & Winstanley, 2010).

Medial prefrontal cortex (mPFC). mPFC can be subdivided into prelimbic cortex (PrLC) and infralimbic cortex (ILC) and is involved in reward-related learning (Balleine & Dickinson, 1998; Richardson & Gratton, 1998).

mPFC is implicated in the reinforcing effects of drugs of abuse, as well as drug relapse (see Perry et al., 2011; Tzschentke, 2000 for reviews).

Some studies have shown that mPFC mediates delay discounting. In humans, decreased impulsive choice is associated with increased thickness in mPFC (Bernhardt et al., 2014). Also, impulsive choice is negatively correlated with mPFC activation (Antonelli et al., 2014). In animals, mPFC inactivation increases sensitivity to delayed reinforcement (Churchwell et al., 2009), although whole mPFC lesions and ventral mPFC inactivation have no delay-specific effects on choice between small, immediate and large, delayed rewards (Cardinal, Pennicott, Sugathapala, Robbins, & Everitt, 2001; Feja & Koch, 2014).

Nucleus accumbens (NAc). NAc is composed of the core (NAcc) and shell (NAcSh) subregions (Voorn, Gerfen, & Groenewgen, 1989; Zaborsky et al., 1985) and responds to anticipated rewards (Bjork et al., 2004; Breiter, Aharon, Kahneman, Dale, & Shizgal, 2001; Francois, Conway, Lowry, Tricklebank, & Gilmour, 2012; Martin & Ono, 2000; Richardson & Gratton, 2008; Schultz, Apicella, Scarnati, & Ljungberg, 1992) and mediates the reinforcing effects of various drugs of abuse (see Chen, Hopf, & Bonci, 2010; Di Chiara, 2002; Di Chiara et al., 2004; Willuhn, Wanat, Clark, & Phillips, 2010 for reviews). In general, lesions to NAc attenuate drug self-administration in animals (Corrigall, Franklin, Coen, & Clarke, 1992; Dworkin, Guerin, Goeders, & Smith, 1988; Gerrits & Van Ree, 1996).

Animals performing a delay discounting procedure show an increase in Fos expression in NAcc (da Costa Araújo et al., 2010). Also, NAcc lesions increase impulsive choice (Bezzina et al., 2007; Cardinal et al., 2001; da Costa Araújo et al., 2009; Pothuzien, Jongen-Relo, Feldon, & Yee, 2005; Valencia-Torres et al., 2012; but see Winstanley, Theobald, Dalley, & Robbins, 2005), whereas combined NAcc/NAcSh lesions increase preference for a large, delayed reinforcer (Acheson et al., 2006). The findings obtained by Acheson et al. (2006) do not appear to be the result of damage to NAcSh, as selective lesions to this subregion do not alter sensitivity to delayed reinforcement (Pothuzien et al., 2005).

Neurochemical Systems Involved in Impulsive Choice

Several techniques can be used to study the involvement of neurotransmitter systems in impulsive choice. A common method for determining the role of a neurotransmitter in discounting behavior is to administer a drug that acts at specific receptors. Typically, the drug is administered systemically, although receptor ligands can be directly injected into a brain region of interest. Another technique that can be used is microdialysis, in which a neurotransmitter of interest is collected during task performance and later quantified. Through these techniques, serotonin (5-HT) and dopamine (DA) systems have been implicated as important mediators of impulsive choice and will be discussed in detail below.

Serotonin (5-HT). 5-HT is a monoamine synthesized from tryptophan. 5-HT released from a presynaptic neuron can bind to different receptor families, which are primarily G protein-coupled. Currently, there are 14 known 5-HT receptor subtypes within 7 different families (see Barnes & Sharp, 1999; Filip & Bader, 2009 for full reviews). For brevity, only the first three 5-HT receptor families will be discussed in detail. 5-HT_1 receptors can be divided into five subtypes (5-$HT_{1A,B,D,E,F}$) which are distributed throughout the brain, particularly in the raphe nuclei, hippocampus, cerebral cortex, and basal ganglia (Pazos & Palacios, 1985; Weissmann-Nanopoulos, Mach, Magre, Demassey, & Pujol, 1985; Vergé et al., 1986). 5-HT_1 receptors inhibit cyclic adenosine monophosphate (cAMP; Fargin et al., 1989) and are autoreceptors in the raphe nuclei and postsynaptic receptors in the limbic system (see Albert, Lembo, Storring, Charest, & Saucier, 1996; Barnes & Sharp, 1999). 5-HT_2 receptors can be subdivided into three subtypes (5-HT_{2A-C}), and like 5-HT_1 receptors, are distributed throughout the brain, such as hippocampus, cortex, basal ganglia, amygdala, hypothalamus, and cerebellum (Bonhaus et al., 1995; Pazos, Cortes, & Palacios, 1985; Pazos, Probst, & Palacios, 1987). 5-HT_2 receptors are coupled to phospholipase C and lead to increased inositol 1,4,5-trisphosphate and intracellular Ca^{2+} (Nakaki, Roth, Chuang, & Costa, 1985; Xu & Chuang, 1987). The 5-HT_3 receptor is the only 5-HT receptor subtype that is a ligand-gated ion channel (Derkach, Surprenant, & North, 1989) and is mainly located in limbic structures such as the hippocampus and amygdala (Tecott, Maricq, & Julius, 1993).

Low 5-HT activity has been linked to impulsive behavior, as individuals prone to suicide often display impulsive behavior and have decreased levels of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA; Åsberg, 1997; Cremniter et al., 1999; Träskman-Bendz, Åsberg, & Schalling, 1986). Forebrain 5-HT depletion also increases impulsive decision making in humans (Schweighofer et al., 2008; but see Crean, Richards, & de Wit, 2002) and animals (Bizot et al., 1999; Mobini et al., 2000; Wogar, Bradshaw, & Szabadi, 1993; but see Winstanley, Dalley, Theobald, & Robbins, 2003, 2004a).

Pharmacological studies also support the role of 5-HT in delay discounting behavior, although discrepancies are reported in the literature. Inhibiting the synthesis of 5-HT with para-chlorophenyl-alanine methyl ester increases impulsive choice in a T-maze paradigm (Denk et al., 2005). The 5-HT indirect agonist fenfluramine decreases impulsive choice (Poulos, Parker, & Le, 1996), whereas 5-HT_{1A} receptor agonists dose-dependently promote choice of the small, immediate reinforcer over the large, delayed reinforcer (Blasio et al., 2012; Liu, Wilkinson, & Robbins, 2004; Stanis et al., 2008; Winstanley et al., 2005). 5-HT_{1A} receptor agonists also decrease choice for the larger reinforcer when the delay to its delivery is set at 0 sec (Liu et al., 2004; Winstanley et al., 2005); thus, sensitivity to reinforcer magnitude may be altered, as well as sensitivity to delay.

Stimulating 5-$HT_{2A/C}$ receptors decreases the capacity for rats to wait for delivery of a large magnitude reinforcer (Blasio et al., 2012; Hadamitzky, Feja, Becker, & Koch, 2009), whereas antagonism of these receptors does not alter discounting behavior (Hadamitzky et al., 2009; Paterson, Wetzler, Hackett, &

Hanania, 2012; Talpos, Wilkinson, & Robbins, 2006). Conversely, antagonism of 5-$HT_{2B/C}$ receptors decreases impulsive choice (Paterson et al., 2012; Talpos et al., 2006).

There is limited evidence that 5-HT_3 receptors are involved in impulsive choice. Administration of the 5-HT_3 receptor antagonist tropisetron decreases impulsive choice in animals with high baseline levels of impulsivity, whereas tropisetron increases impulsive choice in animals with low baseline levels of impulsivity (Cervantes, Biggs, & Delville, 2010).

Stereotaxic techniques show that 5-HT within the mesocorticolimbic pathway is involved in impulsive decision making. Using *in vivo* microdialysis, performance in delay discounting significantly increases 5-HT efflux in mPFC (Winstanley, Theobald, Dalley, Cardinal, & Robbins, 2006b). Furthermore, microinjection of 5-$HT_{2A/C}$ receptor antagonists into the OFC increases impulsive choice (Wischhof, Hollensteiner, & Koch, 2011), whereas 5-HT_{1A} receptor agonists into the OFC decreases impulsive choice (Yates et al., under review). Finally, HiI animals have increased 5-HT_3 receptor expression in amygdala, prefrontal cortex (PFC), and NAc (Cervantes, & Delville, 2009). Taken together, the results of these studies indicate that 5-HT mediates impulsive decision making.

Dopamine (DA). DA belongs to the catecholamine family and is synthesized from the amino acid tyrosine. DA released from a presynaptic neuron can bind to two different types of DA receptors: D1-like and D2-like. D1-

like receptors (D1 and D5) are located on postsynaptic neurons, are G protein-coupled (G_s), and increase cAMP levels (Dearry et al., 1990; Sunahara et al., 1991; Tiberi et al., 1991). D1 receptors are primarily located in the striatum, NAc, cortex, olfactory tubercle, amygdala, and hippocampus (Dearry et al., 1990; Savasta, Dubois, & Scatton, 1986), whereas D5 receptors are primarily located in the olfactory tubercle and hippocampus, although these receptors are observed in other regions, such as striatum, NAc, and cortex (Ciliax et al., 2000; Sunahara et al., 1991).

Like D1-like receptors, D2-like receptors (D2, D3, and D4) are G protein-coupled (G_i); however, these receptors are located on both presynaptic and postsynaptic neurons and decrease cAMP when stimulated (Dal Toso et al., 1989). D2 receptors are primarily located in the striatum, NAc, olfactory tubercle, amygdala, hippocampus, hypothalamus, ventral tegmental area, and substantia nigra (Camus, Javoy-Aqid, Dubois, & Scatton, 1986; Charuchinda, Supavilai, Karobath, & Palacios, 1987). D3 receptors are located in the nucleus accumbens, hypothalamus, and olfactory tubercle (Bouthenet et al., 1991; Sokoloff, Giros, Martres, Bouthenet, Schwartz, 1990). D4 receptors are located in the cortex, amygdala, hypothalamus, hippocampus, and substantia nigra (O'Malley, Harmon, Tang, & Todd, 1992; Wedzony, Chocyk, Maćkowiak, Fijał, & Czyrak, 2000).

The role of DA in delay discounting is of particular interest because many drugs of abuse, as well as medications used to treat impulse-control disorders (e.g., ADHD; see Biederman & Faraone, 2005 for a review), increase

extracellular DA levels (Caillé & Parsons, 2003; Creese & Iverson, 1975; Jones, Gainetinov, Wightman, & Caron, 1998; Kuczenski & Segal, 1997; Moghaddam & Bunney, 1989; Volkow, Fowler, Wang, Ding, & Gatley, 2002). As expected, psychostimulant medications such as amphetamine and methylphenidate decrease impulsive choice (e.g., Broos et al., 2012a; Cardinal, Robbins, & Everitt, 2000; de Wit et al., 2002; Pitts & McKinney, 2005; van Gaalen, van Koten, Schoffelmeer, & Vanderschuren, 2006b; Winstanley et al., 2003).

Based on the findings observed with ADHD medications, drugs that stimulate DA neurotransmission should decrease impulsive choice, whereas drugs that inhibit DA release should increase impulsive choice. More specifically, drugs that stimulate postsynaptic D1-like receptors or inhibit presynaptic D2-like receptors should decrease impulsivity, whereas inhibiton of D1-like receptors and stimulation of D2-like autoreceptors should increase impulsivity. There is some support for this hypothesis, as systemic administration of the nonselective DA receptor antagonist flupenthixol (Cardinal et al., 2000; Floresco, Tse, & Ghods-Sharifi, 2008; Wade, de Wit, & Richards, 2000), as well as selective antagonism of D1 receptors promote impulsive choice (Broos et al., 2012a; Koffarnus, Newman, Grundt, Rice, & Woods, 2011; van Gaalen et al., 2006b; but see Wade et al., 2000). However, contrary to the hypothesis that DA stimulation decreases impulsive choice, systemic administration of D1-like receptor agonists do not alter delay discounting (Koffarnus et al., 2011).

Research examining the role of DA D2-like receptors has yielded mixed results. A couple of reports found increases in impulsive choice following

antagonism of D2-like receptors (Denk et al., 2005; Wade et al., 2000), whereas others did not observe changes in delay discounting (Evenden & Ryan, 1996; Koffanus et al., 2011; van Gaalen et al., 2006b). Considering that D2-like receptors are composed of three subtypes, perhaps D3 and D4 receptors have a more specific role in mediating impulsive decision making. Administration of the D3 agonist 7-OH-DPAT and the D4 partial agonist ABT-724 increase delay discounting (Koffarnus et al., 2011; van den Bergh, Bloemarts, Groenink, Olivier, & Oosting, 2006). However, it is important to note that administration of D3 receptor agonists do not necessarily affect sensitivity to delayed reinforcement, as choice for the large reinforcer decreases when its delivery is immediate (Koffarnus et al., 2011; Madden, Johnson, Brewer, Pinkston, & Fowler, 2010; van den Bergh et al., 2006).

DA activity specifically in prefrontal cortical regions has been associated with impulsive choice. Using microdialysis, an increase in intra-OFC 3,4-di-hydroxyl-phenylacetic acid (DOPAC) is observed in rats performing a delay discounting task (Winstanley et al., 2006b). HiI rats show reduced DA release in mPFC and NAc relative to LoI rats (Diergaarde et al., 2008). Depleting DA levels in mPFC also increases impulsive decision making (Loos et al., 2010; Pardey et al., 2013), and overexpression of the DA transporter (DAT) gene in NAc is associated with increased impulsive choice (Adriani et al., 2009). As with systemic drug administration, one unexpected finding is that antagonism of DA D2-like receptors within OFC and mPFC increases impulsive choice (Pardey, Kumar, Goodchild, & Cornish, 2013; Yates et al., under review; Zeeb et al., 2010)

and administration of a D1-like agonist into mPFC *increases* impulsive choice (Loos et al., 2010). Thus, while some inconsistencies exist, results overall suggest that decreased DA levels is associated with increased impulsive choice.

In addition to DA specifically, Winstanley et al. (2005) argue that 5-HT and DA interactions within NAc contribute to impulsive decision making. For example, the 5-HT_{1A} agonist 8-OH-DPAT decreases choice for a large, delayed reinforcer; however, this effect is not observed in rats with intra-NAc 6-hydroxydopamine lesions (Winstanley et al., 2005). The results obtained by Winstanley et al. (2005) are difficult to interpret because 8-OH-DPAT decreases choice for the large reinforcer when its delivery is not delayed. Therefore, DA and 5-HT interactions within NAc may be important for discriminating reinforcers of differing magnitudes, as opposed to discriminating delays to reinforcement.

Although 5-HT and DA have received considerable attention in delay discounting research, there is evidence that other neurotransmitter systems are important in mediating impulsive decision making, including norepinephrine (Robinson et al., 2008; van Gaalen et al., 2006b), acetylcholine (specifically muscarinic receptors; Mendez, Gilbert, Bizon, & Setlow, 2012), opioid peptides (Pattij, Schetters, Janssen, Wiskerke, & Schoffelmeer, 2009; Schippers et al., 2012), and glutamate (Glu; Cottone et al., 2013; Floresco et al., 2008; Sukhotina et al., 2008). Thus, multiple neurotransmitter systems working in an interactive fashion are involved in impulsive choice.

Glutamate (Glu). Glu is the major excitatory neurotransmitter in the mammalian brain and acts at both metabotropic (mGluR, G protein-coupled) and ionotropic receptors (iGluR, ion channel-coupled; see Ozawa, Kamiya, & Tsuzuki, 1998 for a review). mGluRs can be subdivided into three classes: group I mGluRs consists of mGluR1 and mGluR5, which are located on postsynaptic terminals and are stimulatory; in contrast, group II and group III mGluRs consist of mGluR2-8, which are mainly presynaptic and are inhibitory (Ozawa et al., 1998; Riedel, Platt, & Micheau, 2003). Like mGluRs, iGluRs can be subdivided into three groups: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA), kainate, and N-methyl-D-aspartate (NMDA), which are discussed in more detail below.

AMPA receptors are tetramers composed of four subunits (GluR1-4) and are found ubiquitously throughout the brain, with high levels observed in the CA1 and CA3 regions of the hippocampus, as well as cerebral cortex, basal ganglia, thalamus, hypothalamus, cerebellum, and spinal cord (Blackstone et al., 1992; Dure & Young, 1995; see Ozawa et al., 1998; Riedel et al., 2003 for reviews). Activation of AMPA receptors increases Na^+ and Ca^{2+} influx and K^+ efflux (see Forman, Chou, Strichartz, & Lo, 2008 for a discussion), and these receptors are responsible for the fast, immediate postsynaptic response to glutamate release (see Riedel et al., 2003). Like AMPA receptors, kainate receptors are tetramers composed of various subunits (GluR5-7 and KA1-2), with high levels located in the CA3 region of the hippocampus and in the cerebellum (see Ozawa et al.,

1998). Because dissociating AMPA and kainate receptors can be difficult, these receptors are often labeled as “non-NMDA” receptors (see Riedel et al., 2003).

NMDA receptors are heteromeric complexes with the NR1 as the primary constitutive subunit and NR2 (A-D) as functional subunits that affect channel kinetics and sensitivity (Mori & Mishina, 1995). Individual subunits are trafficked to synapses and can be substituted with one another. For example, NR2B-containing receptors can be replaced by NR2A-containing receptors (Barria & Malinow, 2002). Like non-NMDA receptors, NMDA receptors are found throughout the brain, with the highest concentrations observed in the CA1 region of the hippocampus, thalamus, and cerebral cortex (see Ozawa et al., 1998; Riedel et al., 2003). The NMDA receptor channel will open following voltage dependent removal of a Mg^{2+} ion (Novak Bregestovski, Ascher, Herbet, & Prochiantz, 1994), glycine binding to the NR1 subunit, and binding of Glu or NMDA receptor agonist to the NR2 subunit (see Lynch & Guttmann, 2001; Ozawa et al., 1998 for reviews). Once the channel opens, Na+ and Ca^{2+} are able to enter the neuron, and there is an increase in K^{+} efflux (see Riedel et al., 2003).

There is evidence that the glutamatergic system interacts with monoamine neurotransmitters. Stimulation of 5-HT_1 receptors inhibits Glu release (Choi, Cho, & Jang, 2013; Guo & Rainnie, 2010; Mauler, Fahrig, Horváth, & Jork, 2001). Furthermore, there is evidence that 5-HT_{1B} and 5-HT_{1D} receptors are heteroreceptors on glutamate neurons, which control the release of Glu (see Sari, 2013 for a discussion). There is speculation that 5-HT_{2A} regulates presynaptic release of Glu. For example, lysergic acid diethylamide (LSD)

increases Glu levels in PFC, an effect that is blocked by a selective 5-HT_{2A} antagonist (Muschamp, Regina, Hull, Winter, & Rabin, 2004). Glu is proposed to modulate the release of DA, as stimulation of NMDA receptors within PFC decreases DA release in the same region (Del Arco & Mora, 2001). Furthermore, antagonism of NMDA receptors within PFC increases DA levels within NAc (Del Arco, Segovia, & Mora, 2008).

Glutamatergic activity is important in learning (see Riedel et al., 2003 for a comprehensive review), and is hypothesized to be abnormal in several psychiatric conditions, including ADHD (MacMaster, Carrey, Sparkes, & Kusumakar, 2003). Also, evidence suggests a role for Glu in the initiation, maintenance, and relapse of abuse-related behaviors (see Kalivas, 2009 for a review).

Some evidence suggests a role for Glu in impulsive choice. Antagonism of mGluR1 receptors decreases sensitivity to delayed reinforcement (Sukhotina et al., 2008). Furthermore, administration of the mGluR2/3 receptor agonist LY379268 attenuates 5-HT_{2A}-induced impulsive choice, although administration of LY379268 alone does not alter discounting (Wischof et al., 2011). Blockade of NMDA receptors with the noncompetitive antagonists ketamine and/or memantine increase impulsive choice (Cottone et al., 2013; Floresco et al., 2008; but see Oberlin, Bristow, Heighton, & Grahame, 2010). However, interpreting the results obtained by Cottone et al. (2013) and Floresco et al. (2008) is difficult because ketamine and memantine inhibit 5-HT receptors (Kapur & Seeman,

2002; Rammes, Rupprecht, Ferrari, Zieglgänsberger, & Parsons, 2001). Overall, more work is needed to elucidate the role of Glu in impulsive choice.

Overview of the Current Experiments

Due to the complexity of impulsive decision making, there is a need to elucidate the underlying neuromechanisms of this facet of impulsivity. Understanding the precise role of Glu and DA in this behavior may shed light as to why increased impulsive choice is a predictor and consequence of substance use disorders. Although NAcc is consistently shown to mediate impulsivity, it is unclear which neurotransmitters within this region are involved in discounting. Thus, the overall goal of the current experiments was to elucidate the role of NAcc glutamatergic and dopaminergic systems in mediating impulsive choice.

Studies using systemic drug administration have examined the role of DA receptors in discounting performance. Although there are some discrepancies, findings generally support the hypothesis that increasing DA levels decreases impulsive decision making. However, the role of Glu in delay discounting is not as clear. Therefore, Experiment 1 was conducted to further clarify the role of ionotropic Glu receptors in impulsive decision making. The effects of the noncompetitive NMDA channel blocker MK-801 and the AMPA receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione disodium salt hydrate (CNQX) on delay discounting performance were examined. It was hypothesized that blocking NMDA and AMPA receptors would *increase* impulsive choice.

Experiment 2 was conducted to determine if NMDA receptor and dopamine transporter expression differed in HiI and LoI animals. DAT was selected because drugs used to treat impulse control disorders exert their therapeutic effects by blocking DAT (see Biederman & Faraone, 2005 for a review). The hypothesis was that high impulsive animals would have *decreased* NMDA receptor, but *increased* DAT, expression within NAcc relative to low impulsive animals.

The goal of Experiment 3 was to determine the role of NAcc NMDA and DA receptors in mediating impulsive choice. Furthermore, the goal was to determine if NR2B containing NMDA receptors are important for controlling impulsive choice. One group of rats received intra-NAcc bilateral infusions of the Glu-selective ligands MK-801, AP-5 (NMDA competitive antagonist), ifenprodil (NR2B antagonist), and CNQX. Another group of rats received the DA D1-like ligands SKF 38393 (agonist) and SCH 23390 (antagonist) and the DA D2-like ligands quinpirole (agonist) and eticlopride (antagonist). There were two major hypotheses. First, antagonism of NMDA receptors, specifically NR2B containing receptors, would *decrease* impulsive choice. Second, antagonism of D1-like and D2-like receptors would *increase* impulsive choice.

Chapter 2: Experiment 1

Introduction

Although evidence shows that 5-HT and DA receptors are involved in impulsive choice (e.g., Cardinal et al., 2000; Floresco et al., 2008; Koffarnus et al., 2011; Liu et al., 2004; van Gaalen et al., 2006b; Winstanley et al., 2005), the specific role of iGluRs in this task is unknown. Some evidence suggests that blockade of NMDA receptors with the noncompetitive antagonists ketamine and memantine increase impulsive choice (Cottone et al., 2013; Floresco et al., 2008). However, ketamine and memantine interact with 5-HT receptors (Kapur & Seeman, 2002; Rammes et al., 2001), thus complicating the results of these studies. This study was performed to further clarify the role of NMDA receptors in impulsive choice by testing the effects of the noncompetitive NMDA receptor antagonist MK-801 in delay discounting. To determine the potential role of AMPA receptors in delay discounting, a subset of rats were treated with the AMPA receptor antagonist CNQX.

Materials and Methods

Animals

Twelve male Sprague Dawley rats were obtained from Harlan Industries (Indianapolis, IN). They were acclimated to a colony room held at a constant temperature and handled for 5 days upon arrival. Rats had no prior operant training before the current experiment; however some were treated with amphetamine (1.0 mg/kg; 4 injections) or saline (4 or 8 injections) during

adolescence in a previous experiment. Amphetamine treatment during adolescence did not significantly alter discounting of delayed or probabilistic reinforcement in the current study (data not shown). Rats were individually housed during the current experiment. Light and dark phases were on a 12:12 h cycle, and all experiments occurred in the light phase. Rats were food restricted (approximately 80% of free feed body weight) during behavioral studies. All procedures were in accordance with the "Guide for the Care and Use of Laboratory Animals" (National Research Council, 2011) and were approved by the Institutional Animal Care and Use Committee at the University of Kentucky.

Drugs

(+)-MK-801 hydrogen maleate and 6-cyano-7-nitroquinoxaline-2,3-dione disodium salt hydrate (Sigma, St. Louis, MO) were prepared in sterile 0.9% NaCl (saline) and subcutaneously injected in a volume of 1 ml/kg. The doses were calculated based on salt weight.

Apparatus

Operant conditioning chambers (28 × 21 × 21 cm; ENV-008; MED Associates, St. Albans, VT) located inside sound-attenuating chambers (ENV-018M; MED Associates) were used. The front and back walls of the experimental chambers were made of aluminum, while the side walls were made of Plexiglas. There was a recessed food tray (5 x 4.2 cm) located 2 cm above the floor in the bottom-center of the front wall. An infrared photobeam was used to record headentries into the food tray. A 28-V white cue light was located 6 cm

above each response lever. A white houselight was mounted in the center of the back wall of the chamber. All responses and scheduled consequences were recorded and controlled by a computer interface. A computer controlled the experimental session using Med-IV software.

Procedure

Rats were given 2 days of magazine training, in which sucrose-based 45 mg pellets (F0021 dustless precision pellet, Bio-Serve, Frenchtown, NJ) were noncontingently delivered into the food tray. These sessions were used to habituate rats to the operant chamber. Following magazine training, rats were given lever press training. Each session began with illumination of the houselight. A head entry into the food hopper resulted in presentation of one lever. Levers were presented semi-randomly, with no more than two consecutive presentations of the same lever. A response on either lever resulted in delivery of one sucrose pellet. Pellets were also delivered noncontingently on a random time 100-sec schedule of reinforcement. Following a response on either lever, the houselight was extinguished, and the lever was retracted for 5 sec. After 5 sec, the houselight was illuminated. Each session lasted 30 min.

After 3 sessions, rats received reward magnitude discrimination training, which consisted of 40 trials. Each trial lasted 40 sec and began with illumination of the houselight. A headentry into the food hopper extended one of the levers (semi-randomly presented, with no more than two consecutive presentations of the same lever). A response on one lever resulted in immediate delivery of one

pellet, whereas a response on the other lever resulted in immediate delivery of four pellets (the lever associated with the large reward magnitude was counterbalanced across rats). Following a response, the houselight was extinguished, and the lever was retracted for the remainder of the trial. If a response was not made within 10 sec, the trial was scored as an omission, and the houselight was extinguished for the remainder of the trial. After 7 days of reward magnitude discrimination training, rats were trained in a delay discounting task.

Delay discounting sessions consisted of 5 blocks of 9 trials, and each trial lasted 60 sec. The first 4 trials in a block were forced-choice trials, in which only one lever was semi-randomly presented (no more than 2 consecutive presentations of the same lever). The last 5 trials were free-choice trials, in which both levers were extended. As in reward magnitude discrimination training, a response on one lever always resulted in immediate delivery of one food pellet. A response on the other lever resulted in delivery of 4 pellets; however, the delay to the delivery of the large magnitude reward increased across blocks of trials (0, 5, 10, 20, 50 sec). Following a response on either lever, the houselight was extinguished, and the lever was retracted for the remainder of the trial. If a response was not made within 10 sec, the trial was scored as an omission, and the houselight was extinguished for the remainder of the trial.

After training, rats received various doses of the NMDA receptor antagonist MK-801 (0, 0.01, 0.03, 0.1, or 0.3 mg/kg, s.c.) 15 min prior to the

session. The doses and pretreatment time were chosen based on previous work (Almasi-Nasrabadi et al., 2012; Fredriksson & Archer, 2002; Wooters, Dwoskin, & Bardo, 2011). A subset of rats (n = 6) received additional training in the delay discounting task before receiving various doses of the AMPA receptor antagonist CNQX (0, 1, 3, or 5.6 mg/kg, i.p.) 20 min prior to the session. The doses and pretreatment time were chosen based on previous work (Bäckström & Hyytiä, 2004; Wooters et al., 2011). In each experiment, pretreatments occurred once every 4 days, and dose order was randomized.

Statistical Analyses

To determine if MK-801 or CNQX altered delay discounting, two analyses were used. First, the hyperbolic discounting function was used and was defined with the equation $V = A/(1+kX)$, where V is the subjective value of the reinforcer, A is reinforcer amount, k is the rate of discounting, and X represents the delay to reinforcer delivery (Mazur, 1987). Second, area under the curve (AUC) was calculated as previously described (Myerson et al., 2001). The delay and subjective value for each data point were first normalized. Delay was expressed as a proportion of the maximum delay, and the subjective value was expressed as a proportion of the nominal amount. These normalized values were used as x coordinates and y coordinates, respectively, to construct a graph of the discounting data. Vertical lines were drawn from each data point to the x axis, subdividing the graph into a series of trapezoids. The area of each trapezoid is equal to $(x_2 - x_1)[(y_1 + y_2)/2]$, where x_1 and x_2 are successive delays, and y_1 and y_2 are the subjective values associated with these delays. The area under the

discounting function is equal to the sum of the areas of these trapezoids. AUC values range from 0 to 1, with values closer to 0 indicating steeper discounting and values closer to 1 representing shallower discounting.

K parameter estimates (log transformed) and AUCs were analyzed with repeated measures analyses of variance (ANOVA), with treatment as a within-subjects factor. Main effects were probed with Bonferroni post hoc tests. Cohen's *f* was calculated as a measure of effect size, with 0.10, 0.25, and 0.40 defined as small, medium, and large, respectively (Cohen, 1988). Because omissions and *A* parameter estimates were not normally distributed, these data were analyzed with Friedman tests. Main effects were probed with Wilcoxon signed-ranked post hoc tests. Startisitical significance was defined as $p < .05$ in all cases, except for the use of Wilcoxon signed-ranked post hoc test, in which a Bonferroni adjustment was used to correct for multiple comparisons.

Results

Figure 2.1 shows the proportion of choices for the delayed reinforcer following all doses of MK-801 (Figure 2.1A) and CNQX (Figure 2.1B). The proportion of choices for the large delayed reinforcer decreased as function of the delay to receiving reinforcement, although the highest doses of MK-801 (0.1 and 0.3 mg/kg) flattened the discounting function. The flattening of the discounting function following MK-801 (0.1 and 0.3 mg/kg) can be attributed to a loss in schedule control, as these doses significantly increased omissions ($\chi^2(2) = 41.02$, $p < .05$; Figure 2.2A). The highest dose of MK-801 (0.3 mg/kg) disrupted

behavior across all blocks of trials, whereas the 0.1 mg/kg dose suppressed behavior in the first three blocks of delay discounting (data not shown). Because the higher doses of MK-801 produced a general suppression in behavior, hyperbolic discounting functions could not be generated for all animals; thus, these doses were excluded from subsequent analyses of parameters *A* and *k*, as well as AUC. CNQX did not significantly alter omissions (Figure 2.2B), so each dose (1, 3, 5.6 mg/kg) was included in all subsequent analyses.

Parameters *k* and *A* were derived and plotted in Figure 2.3 and Figure 2.4, respectively, for each drug dose, except for the two highest doses of MK-801 (0.1 and 0.3 mg/kg). MK-801 (0.03 mg/kg) decreased sensitivity to delayed reinforcement ($F(2, 22) = 5.04$, $p < .05$, Cohen's $f = .67$; Figure 2.3A). The overall nonparametric analysis indicated that MK-801 also increased sensitivity to reinforcer magnitude in the delay discounting task ($\chi^2(2) = 7.64$, $p < .05$); however, post hoc tests revealed no significant differences between doses (p's > .025, Bonferroni correction; Figure 2.4A). CNQX did not alter sensitivity to delayed reinforcement (Figure 2.3B) or reinforcer magnitude (Figure 2.4B).

Figure 2.5 shows AUCs for each drug dose, except for the highest dose of MK-801 (0.3 mg/kg; this dose was excluded because AUCs were virtually 0 for all animals). Repeated measures ANOVA revealed that MK-801 (0.03 mg/kg) significantly increased AUCs ($F(2, 22) = 6.35$, $p < .01$, Cohen's $f = .77$; Figure 2.5A), whereas CNQX did not significantly alter AUCs (Figure 2.5B).

Discussion

There were two important findings from the current experiment. First, NMDA receptor blockade with MK-801 dose-dependently decreased sensitivity to delayed reinforcement. The decrease in sensitivity occurred at a dose of MK-801 (0.03 mg/kg) that did not alter omissions, suggesting a specific effect on choice behavior. Second, AMPA receptor blockade did not alter sensitivity to delayed reinforcement. Together, these results demonstrate a differential involvement of NMDA and AMPA receptors in delay discounting, with NMDA receptors playing a more critical role.

The current results show that the non-competitive NMDA receptor antagonist MK-801 decreases sensitivity to delayed reinforcement (*k* parameter). This finding contrasts with previous studies showing that the non-competitive antagonists ketamine and memantine increase delay discounting (Cottone et al. 2013; Floresco et al. 2008). However, in addition to the different NMDA antagonists used, a number of methodological differences exist which prevent direct comparisons across studies. For example, in contrast to the current study, Cottone et al. (2013) used an adjusting delay procedure, whereas the current study used a progressive discounting procedure derived from Evenden and Ryan (1996). Interpreting results from the adjusting delay procedure used by Cottone et al. (2013) is difficult because the dependent variable confounds sensitivity to delayed reinforcement and reinforcer magnitude, which are proposed to independently influence discounting of a reinforcer (Ho, Mobini, Chiang, Bradshaw, & Szabadi, 1999). Additionally, there is evidence to suggest that

animals trained in an adjusting delay procedure may not be sensitive to the adjusting delay to reinforcement (Cardinal et al., 2002). Although Floresco et al. (2008) used a similar discounting procedure as the current study, a maximum delay of 6.5 sec was imposed, which is considerably shorter than the maximum delay used in the current study (50 sec). Importantly, ketamine administration produced a parallel negative shift in the discounting curve at each delay, suggesting that sensitivity to reinforcer magnitude, but not the rate of discounting, was altered. Future studies employing discounting functions may be better suited to determine the effect of various drug treatments on sensitivity to reinforcer amount and/or sensitivity to delayed reinforcement within discounting tasks.

Beyond these methodological differences, an important pharmacological consideration for comparing results across studies is that MK-801, ketamine, and memantine show differential selectivity for non-NMDA receptors. For example, in contrast to MK-801, ketamine acts at sigma receptors (Robson, Elliott, Seminerio, & Matsumoto, 2012) and opioid receptors (Gupta, Devi, & Gomes, 2011). Similarly, in contrast to MK-801, memantine reduces the physical signs of opiate withdrawal (Maldonado, Cauli, Rodriguez-Arias, Aguilar, & Minarro, 2003). Ketamine also acts as an antagonist at 5-HT_2 receptors (Kapur & Seeman, 2002), and memantine blocks 5-HT_3 receptors (Rammes et al., 2001), although antagonism of 5-HT receptors typically does not increase the rate of discounting (Hadamitzky et al., 2009; Liu et al., 2004; Talpos et al., 2006). MK-801 also has non-NMDA activity, as it inhibits nicotinic acetylcholine receptors (Amador &

Dani, 1991; Briggs & McKenna, 1996); however, blockade of nicotinic receptors does not alter discounting of delayed reinforcement (Mendez et al., 2012).

Another important consideration is that memantine and MK-801 block NMDA receptor channels in different ways and show differential affinity for synaptic and extrasynaptic NMDA receptors. Specificially, memantine reduces NMDA receptor-mediated excitatory postsynaptic potentials in a voltage-dependent manner, whereas the effects of MK-801 on postsynaptic potentials appear to be less voltage-dependent (Frankiewicz, Potier, Bashir, Collingridge, & Parsons, 1996). Furthermore, memantine shows fast blocking and unblocking kinetics, whereas MK-801 shows slow blocking and unblocking kinetics (see Danysz, Parsons, Kornhuber, Schmidt, & Quack, 1997 for a review). Finally, memantine preferentially blocks extrasynaptic NMDA receptors, whereas MK-801 blocks extrasynaptic and synaptic NMDA receptors (Xia et al., 2010). Thus, the different pharmacological profiles of memantine and MK-801 may account for the differential effects observed in delay discounting.

As for DA activity, previous work has shown that acute administration of MK-801 (0.03 and 0.1 mg/kg) increases DA levels in PFC (Tsukada et al., 2005). Interestingly, drugs that increase DA levels typically decrease sensitivity to delayed reinforcement (Broos et al., 2012a; Cardinal et al., 2000; de Wit et al., 2002; Pitts & McKinney, 2005; van Gaalen et al., 2006b; Winstanley et al., 2003). Thus, the decrease in discounting observed following MK-801 administration might be explained from its interaction with the prefrontal DA system.

Interpreting AUCs can be problematic because this measure does not take into consideration sensitivity to reinforcer magnitude. For example, AUCs for MK-801 (0.1 mg/kg) and vehicle did not differ significantly, which might suggest that MK-801 did not alter task performance at this dose. However, 0.1 mg/kg MK-801 flattened the discounting curve, demonstrating a general disruption in task performance at the 0 sec delay. Overall, these results show that AUCs do not always describe discounting performance accurately when sensitivity to reinforcer magnitude is altered.

In conclusion, results from the current study show that NMDA and AMPA receptors differentially mediate discounting of delayed reinforcement. Blockade of NMDA receptors with the non-competitive antagonist MK-801 decreased sensitivity to delayed reinforcement, whereas antagonism of AMPA receptors with CNQX did not alter delay discounting. Understanding the precise role of glutamate systems might be beneficial in developing treatments for disorders characterized by increased impulsivity, such as drug abuse.

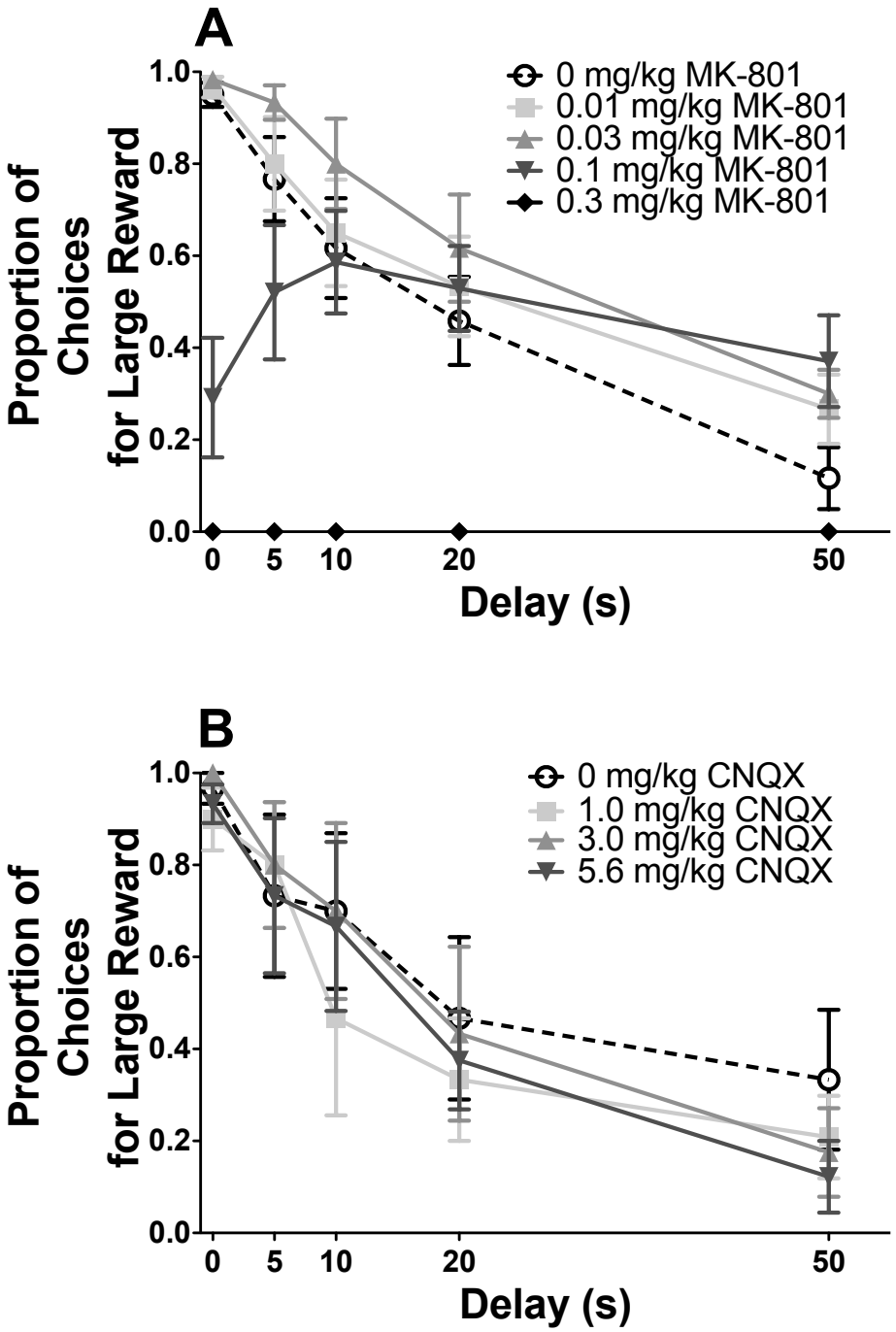


Figure 2.1. Mean (± SEM) proportion of choices for the large magnitude reinforcer as a function of the delay to receiving reinforcement following pretreatments with MK-801 (Panel A) and CNQX (Panel B).

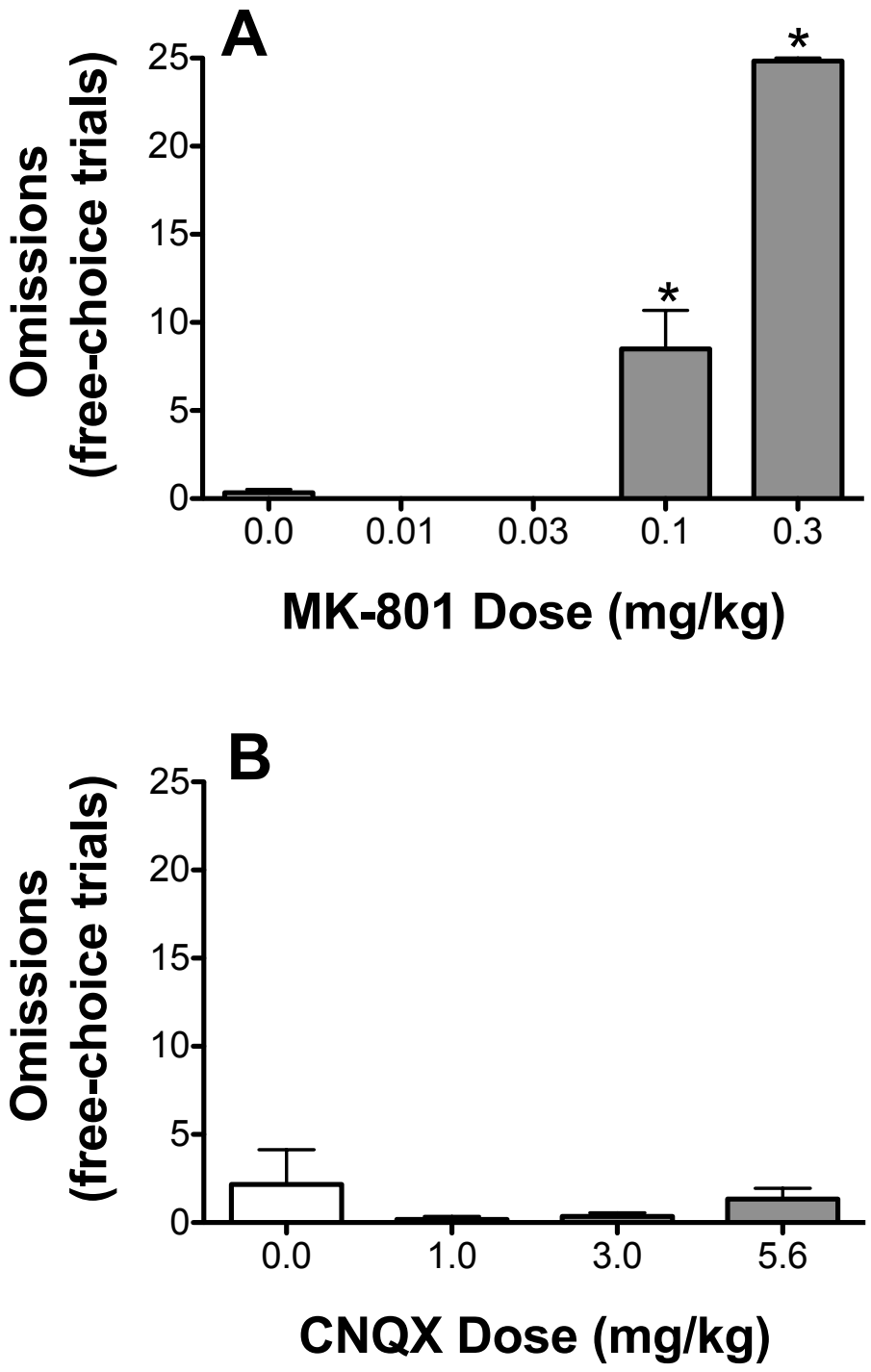


Figure 2.2. Mean (± SEM) omissions during free-choice trials following pretreatments with MK-801 (A) and CNQX (B). *p < .05, relative to vehicle.

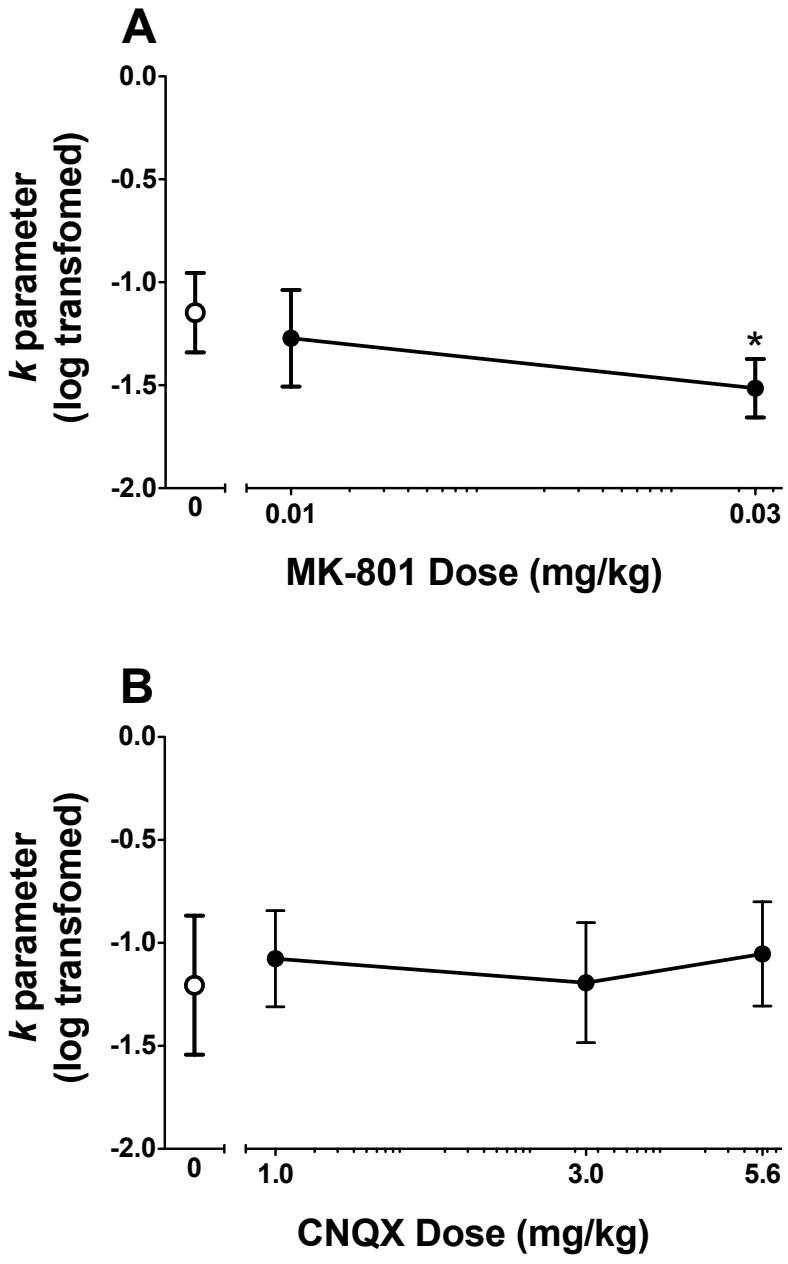


Figure 2.3. Mean (± SEM) parameter estimate *k* values (log transformed) following pretreatments with MK-801 (A) and CNQX (B). *$p < .05$, relative to vehicle.

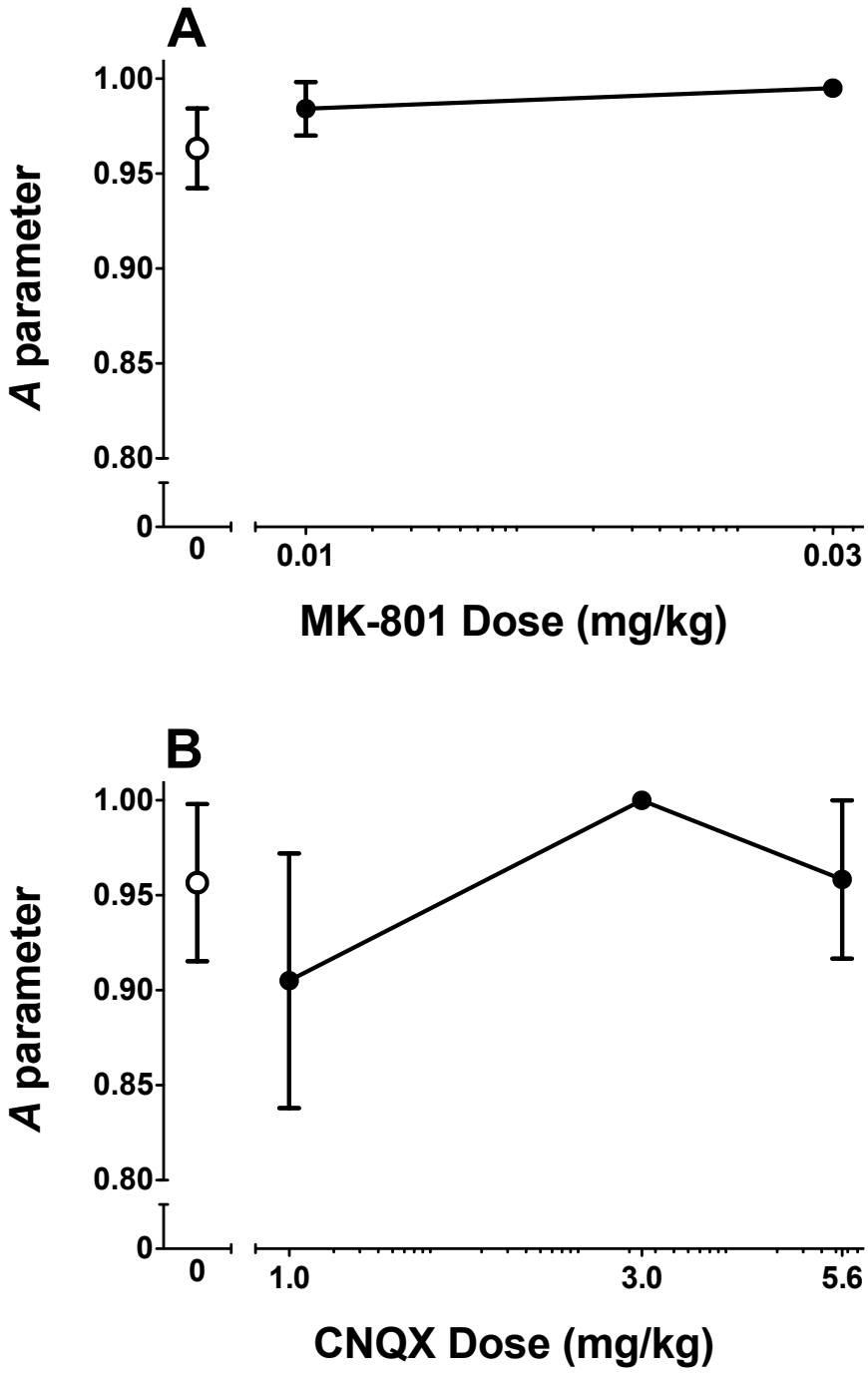


Figure 2.4. Mean (± SEM) parameter estimate *A* values following pretreatments with MK-801 (A) and CNQX (B).

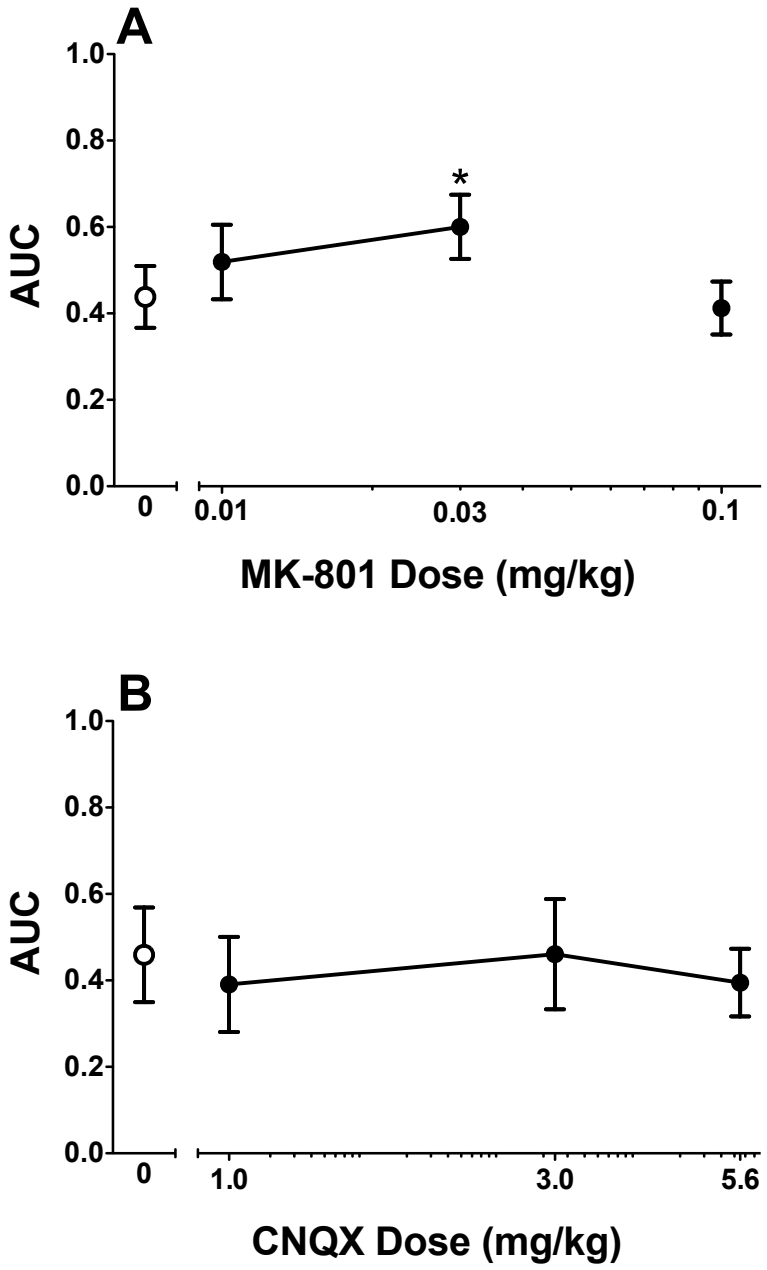


Figure 2.5. Mean (± SEM) area under the curve (AUC) values following pretreatments with MK-801 (A) and CNQX (B). *p < .05, relative to vehicle. Note that MK-801 (0.1 mg/kg) is not connected to the line in the graph because this dose was not used in analyses due to the large increase in omissions.

Chapter 3: Experiment 2

Introduction

The results from Experiment 1 showed that blockade of NMDA receptors with MK-801 decreased impulsive choice. However, it is unknown if NMDA receptor densities are altered in animals that show differential sensitivity to delayed reinforcement. Therefore, the goal of the present experiment was to use *in vitro* receptor autoradiography to quantify NMDA receptor density in the NAcc. This region was chosen because it has been consistently shown to be involved in impulsive choice (Bezzina et al., 2007; Cardinal et al., 2001; da Costa Araújo et al., 2009; Valencia-Torres et al., 2012), and NAcc NMDA receptors play a critical role in addiction (see Kalivas, 2009 for a review). Because damage to the NAcSh does not alter delay discounting (Pothuzien et al., 2005), this region was examined as a negative control.

A secondary goal of the present experiment was to determine if DAT is altered in HiI and LoI impulsive rats. DAT was also examined because psychostimulant medications exert their therapeutic effects by blocking DAT (see Biederman & Faraone, 2005 for a review). Furthermore, there is evidence that overexpression of DAT within NAc leads to increased impulsive decision making in a delay discounting task (Adriani et al., 2009). The hypothesis for this experiment was that HiI animals would have *decreased* NMDA receptor, but *increased* DAT, expression within NAcc relative to LoI animals.

Materials and Methods

Animals

A total of 24 experimentally naïve (i.e., have not received any pharmacological treatments) male, Sprague Dawley rats were obtained from Harlan Industries (Indianapolis, IN). Rats weighed approximately 250-275 g upon arrival to the laboratory and were housed individually. Rats were acclimated to a colony room held at a constant temperature and were handled for 5 days upon arrival. Light and dark phases were on a 12:12 h cycle, and all experiments occurred during the light phase. Rats were food restricted (approximately 80% of free feed body weight) 3 days before the beginning of behavioral training, and rats remained on food restriction during the remainder of the study, unless otherwise noted.

Apparatus

The apparatus was the same as described in Experiment 1.

Procedure

Pre-training was similar to the training described in Experiment 1, with one exception. During the initial lever press training, sessions ended after 30 min or following 40 trials (20 trials for each lever), whichever occurred first. The magnitude discrimination and delay discounting sessions were conducted as described in Experiment 1.

Following 28 sessions of delay discounting, rats were killed, and brains were removed and flash-frozen in chromasolv (Sigma Aldrich; St. Louis, MO) on dry ice and stored at -80°C until sectioning was completed. Coronal brain sections (16 μm) were taken and used for *in vitro* receptor autoradiography.

For NMDA receptor autoradiography, sections were first preincubated for 30 min at room temperature (RT) in buffer containing 5 mM Tris HCL and 2.5 mM $CaCl_2$ (pH 7.4), then incubated for 90 min at room RT in fresh buffer containing 10 nM [^{3}H]MK-801, 5 μM glutamic acid, 100 μM glycine, and 5 μM spermidine. After incubation, slides were washed three times in ice cold 5 mM Tris-HCl buffer for 20 min, followed by one wash in 0.5 mM Tris-HCl buffer and one wash in double distilled water. Slides were air dried and stored overnight before filming. Slides containing the brain sections were placed into a light-proof cassette and exposed to Kodak film. Films were developed following 6 weeks of exposure.

For DAT autoradiography, sections were preincubated for 15 min at RT in buffer containing 50 mM Tris-HCL, 120 mM NaCl, and 5 mM KCl (pH 7.4), then incubated for 120 min in fresh buffer containing 50 pM [^{125}I]-RTI-121, 120 mM NaCl, 5 mM KCl, .001% ascorbic acid, .025% BSA, and 1 μM fluoxetine. After incubation, slides were washed four times in ice cold 50 mM Tris-HCl buffer for 30 min, followed by one wash in 5 mM Tris-HCl buffer and one wash in double distilled water. Slides were air dried and stored overnight before filming. Slides containing the brain sections were placed into a light-proof cassette and exposed to Kodak film. Films were developed following 3 days of exposure.

For NMDA receptor and DAT autoradiography, [^{3}H]-MK-801 and [^{125}I]-RTI-121 binding data were analyzed with Image J (http://imagej.nih.gov/ij). NAcc and NAcSh in each hemisphere were outlined manually, and mean binding density was calculated for each individual animal (4-6 coronal sections were analyzed for each animal). Binding densities in the left and right hemisphere were averaged to form one value for each animal.

Statistical Analyses

For the autoradiography experiment, only the top third of impulsive rats (HiI; n =8) and bottom third of impulsive rats (LoI; n = 7; one brain for a LoI rat was destroyed during extraction) were used in data analysis. To ensure that discounting in rats selected as HiI and LoI was different, parameter estimates *k* (log transformed; note: there were a couple of instances in which an animal chose the large magnitude reinforcer every single free-choice trial; therefore, their log-transformed *k* value had to be arbitrarily set at -5.0) and *A* were analyzed with a mixed-factor ANOVA, with session block (7 levels; 7 4-day blocks) as a within-subjects factor and impulsivity (HiI vs. LoI) as a between-subjects factor (note: separate ANOVAs were conducted for *k* and *A*).

For NMDA receptor and DAT binding, mean [^{3}H]-MK-801 and [^{125}I]-RTI-121 binding densities in the NAcc and NAcSh were compared between HiI and LoI rats with independent-samples *t* tests. Statistical significance was set at $p < .05$ in all cases.

Results

Figure 3.1 shows discounting performance in HiI and LoI rats at different time points during training. During training, the proportion of choices for the large, delayed reinforcer decreased as a function of delay for both HiI and LoI rats, although HiI rats responded less for the large magnitude reinforcer relative to LoI rats as the delay to its delivery increased. Figure 3.2 shows parameter estimates of *k* (log transformed) and *A* in HiI and LoI rats across 4-day blocks. For *k* (log transformed) parameter estimates, results from the mixed-factor ANOVA indicated main effects of session block ($F(6, 84) = 6.96$, $p < .05$, $\eta_p^2 = .33$) and impulsivity ($F(1, 14) = 12.79$, $p < .05$, $\eta_p^2 = .48$). The session block × impulsivity interaction approached statistical significance ($F(6, 84) = 2.17$, $p = .054$, $\eta_p^2 = .13$). These results show that across training, both HiI and LoI rats became more sensitive to delay; however, HiI rats showed greater sensitivity to delay reinforcement relative to LoI across training (Figure 3.2A). For *A* parameter estimates, results from the mixed-factor ANOVAs revealed a main effect of impulsivity ($F(1, 14) = 4.80$, $p < .05$, $\eta_p^2 = .26$; Figure 3.2B). Overall, HiI rats were less sensitive to reinforcer magnitude relative to LoI rats. This difference was most pronounced during the first three session blocks. A separate Mann-Whitney *t* test was conducted to compare *A* parameter estimates in HiI and LoI rats during the final block of sessions. Results from the *t* test revealed no differences in sensitivity to reinforcer magnitude.

Figure 3.3 shows a schematic of the NAcc and NAcSh, and Figure 3.4 shows representative autoradiograms for [^{3}H]-MK-801 (Panel A) and [^{125}I]-RTI-

121 binding (Panel B). For NMDA receptor binding (Figure 3.5A), there were no differences between HiI and LoI rats in NMDA receptor binding within NAcc or NAcSh.

For DAT binding (Figure 3.5B), there were no differences between HiI and LoI rats in DAT binding within NAcc or NAcSh.

Discussion

In the current experiment, there were no statistically significant differences in NMDA receptor or DAT expression in HiI and LoI rats. Overall, these results suggest that differences in delay discounting do not result from baseline differences in NAc NMDA receptor or DAT expression.

There is a growing interest in the role of Glu, particularly the NMDA receptor, in impulse control disorders such as attention deficit hyperactivity disorder (ADHD; see Chang, Lane, & Tsai, in press for a recent review). A recent pilot study showed that the noncompetitive NMDA receptor antagonist memantine is efficacious in reducing the inattentive and hyperactivity subtypes of ADHD (Surman et al., 2013). Also, atomoxetine, a norepinephrine reuptake inhibitor, acts as an NMDA receptor antagonist at clinically relevant concentrations (Ludolph et al., 2010). Recent evidence suggests that drugs currently used to treat ADHD decrease NMDA receptor expression (Udvardi et al., 2013; Urban, Li, & Gao, 2013).

Given the growing interest in NMDA receptors in impulsivity, the current experiment sought to determine if NMDA receptor binding is altered in HiI and

LoI impulsive rats. The results showed that NMDA receptor density within NAcc and NAcSh did not differ significantly in HiI and LoI rats. Considering NMDA receptors are upregulated following MK-801 administation (McDonald, Silverstein, & Johnston, 1990), the hypothesis of the current experiment was that HiI rats would have decreased NMDA receptor expression in NAcc relative to LoI rats. The current results suggest that differential sensitivity to delayed reinforcement does not result from baseline differences in NMDA receptor expression in NAc.

Interpreting the current results is somewhat difficult for a couple of reasons. First, NMDA receptors are composed of different subunits: NR1 and NR2 (A-D; see Ozawa et al., 1998). Using the current protocol, [^{3}H]MK-801 binding does not show selectivity for NMDA receptor NR2 subunits. Examining NMDA subunit expression (e.g., using [^{3}H]ifenprodil to target NR2B containing receptors) in HiI and LoI rats may provide some insight for the individual differences observed in delay discounting performance. Second, MK-801 blocks synaptic and extrasynaptic NMDA receptors (Xia, Chen, Zhang, & Lipton, 2010). Synaptic NMDA receptors are functional receptors that are activated by Glu released during low-frequency synaptic events, whereas extrasynaptic receptors are not activated during low-frequency synaptic events are found at various locations on a neuron (see Hardingham & Bading, 2010 for a review). Future work will need to determine if HiI and LoI rats differ in the number of synaptic or extrasynaptic NMDA receptors.

Studying DAT binding in the NAc was of interest because DAT is believed to mediate impulsive behavior, as administration of DAT inhibitors are efficacious in treating impulse control disorders (see Biederman & Faraone, 2005) and decrease impulsive choice in humans (de Wit et al., 2002; Pietras, Cherek, Lane, Tcheremissine, & Steinberg, 2003; Shiels et al., 2009) and animals (Baarendse & Vanderschuren, 2012; Broos et al., 2012; Floresco et al., 2008; Pitts & McKinney, 2005; van Gaalen et al., 2006). Also, DAT binding is lower in individuals with ADHD (Krause, Dresel, Krause, Kung, & Tatsch, 2000). In the current experiment, there were no differences in DAT density within NAcc and NAcSh between HiI and LoI rats. These results were somewhat surprising because previous studies have shown that lentiviral-mediated overexpression of DAT in the NAcc increases impulsive choice (Adriani et al., 2009) and that LoI rats have greater electrically evoked DA release within NAcc and NAcSh (Diergaarde et al., 2008). Despite these discrepancies, the current findings are consistent with data showing no correlation between impulsive choice and DAT function (as assessed with kinetic analysis of [^{3}H]DA uptake) within OFC or mPFC (Marusich, Darna, Charnigo, Dwoskin, & Bardo, 2011). Directly comparing the current results with previous studies is difficult because the methodologies used to assess the relationship between DAT and impulsive decision differed across studies (e.g., in vitro receptor autoradiography vs. electrically evoked DA release).

One major caveat of *in vitro* autoradiography needs to be discussed. Autoradiography provides a measure of the number of receptors/transporters in a brain region but does not identify functional differences. Although the number of

NMDA receptors or DATs did not differ in the NAcc between HiI and LoI rats, there is a possibility that functional differences exist. For example, Diergaarde et al. (2008) found reduced DA release in mPFC and NAc of HiI rats relative to LoI rats. Using alternative approaches that measure receptor/transporter function are needed to determine the precise phenotypic differences in HiI and LoI animals. Despite this caveat, the current results show that differences in delay discounting are not necessarily the result of baseline differences in NAc NMDA receptor or DAT expression.

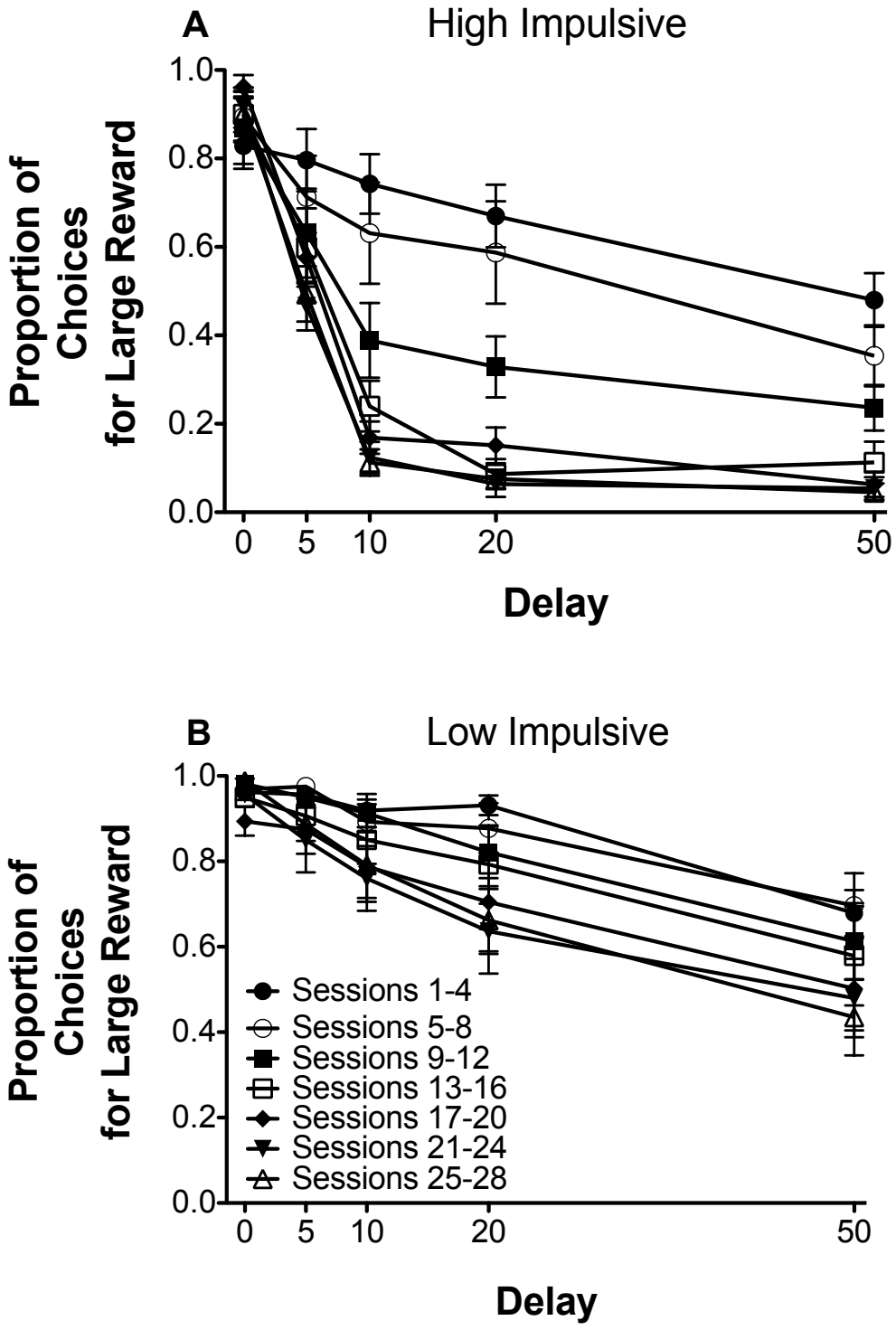


Figure 3.1. Delay discounting performance in HiI rats (Panel A) and LoI rats (Panel B) across session blocks (average of four sessions per block).

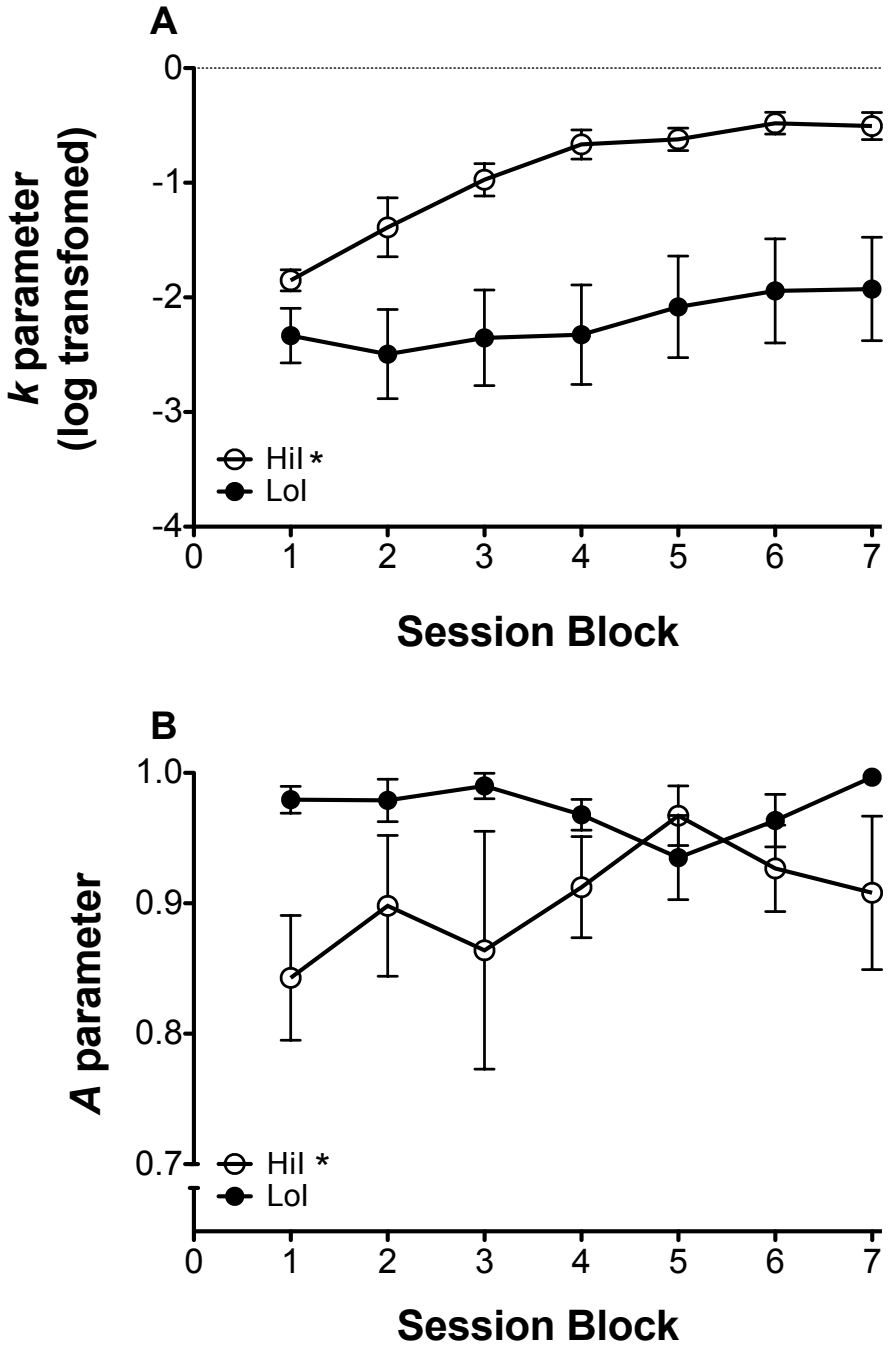


Figure 3.2. Mean (± SEM) *k* parameter estimates (log transformed; Panel A) and *A* parameter estimates (Panel B) in HiI rats and LoI rats across session blocks (average of four sessions per block). *$p < .05$, relative to LoI rats.

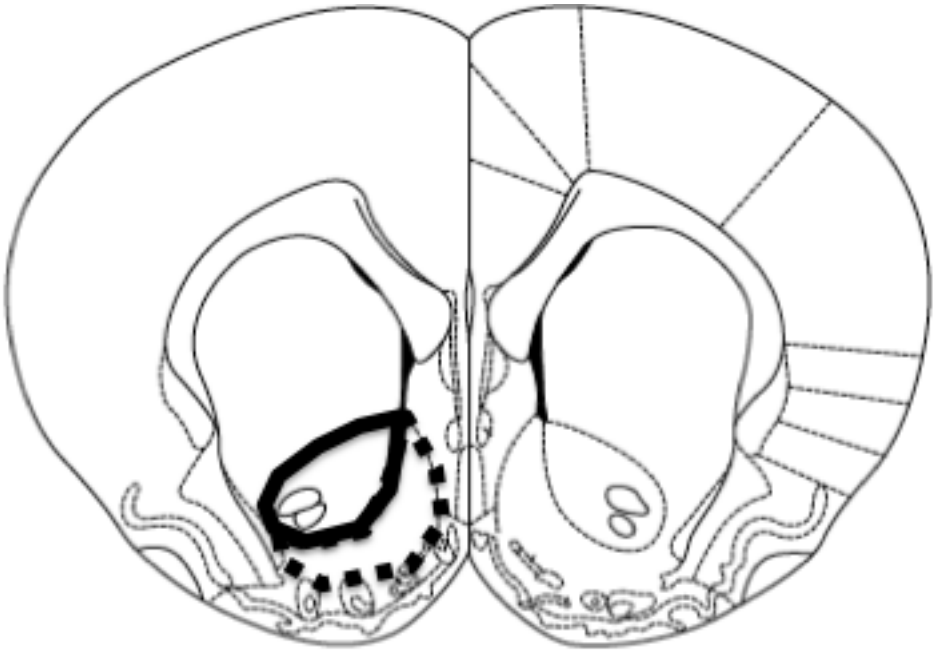
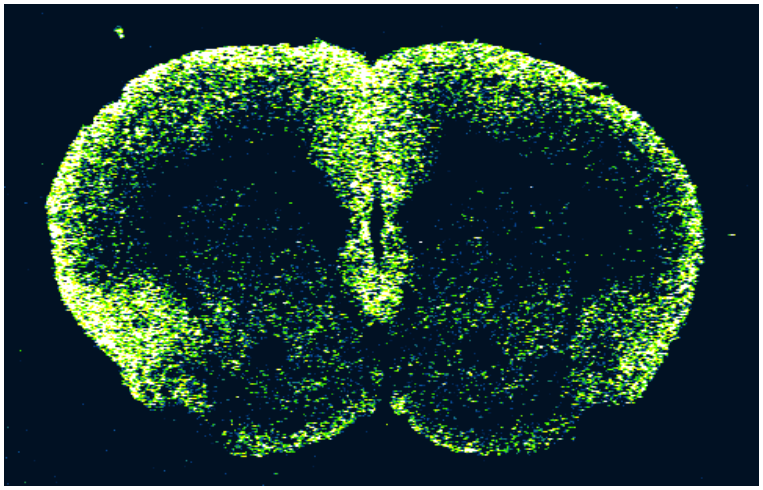


Figure 3.3. Schematic showing the location of NAcc (outlined in solid line) and NAcSh (outlined in dashed line).

A



B

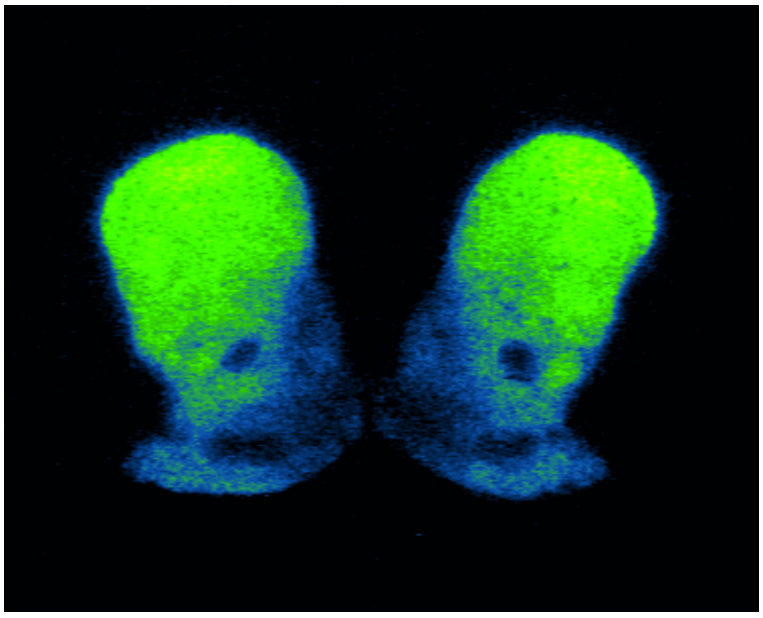


Figure 3.4. Representative autoradiograms of [^{3}H]-MK-801 radioligand NMDA receptor binding (Panel A) and [^{125}I]-RTI-121 radioligand DAT binding (Panel B).

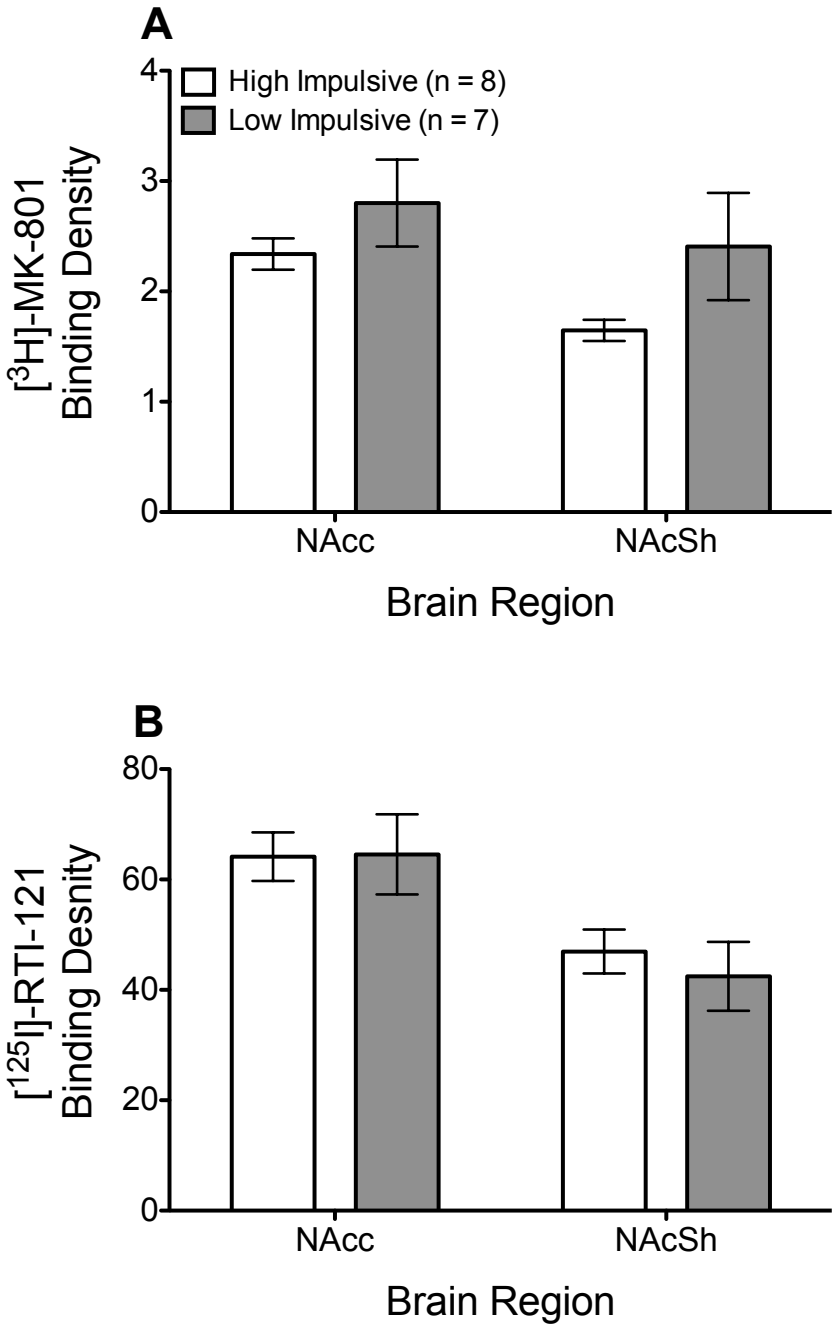


Figure 3.5. Binding densities of [^{3}H]-MK-801 to NMDA receptors (Panel A) and [^{125}I]-RTI-121 to DAT (Panel B) in HiI and LoI rats.

Chapter 4: Experiment 3

Introduction

Although MK-801 decreased impulsive choice in Experiment 1, interpreting the results can be difficult considered MK-801 blocks nicotinic acetylcholine receptors (Amador & Dani, 1991; Briggs & McKenna, 1996) and increases DA levels within the prefrontal cortex (Tsukada et al., 2005). To better evaluate the role of Glu NMDA receptors in impulsive decision making, a drug that shows higher selectivity for NMDA receptors can be administered. One such drug is AP-5, which is competitive antagonist at NMDA receptors (Crunelli, Forda, & Kelly, 1983).

Another issue is that using MK-801 as a pharmacotherapy for impulse control disorders is not ideal because MK-801 disrupts learning in animals (Harder, Aboobaker, Hodgetts, & Ridley, 1998; Li et al., 2011; Rapanelli, Frick, Bernardez-Vidal, & Zanutto, 2013; van der Staay, Rutten, Erb, & Blokland, 2011) and is often used to model symptoms of schizophrenia (see Lim, Taylor, & Malone, 2012 for a review). One potential alternative approach is to use an antagonist that targets a specific splice variant of the NMDA receptor, as eight variants of the NR1 subunit (1a-4a; 1b-4b) and four variants of the NR2 subunit (A-D) have been identified (Hollmann et al., 1993; Monyer et al., 1992; see Ozawa et al., 1998 for a review). One such drug is ifenprodil, which selectively antagonizes NR2B-containing NMDA receptors (Perin-Dureau, Rachline, Neyton, & Paoletti, 2002). Ifenprodil is neuroprotective in *in vivo* models of ischemia (Gotti et al., 1988), but lacks the psychomimetic-like effects observed with NMDA

receptor antagonists like MK-801 (Narita, Aoki, & Suzuki, 2000). Furthermore, ifenprodil attenuats the rewarding effects of opiates (Ma, Yu, Guo, & Cui, 2011; Ma et al., 2006; Suzuki, Kato, Tsuda, Suzuki, & Misawa, 1999), suggesting that NR2B subunits are important mediators of the drug addiction process.

Thus, the primary goal of Experiment 3 was to determine the effects of intra-NAcc infusions of MK-801, AP-5, and ifenprodil on delay discounting performance. Animals also received infusions of the AMPA receptor antagonist CNQX. CNQX was included as a negative control, as the results from Experiment 1 showed that CNQX does not alter impulsive decision making. The primary hypothesis of this study was that intra-NAcc infusions of NMDA receptor antagonists would decrease impulsive choice.

A secondary goal was to examine the effects of intra-NAcc infusions of selective DA receptor ligands on impulsive choice. Typically, increasing DA levels decreases impulsive choice (e.g., Broos et al., 2012a; Cardinal, Robbins, & Everitt, 2000; de Wit et al., 2002; Pitts & McKinney, 2005; van Gaalen, van Koten, Schoffelmeer, & Vanderschuren, 2006b; Winstanley et al., 2003). Thus, the hypothesis was that stimulating D1-like receptors with SKF-38393 or blocking D2-like autoreceptors with eticlopride would decrease impulsive choice.

Materials and Methods

Animals

A total of 24 male, individually-housed Sprague Dawley rats (Harlan Industries; Indianapolis, IN) were used in the experiments. Rats weighed

approximately 250-275 g upon arrival to the laboratory. Rats were acclimated to a colony room held at a constant temperature and were handled for 5 days upon arrival. Light and dark phases were on a 12:12 h cycle, and all experiments occurred during the light phase. Rats were food restricted (approximately 80% of free feed body weight) 3 days before the beginning of behavioral training, and rats remained on food restriction during the remainder of the study, unless otherwise noted.

Drugs

(+)-MK-801 hydrogen maleate, D(-)-2-amino-5-phosphonopentanoic acid, 6-cyano-7-nitroquinoxaline-2,3-dione disodium salt hydrate, (±)-SKF-38393 hydrochloride, (±)-SCH-23390 hydrochloride, (-)-quinpirole hydrochloride, and S-(-)-eticlopride hydrochloride were purchased from Sigma Aldrich (St. Louis, MO). Ifenprodil hemitartrate was purchased from Tocris Bioscience (Ellisville, MO). Each drug was prepared in sterile 0.9% NaCl (saline), and concentrations were calculated based on salt weight.

Apparatus

The apparatus was identical to the one used in the Experiment 1.

Procedure

The procedures were identical to those described in Experiment 2.

Surgery

After 32 sessions of delay discounting, rats were treated with the nonopioid analgesic carprofen one day prior to surgery. Rats were anesthetized with a mixture of ketamine, xylazine, and acepromazine (75, 7.5, and 0.75 mg/kg, i.p., respectively) and were secured into a stereotaxic frame. Cannulae were implanted bilaterally into NAcc (+1.6 AP, ± 1.5 ML, -5.5 DV) at the 10° angle off the midline; Paxinos & Watson, 1998). Following surgery, rats were treated with carprofen for two days.

Microinfusions

Rats recovered for 3-5 days and were food restricted before receiving 12 additional training sessions in the delay discounting task. This additional training was important to ensure that surgery did not alter discounting behavior. For intracranial infusions, rats were gently restrained by the experimenter, and a stainless-steel injection cannula (33 gauge; Small Parts, Inc, Miramar, FL) was inserted 2 mm below the tip of the guide cannulae. The cannulae were connected to 10 µl syringes (Hamilton, Reno, NV) via PE10 tubing (Small Parts, Inc, Miramar, FL). The Hamilton syringes were mounted on an infusion pump (KDS Scientific, Holliston, MA). Half of the rats (n = 12) received direct infusions of ionotropic glutamate receptor ligands MK-801 (noncompetitive NMDA channel blocker; 0.0, 0.3, and 1.0 µg/0.5 µl; Bakshi & Geyer, 1998; Zhang, Bast, & Feldon, 2000), AP-5 (competitive NMDA antagonist; 0.0, 0.3, and 1.0 µg/0.5 µl; Baldwin, Holahan, Sadeghian, & Kelley, 2000; Dar, 2002; Sombers, Beyene,

Carelli, & Wrightman, 2009), ifenprodil (NR2B subunit antagonist; 0.0, 0.3, and 1.0 µg/0.5 µl; Parkes & Balleine, 2013; Laurent & Westbook, 2008), and CNQX (AMPA antagonist; 0.0, 0.2 and 0.5 µg/0.5 µl; Hitchcott & Phillips, 1997; Mesches, Bianchin, & McGaugh, 1996). The other half of the rats (n = 12) received direct infusions of the dopamine receptor ligands SKF 38393 (D1-like agonist; 0.0, 0.03 and 0.1 µg/0.5 µl; Loos et al., 2010; Yates et al., under review), SCH 23390 (D1-like antagonist; 0.0, 0.3, and 1.0 µg/0.5 µl; Loos et al., 2010; Yates et al., under review; Zeeb et al., 2010), quinpirole (D2-like agonist; 0.0, 0.3, and 1.0 µg/0.5 µl; Yates et al., under review), eticlopride (D2-like antagonist; 0.0, 0.3, and 1.0 µg/0.5 µl; Yates et al., under review; Zeeb et al., 2010). Each drug was infused over 2 min at a rate of 0.25 µl/min. Injectors were left in place for 1 min following the infusion. Rats were placed into the operant chamber immediately following the infusion. Treatments were randomly administered, and rats were given 2 days of washout following each infusion; rats were tested in delay discounting during these washout days.

Following the last day of infusions, rats were anesthetized with ketamine, and brains were removed and flash-frozen in chromasolv (Sigma) on dry ice and stored at -80°C until sectioning was completed. Brain sections (40 µm) were sliced to determine the location of guide cannulae. Probe placements were evaluated according to the atlas of Paxinos and Watson (1998). Only data from rats with correct probe placements in NAcc were used in statistical analyses.

Statistical Analyses

To determine if implantation of guide cannulae into NAcc altered sensitivity to delayed reinforcement or sensitivity to reinforcer magnitude, discounting performance before surgery (average of final four sessions) was compared to discounting performance after surgery (average of final four sessions before first microinfusion). Parameter estimates of *k* (log transformed) and *A* were analyzed with a mixed-factor ANOVA, with surgery (Pre vs. Post) as a within-subjects factor and experiment (Glu vs. DA) as a between-subjects factor. For each individual experiment, omissions and parameter estimates from the hyperbolic discounting function were analyzed as described in Experiment 1.

Results

Figure 4.1 shows the proportion of choices for the large, delayed reinforcer as a function of delay averaged across the final four sessions before surgery and averaged across the final four sessions after surgery, prior to the first microinfusion of either Glu-selective ligands or DA-selective ligands. Analysis of *k* and *A* parameter estimates revealed that surgery did not alter sensitivity to delayed reinforcement or sensitivity to reinforcer magnitude (Figure 4.2). Furthermore, baseline levels of discounting were similar for animals selected to subsequently receive Glu-selective ligands and DA-selective ligands (Figure 4.2).

Figure 4.3 shows a representative image of bilateral guide cannulae implantation into NAcc. Four rats in Experiment 1A (Figure 4.4) and six rats in

Experiment 1B (Figure 4.5) had probe placements outside of NAcc, and were thus excluded from further analyses

Figures 4.6 and 4.7 show the proportion of choices for the delayed reinforcer following all concentrations of MK-801, AP-5, ifenprodil, and CNQX. The proportion of choices for the large delayed reinforcer decreased as function of the delay to receiving reinforcement.

Figures 4.8 and 4.9 show omissions following all concentrations of MK-801, AP-5, ifenprodil, and CNQX. AP-5 increased overall omissions ($\chi^2(2) = 8.00$, $p < .05$), although Wilcoxon post hoc tests did not reveal significant differences between vehicle and either dose (each $p > .025$; Bonferroni correction; Figure 4.8B). MK-801 (Figure 4.8A), ifenprodil (Figure 4.9A), and CNQX (Figure 4.9B) did not alter omissions.

Figures 4.10 and 4.11 show *k* parameter estimates following all concentrations of MK-801, AP-5, ifenprodil, and CNQX. None of the Glu-selective ligands produced a statistically significant change in *k* parameter estimates.

Figures 4.12 and 4.13 show *A* parameter estimates following all concentrations of MK-801, AP-5, ifenprodil, and CNQX. None of the Glu-selective ligands significantly altered sensitivity to reinforcer magnitude.

Figures 4.14 and 4.15 show the proportion of choices for the delayed reinforcer following all concentrations of SKF 38393, SCH 23390, quinpirole, and

eticlopride. The proportion of choices for the large delayed reinforcer decreased as function of the delay to receiving reinforcement.

Figures 4.16 and 4.17 show omissions following all concentrations of SKF 38393, SCH 23390, quinpirole, and eticlopride. Intra-NAcc infusions of DA-selective ligands did not alter omissions.

Figures 4.18 and 4.19 show *k* parameter estimates following all concentrations of SKF 38393, SCH 23390, quinpirole, and eticlopride. None of the DA-selective ligands produced a statistically significant change in *k* parameter estimates.

Figure 4.20 and 4.21 show *A* parameter estimates following all concentrations of SKF 38393, SCH 23390, quinpirole, and eticlopride. None of the DA-selective ligands altered sensitivity to reinforcer magnitude.

Discussion

In the current experiment, intra-NAcc infusions of NMDA-selective ligands and DA-selective ligands did not significantly alter delay discounting. Although none of the ligands infused into NAcc caused a statistically significant difference in the rate of discounting using traditional statistical methods, this does not mean that Glu and DA receptors within this region do not necessarily mediate impulsive choice. Large effect sizes were reported for MK-801, ifenprodil, SKF 38393, and eticlopride (Cohen's *f*'s > .60), indicating that these drugs decreased impulsive choice. One potential reason a statistical difference was not detected for these drugs is the small sample sizes used in each experiment (Glu experiment: n = 8;

DA experiment: n = 6). Similarly, baseline levels of impulsive choice may influence the effects of intra-NAcc infusions. For example, administration of methylphenidate increases delay discounting in LoI rats, but decreases discounting in HiI rats (Perry, Stairs, & Bardo, 2008b). Due to the relatively small sample sizes, examining the effects of Glu-selective and DA-selective drugs on discounting in HiI and LoI rats was not feasible.

It has been argued that research needs to switch from null-hypothesis testing (i.e., reporting *p* values) to using effect sizes estimates (i.e., Cohen's *d*, Cohen's *f*, eta squared; Cumming, 2014; Kirk, 2003). Other critics of null-hypothesis testing argue that hypothesis testing impedes scientific progress (Kirk, 2003), and some have even suggested that some research findings are false because hypothesis testing creates bias in data interpretation (Ioannidis, 2005). Based on effect size estimates, the current data provide some evidence that blockade of NR2B containing NMDA receptors and DA receptors within NAcc mediate impulsive decision making.

In Experiment 1, systemic administration of MK-801 significantly decreased impulsive choice. However, intra-NAcc MK-801 infusions did not significantly decrease sensitivity to delayed reinforcement. One possibility for this discrepancy is that direct infusion of MK-801 (1.0 µg) lesioned the NAcc (see Olney, Labruyere, & Price, 1989 for a discussion). However, this interpretation does not seem likely, as lesions to NAcc increase impulsive choice (e.g., Cardinal et al., 2001). Also, considering that the effect size estimates obtained for MK-801 in Experiment 1 (Cohen's *f* = .67) and the current experiment

(Cohen's *f* = .61), the current results provide some support that intra-NAcc infusions of MK-801 decrease impulsive choice.

The current experiment provided some evidence that direct administration of ifenprodil decreased impulsive choice (Cohen's *f* = .62). Thus, the NR2B subunit may be an important mediator of impulsive decision making. This interpretation is further supported by the finding that intercereboventricular and intra-NAcc administration of the competitive NMDA receptor antagonist AP-5 does not affect delay discounting (Cottone et al., 2013; current experiment). Considering that selective blockade of NR2B subunits does not produce amnesiac or dissociative effects like noncompetitive channel blockers (e.g., MK-801; Narita et al., 2000), ifenprodil may be a promising pharmacotherapy for treating impulse control disorders. Furthermore, ifenprodil has been shown to be effective in attenuating the rewarding effects of opiates (Ma et al., 2011; Ma et al., 2006; Suzuki et al., 1999). Future studies will need to test the efficacy of ifenprodil in reducing the reinforcing effects of psychostimulants, although one report showed that ifenprodil blocks the discriminative stimulus effects of cocaine in monkeys (Fujiwara et al., 2007). Furthermore, future work is needed to test the effectiveness of therapeutically relevant doses of ifenprodil in reducing impulsivity.

DA systems are thought to play a critical role in impulsive choice, especially in delay discounting (see Winstanley, 2011 for a review). Considering that medications used to treat impulse control disorders release DA levels (see Biederman & Faraone, 2005) and decrease impulsive decision making (Broos et

al., 2012a; Cardinal et al., 2000; de Wit et al., 2002; Pitts & McKinney, 2005; van Gaalen et al., 2006b; Winstanley et al., 2003), it was hypothesized that increasing SKF 38393 (D1-like agonist) and eticlopride (D2-like antagonist) would decrease impulsive choice. Increasing DA levels by stimulating D1-like receptors and inhibiting D2-like autoreceptors did not significantly alter delay discounting. Similar to the results with MK-801 and ifenprodil, the effect sizes reported for SKF 38393 (Cohen's f = .64) and eticlopride (Cohen's f = .61) were large, which provides some support for the hypotheses. Regardless, these data do not corroborate previous research examining the role of DA receptor ligands in impulsive decision making. A previous study found increased discounting following intra-mPFC infusions of SKF 38393 (Loos et al., 2010). Loos et al. (2010) also observed increases in impulsive choice after blocking D1-like receptors with SCH 23390, an effect not observed in the current experiment. Given that the discounting procedure used by Loos et al. (2010) was similar to the current procedure, it is not entirely clear why discounting was differentially altered following SKF 38393 administration. However, intra-mPFC administration appears to have produced a slight decrease in choice for the large magnitude reinforcer when its delivery was immediate (Loos et al., 2010), an effect observed following systemic administration (Koffarnus et al., 2011). Thus, D1 receptors within mPFC and NAcc may differentially mediate sensitivity to reinforcer amount and delayed reinforcement.

DA D2-like receptors are autoreceptors, which decrease DA synthesis and packaging (Onali, Oliansa, & Bunse, 1988; Pothos, Davila, & Sulzer, 1998).

Therefore, blocking these receptors should decrease the rate of discounting. However, previous studies have observed increases in impulsive choice following intra-mPFC or intra-OFC administration of the D2-like receptor antagonists raclopride and eticlopride (Pardey et al., 2013; Zeeb et al., 2010). One discrepancy between the current experiment and previous studies is the use of a discriminative stimulus to signal the delay to delivery of the large magnitude reinforcer. In the current experiment, no cue was used to signal the delay, whereas Pardey et al. (2013) and Zeeb et al. (2010) used a cue light. Zeeb et al. (2010) found that eticlopride increased impulsive choice when a cue was used, whereas impulsive choice was unaltered if a cue was not used. Thus, future studies are needed to understand how intra-NAcc administration of DA D2-like antagonists affect impulsive decision making when cues are used to signal the delay to reinforcement.

One limitation to this study was the use of two concentrations for each drug tested. The number of drug concentrations was limited because the number of microinfusions needs to be limited in order to minimize damage to the brain region. Future work will be needed to assess a wider range of drug concentrations of NMDA and DA receptor ligands within NAcc and NAcSh to further elucidate the role of NAc Glu and DA systems in controlling impulsive choice. Furthermore, examining the role of other neurotransmitter systems within NAc is merited. For example, NAc contains 5-HT and GABA receptors (Biegon, Rainbow, & McEwen, 1982; Bowery, Hudson, & Price, 1987), and these

neurotransmitters influence impulsive decision making (Bizot et al., 1999; Liu et al., 2004; Zeeb et al., 2010).

Another important consideration is that several brain regions have been implicated in impulsive decision making, such as OFC (Mobini et al., 2002; Winstanley et al., 2004b; but see Churchwell et al., 2009), mPFC (Churchwell et al., 2009; but see Cardinal et al., 2001), amygdala (Churchwell et al., 2009; Winstanley et al., 2004b), dorsal striatum (Dunnett et al., 2012), and hippocampus (Abela & Chudasama, 2013; Cheung & Cardinal, 2005; Mariano et al., 2009). Also, DA receptors within OFC and mPFC are known to contribute to delay discounting performance (Loos et al., 2010; Yates et al., under review; Zeeb et al., 2010). Future studies are needed to assess the role of NMDA receptors in other brain regions (e.g., frontal cortices and hippocampus) in mediating impulsive behavior.

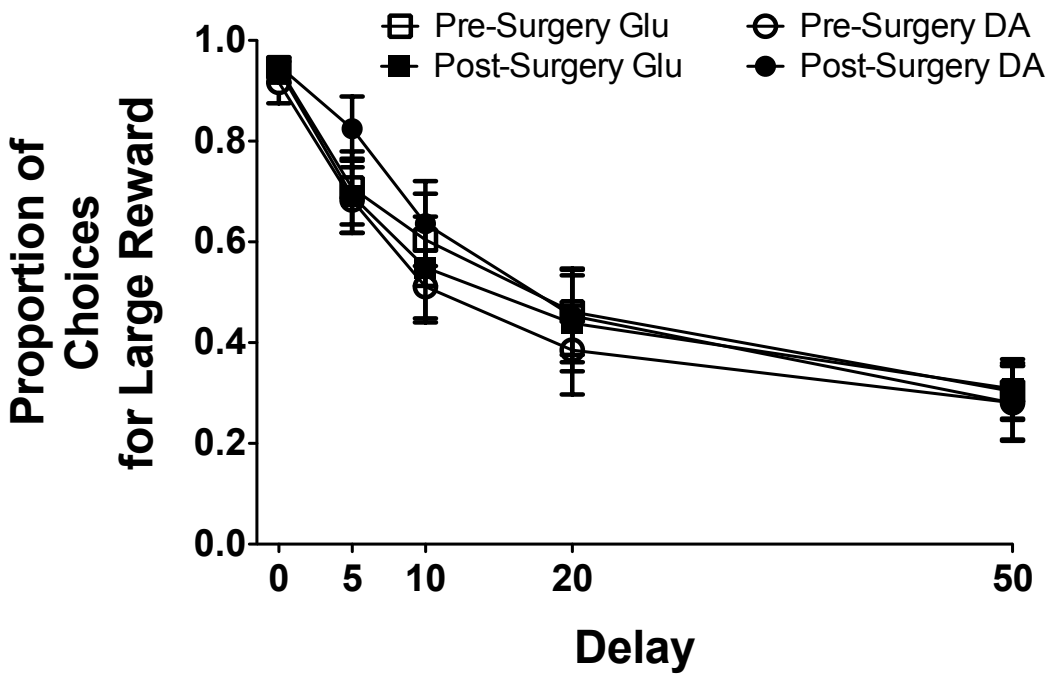


Figure 4.1 Mean (± SEM) proportion of choices for the large magnitude reinforcer as a function of the delay to receiving reinforcement before and after surgery in rats subsequently given Glu-selective ligands and DA-selective ligands.

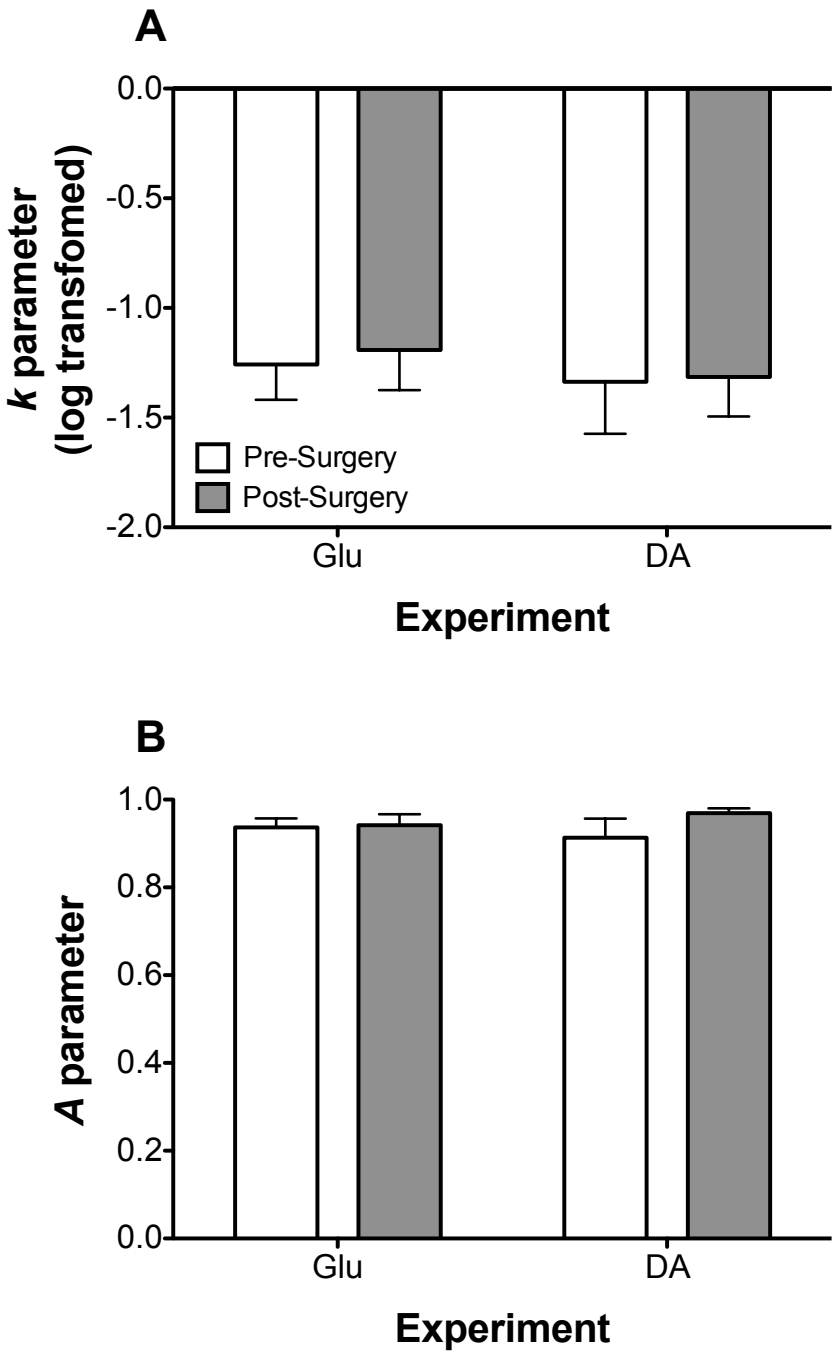


Figure 4.2 Mean (± SEM) *k* parameter estimates (log transformed; Panel A) and *A* parameter estimates (Panel B) before and after surgery in rats subsequently given Glu-selective ligands and DA-selective ligands.

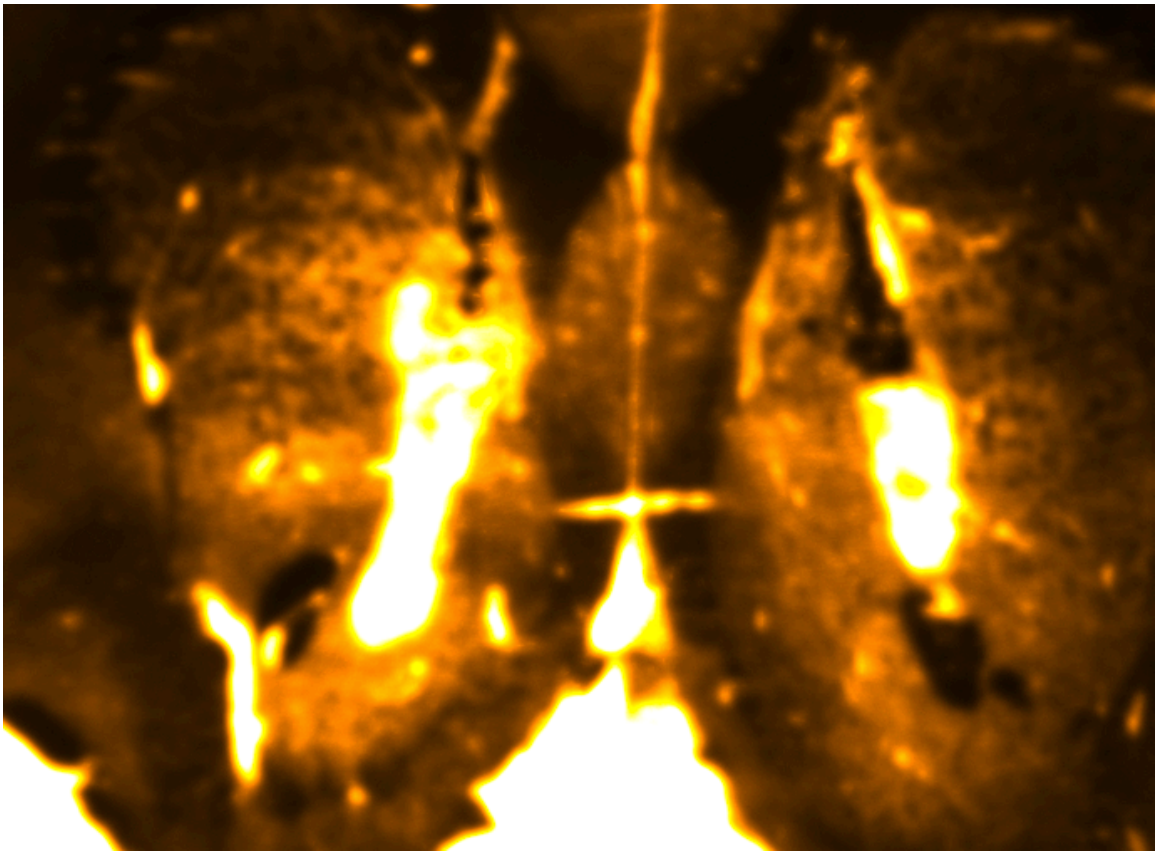


Figure 4.3. Representative image of bilateral guide cannulae implantation into NAcc.

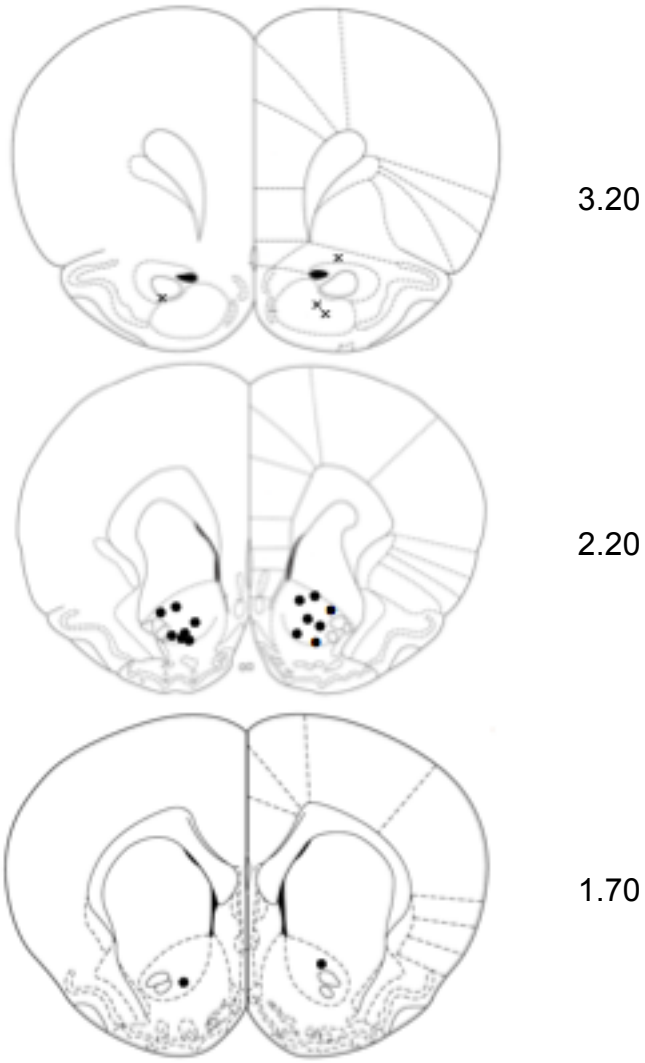


Figure 4.4. Schematic of coronal sections showing probe placements for rats infused with Glu-selective ligands. Black circles indicate probe placements within NAcc, whereas crosses indicate probe place placements outside of NAcc. Note that rats with probe placements outside of NAcc were excluded from data analysis. Numbers beside each plate correspond to mm anterior to bregma.

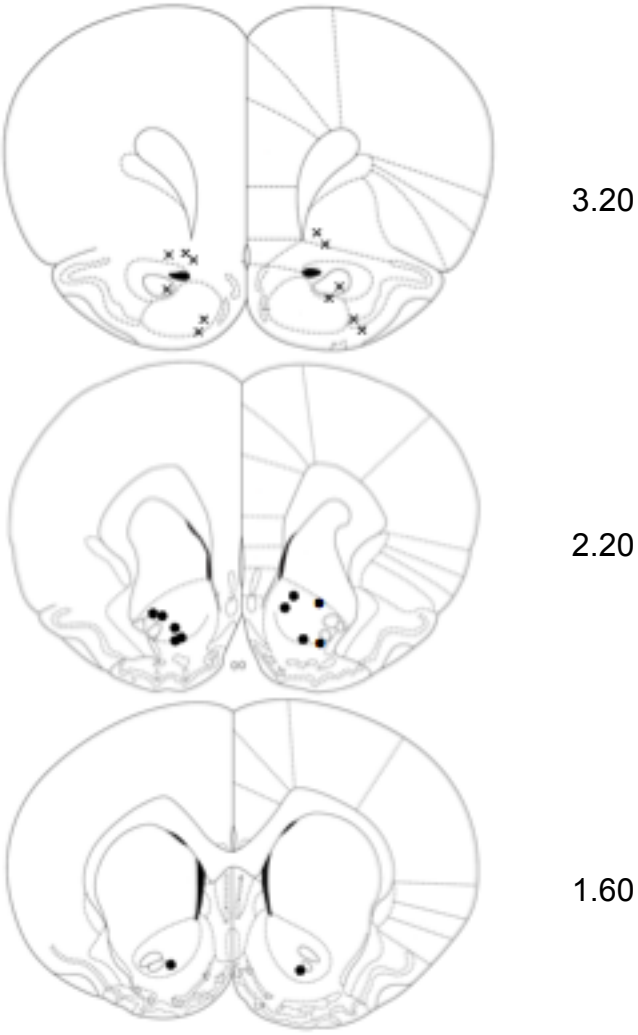


Figure 4.5. Schematic of coronal sections showing probe placements for rats infused with DA-selective ligands. Black circles indicate probe placements within NAcc, whereas crosses indicate probe place placements outside of NAcc. Note that rats with probe placements outside of NAcc were excluded from data analysis. Numbers beside each plate correspond to mm anterior to bregma.

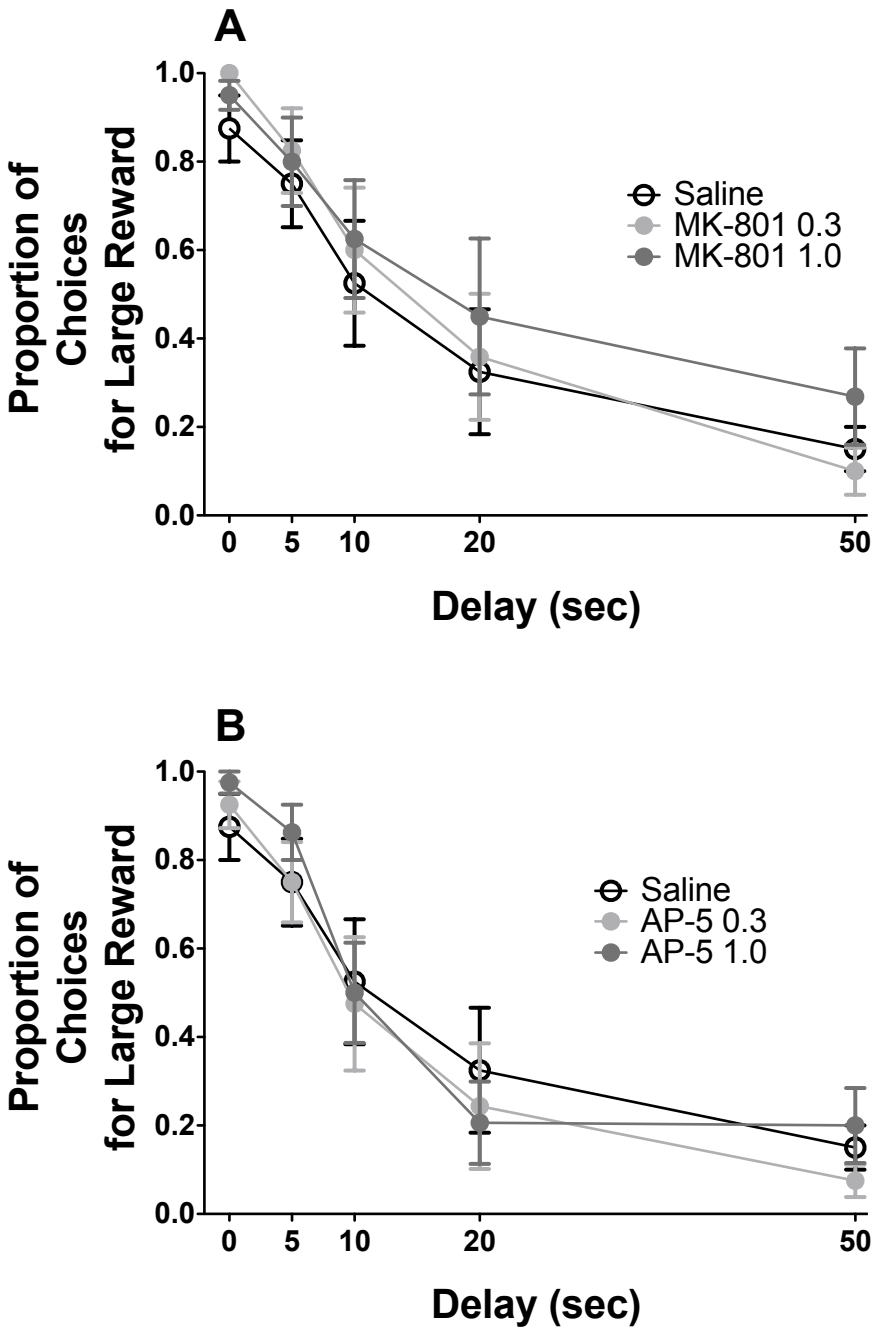


Figure 4.6. Mean (± SEM) proportion of choices for the large magnitude reinforcer as a function of the delay to receiving reinforcement following intra-NAcc infusions of MK-801 (Panel A) and AP-5 (Panel B).

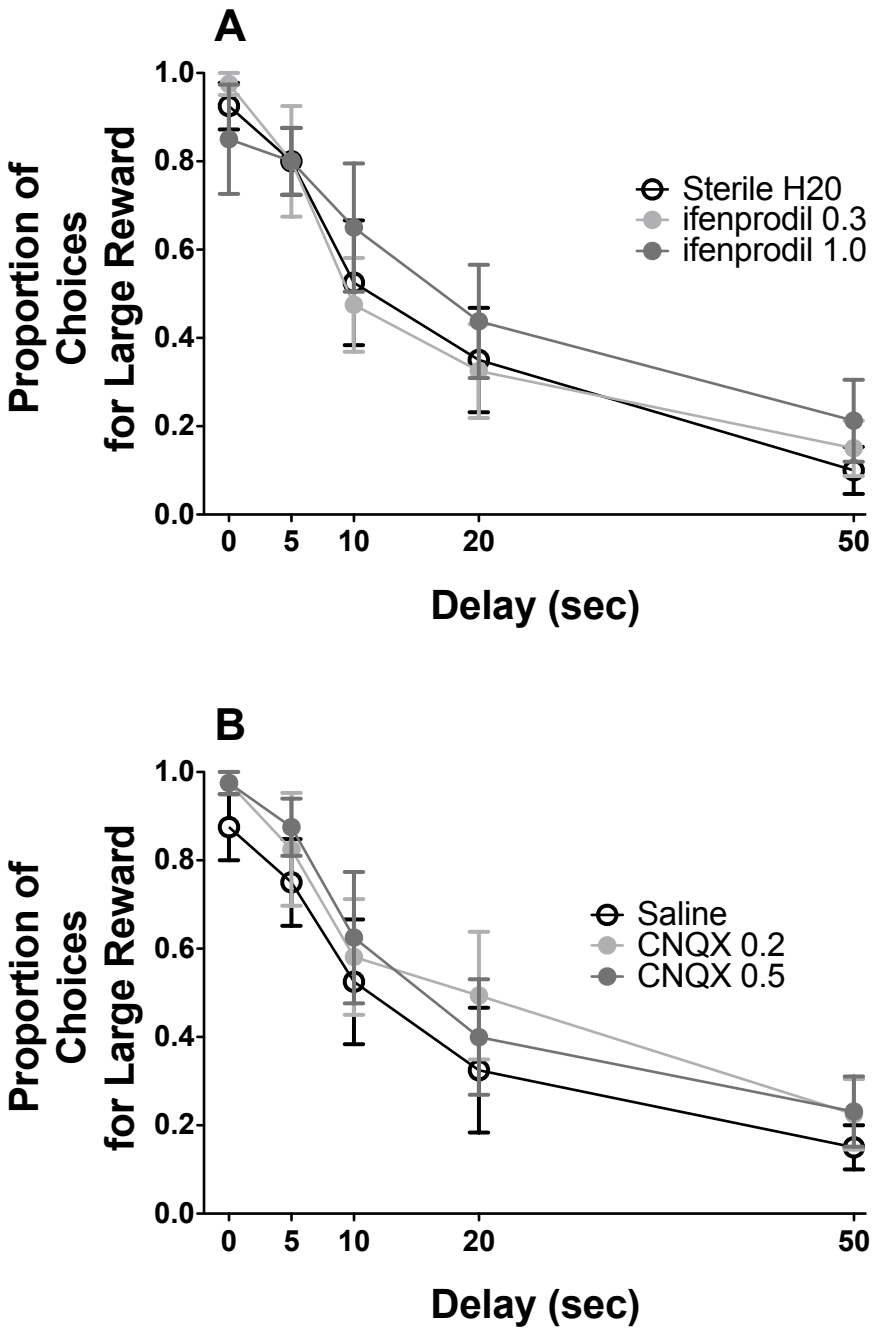


Figure 4.7. Mean (± SEM) proportion of choices for the large magnitude reinforcer as a function of the delay to receiving reinforcement following intra-NAcc infusions of ifenprodil (Panel A) and CNQX (Panel B).

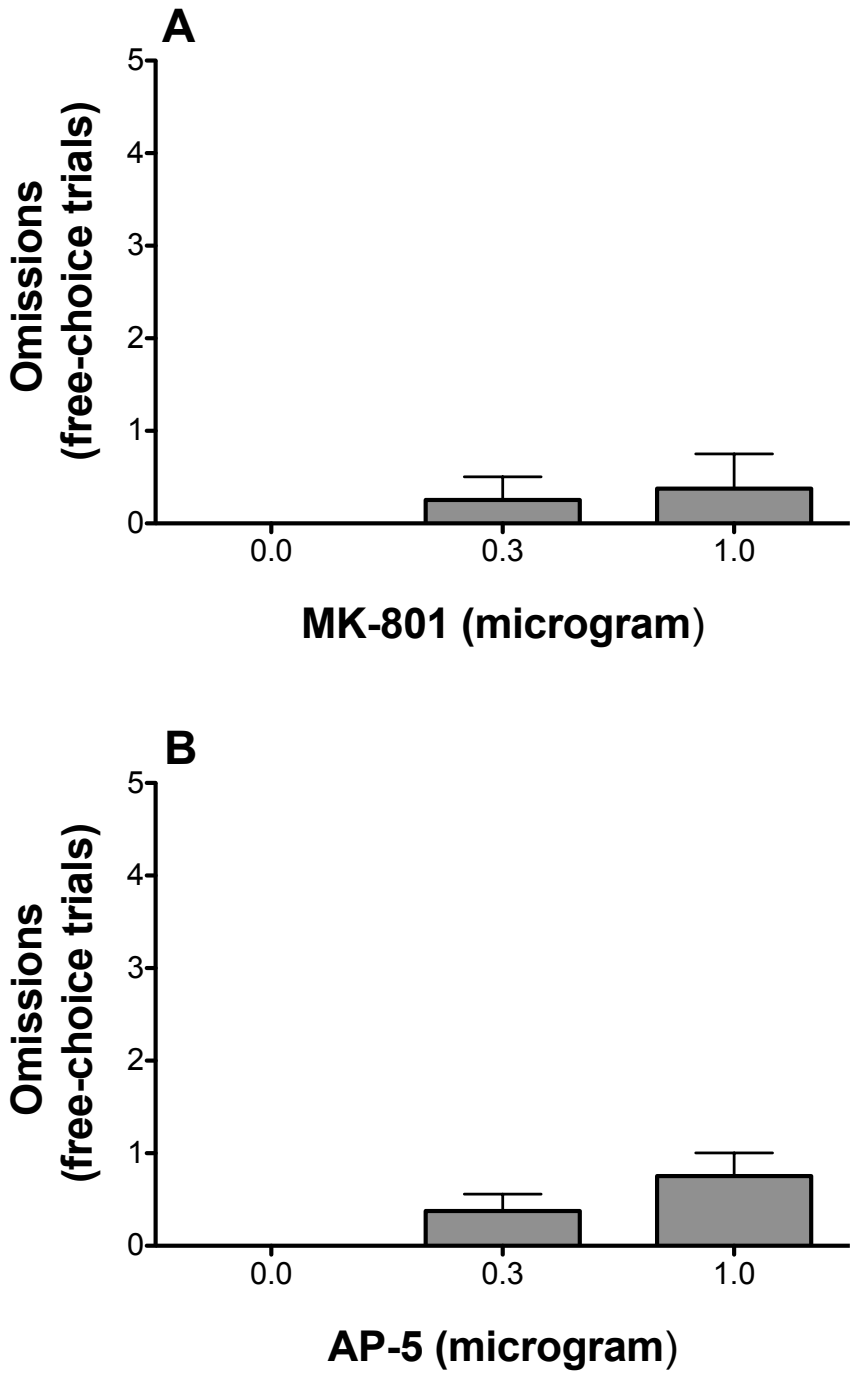


Figure 4.8. Mean (± SEM) omissions during free-choice trials following intra-NAcc infusions of MK-801 (Panel A) and AP-5 (Panel B).

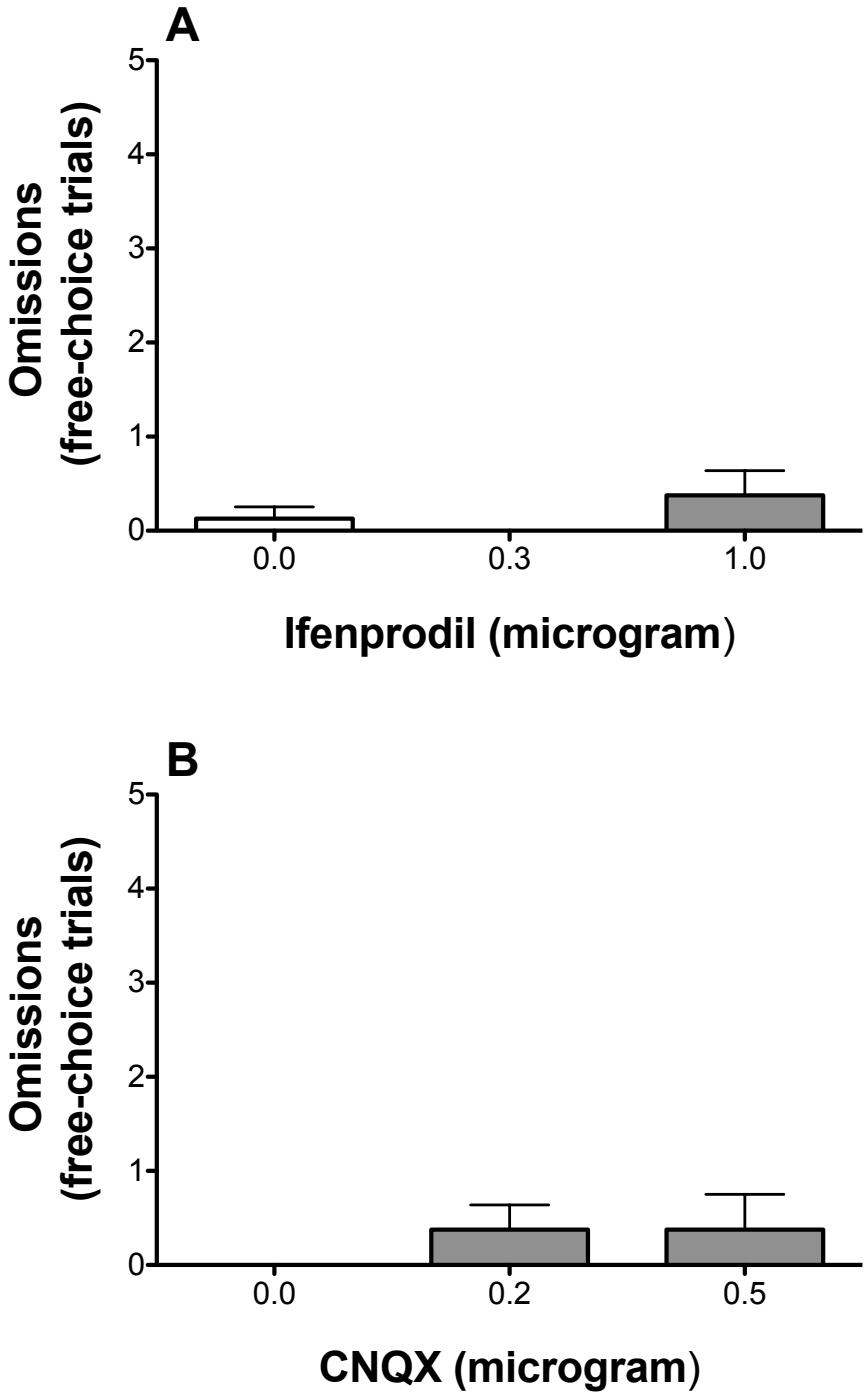


Figure 4.9. Mean (± SEM) omissions during free-choice trials following intra-NAcc infusions of ifenprodil (Panel A) and CNQX (Panel B).

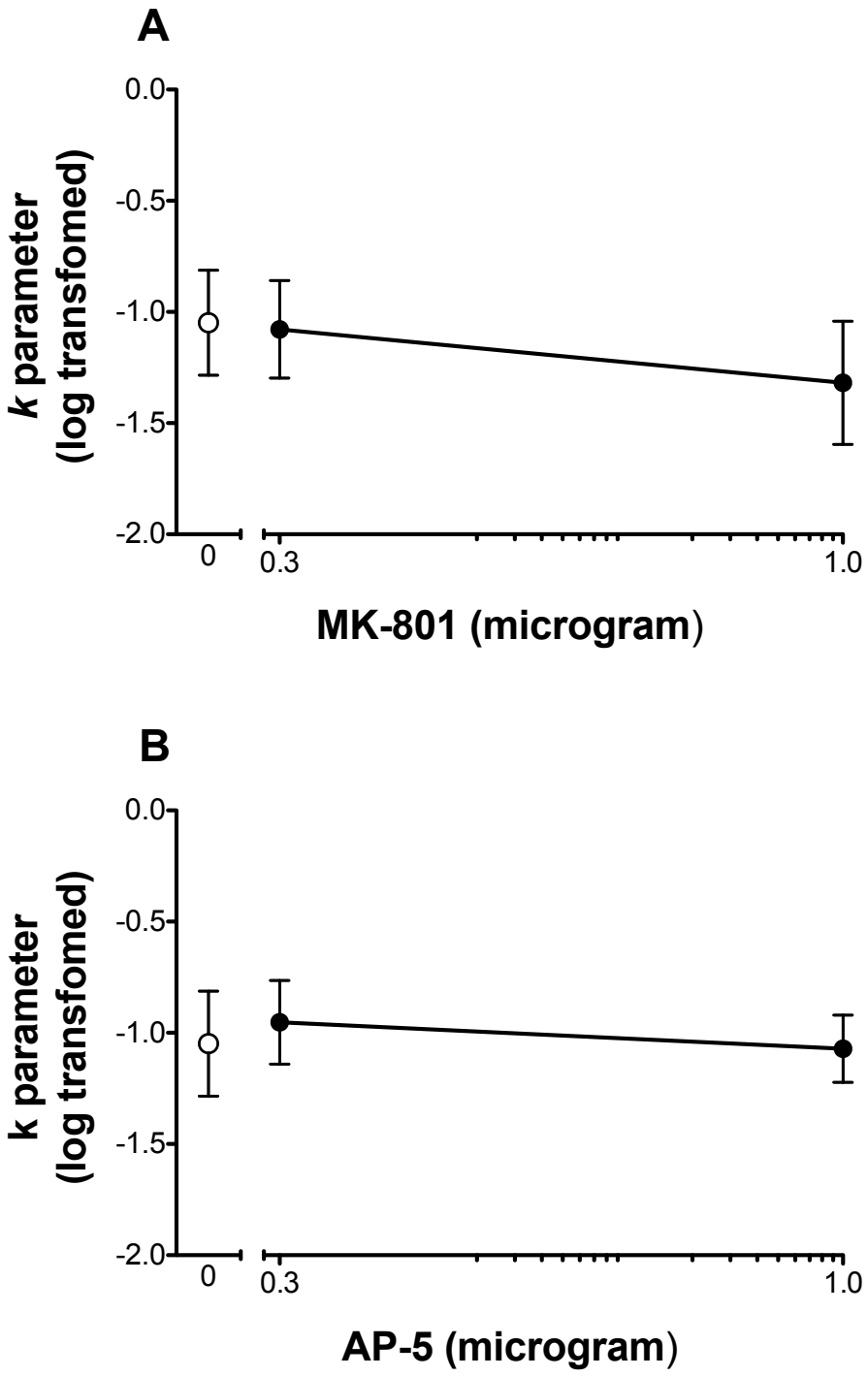


Figure 4.10. Mean (± SEM) *k* parameter estimates (log transformed) following intra-NAcc infusions of MK-801 (Panel A) and AP-5 (Panel B).

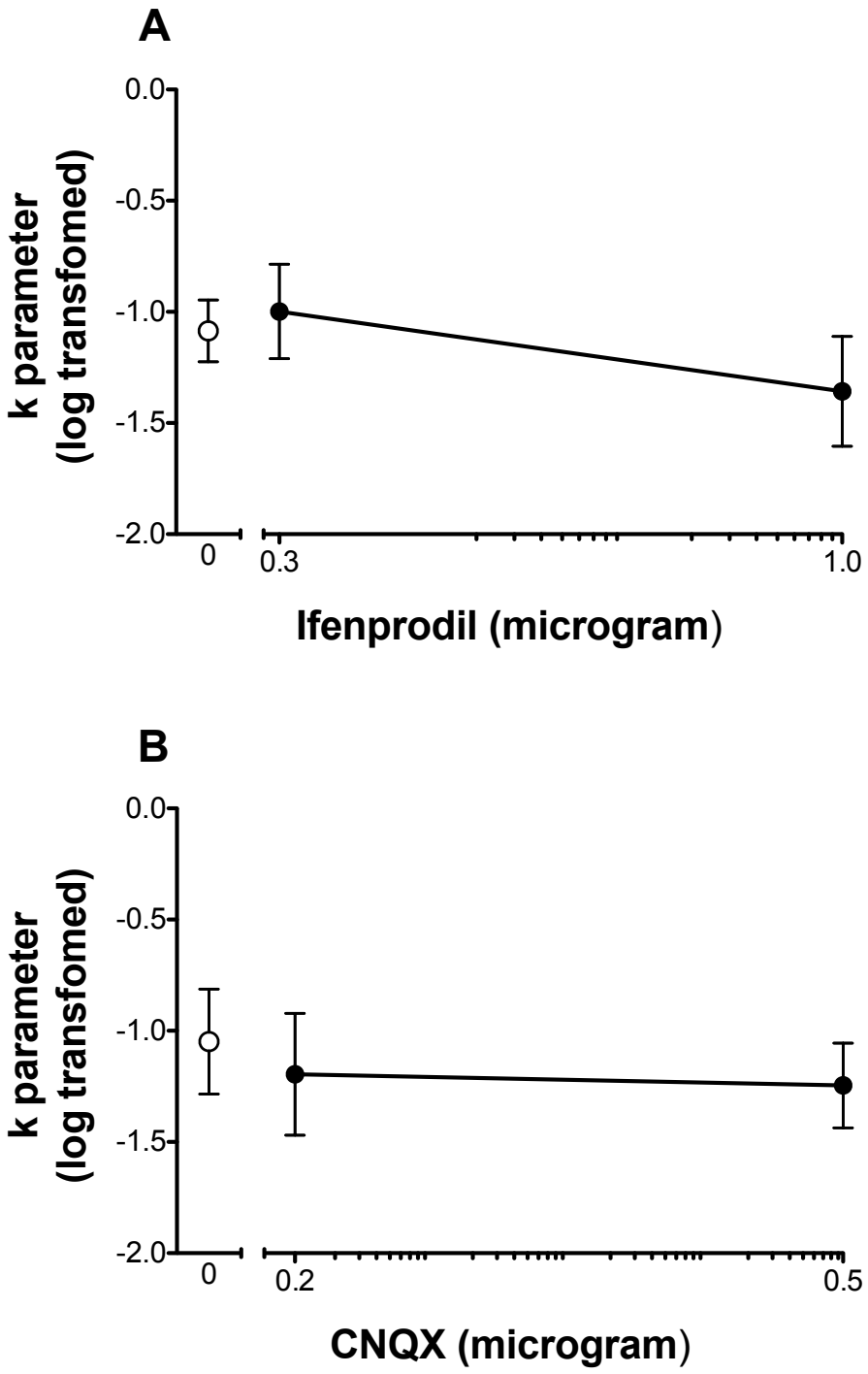


Figure 4.11. Mean (± SEM) *k* parameter estimates (log transformed) following intra-NAcc infusions of ifenprodil (Panel A) and CNQX (Panel B).

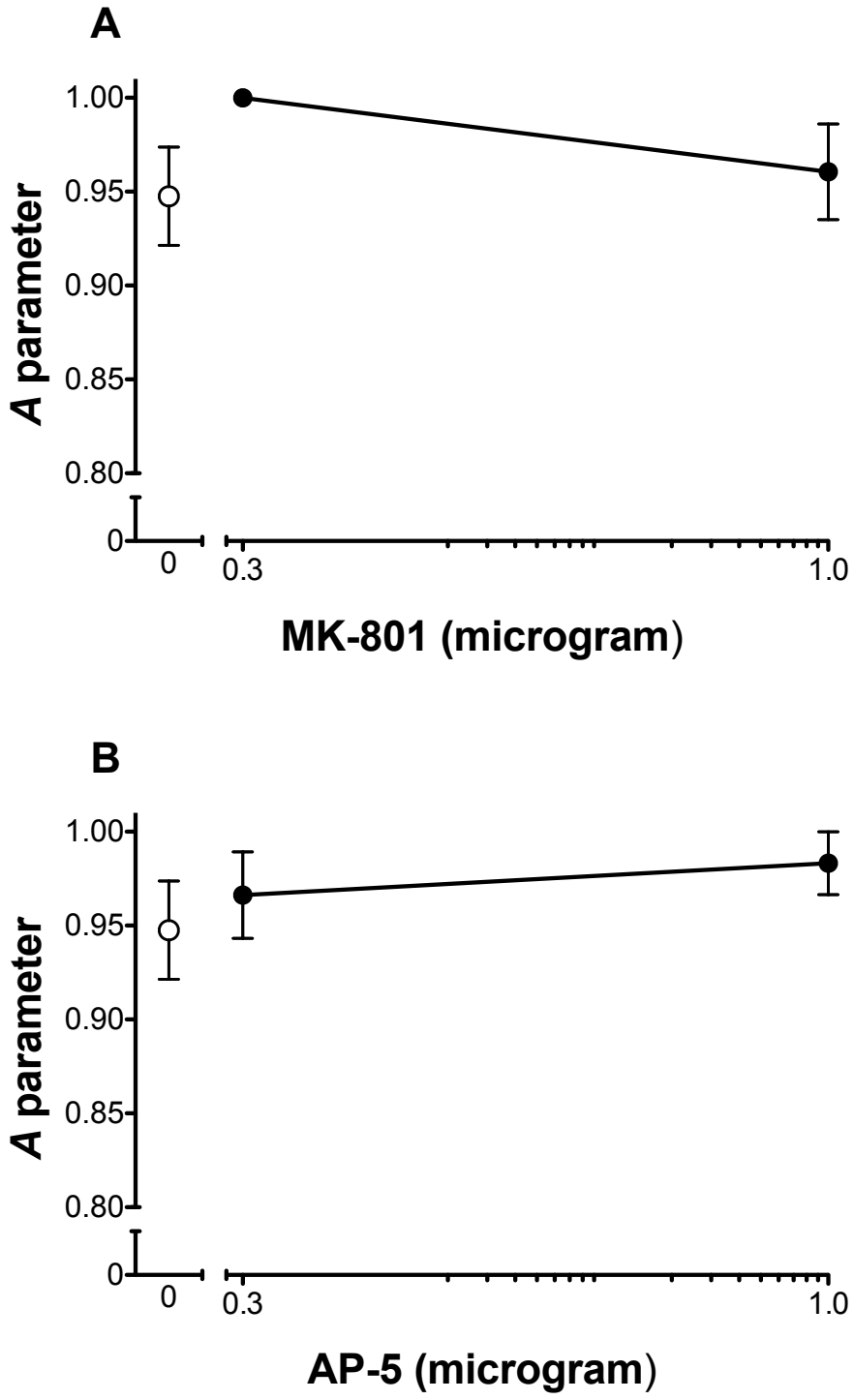


Figure 4.12. Mean (± SEM) *A* parameter estimates following intra-NAcc infusions of MK-801 (Panel A) and AP-5 (Panel B).

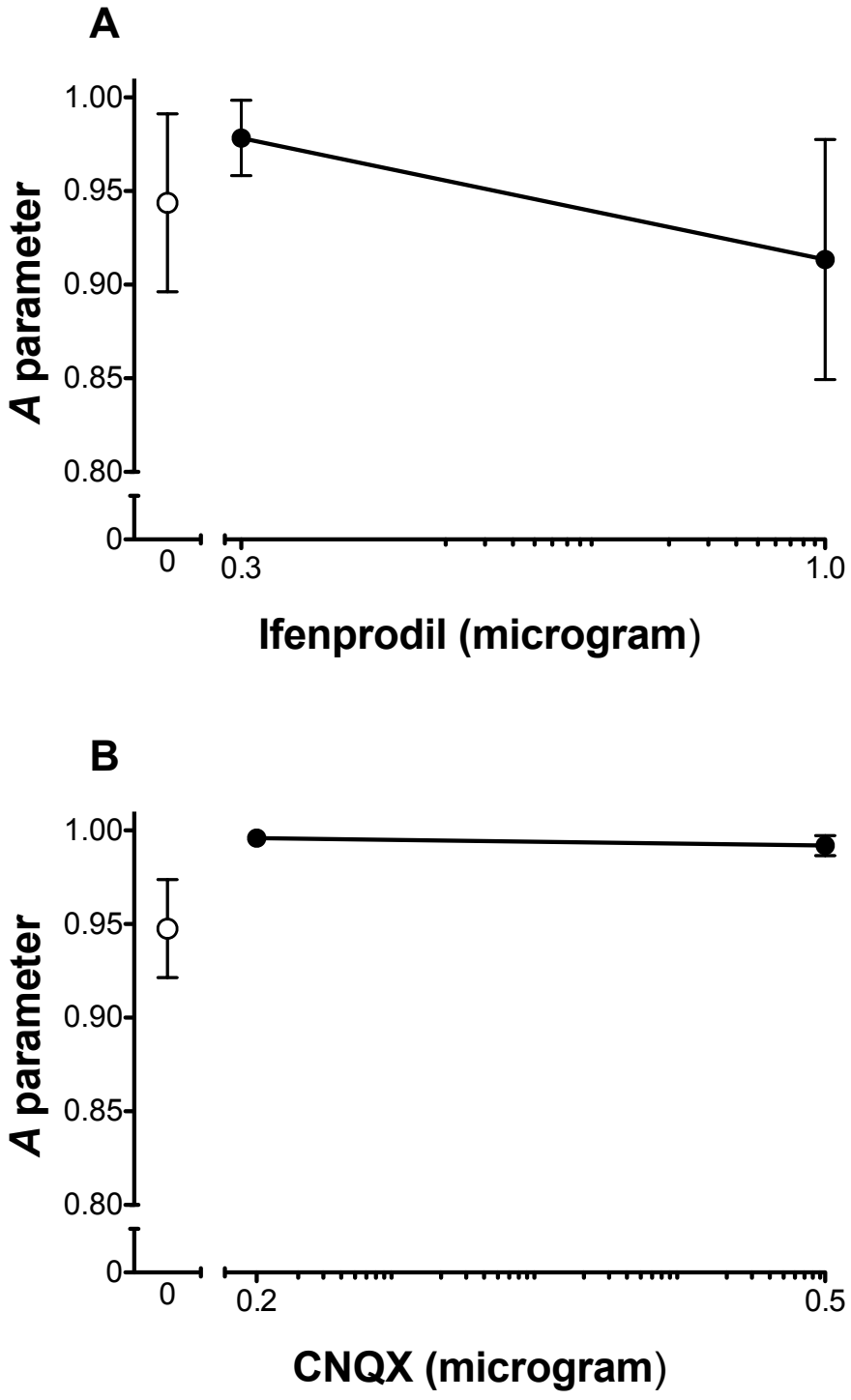


Figure 4.13. Mean (± SEM) *A* parameter estimates following intra-NAcc infusions of ifenprodil (Panel A) and CNQX (Panel B).

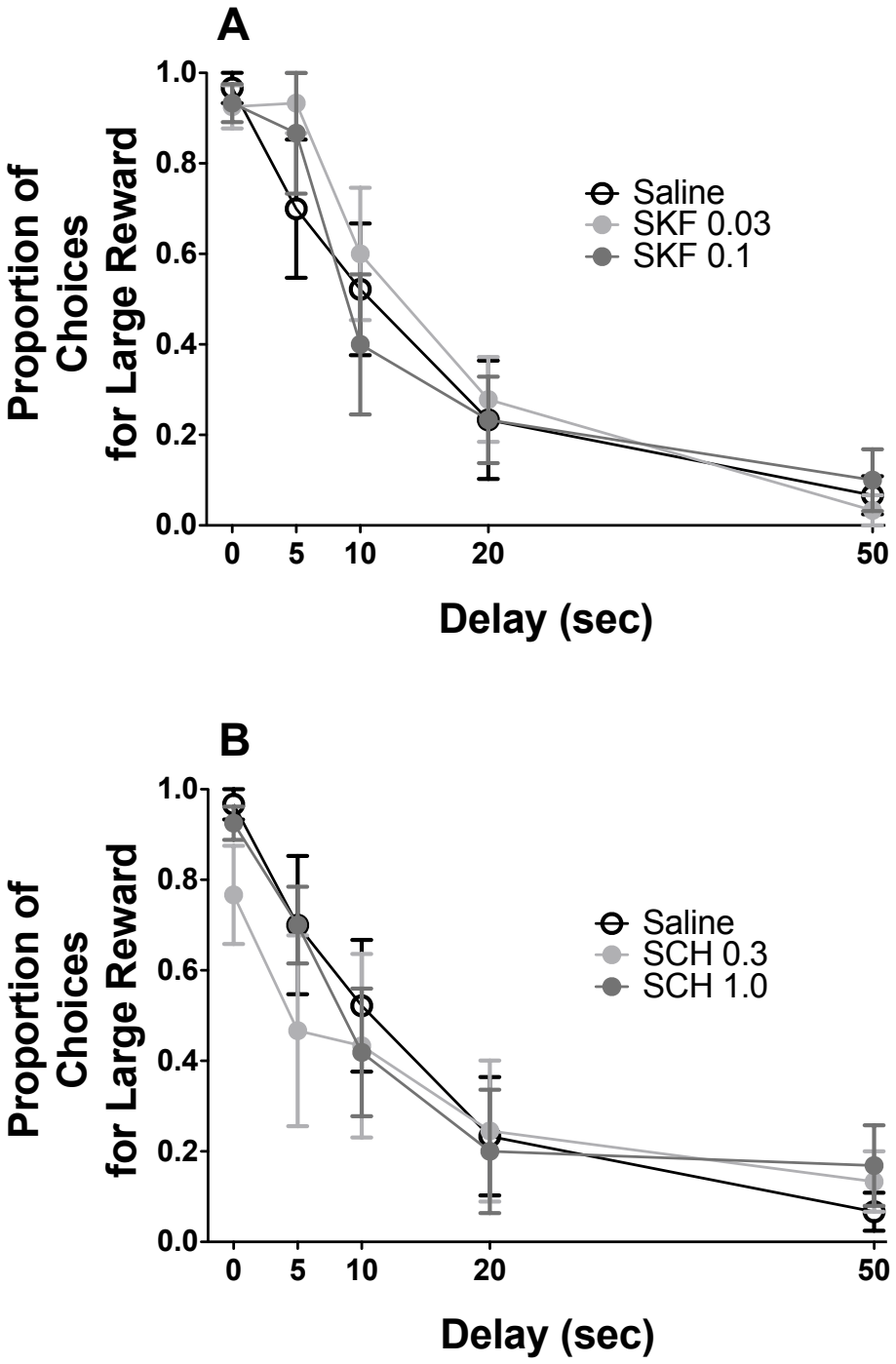


Figure 4.14. Mean (± SEM) proportion of choices for the large magnitude reinforcer as a function of the delay to receiving reinforcement following intra-NAcc infusions of SKF 38393 (Panel A) and SCH 23390 (Panel B).

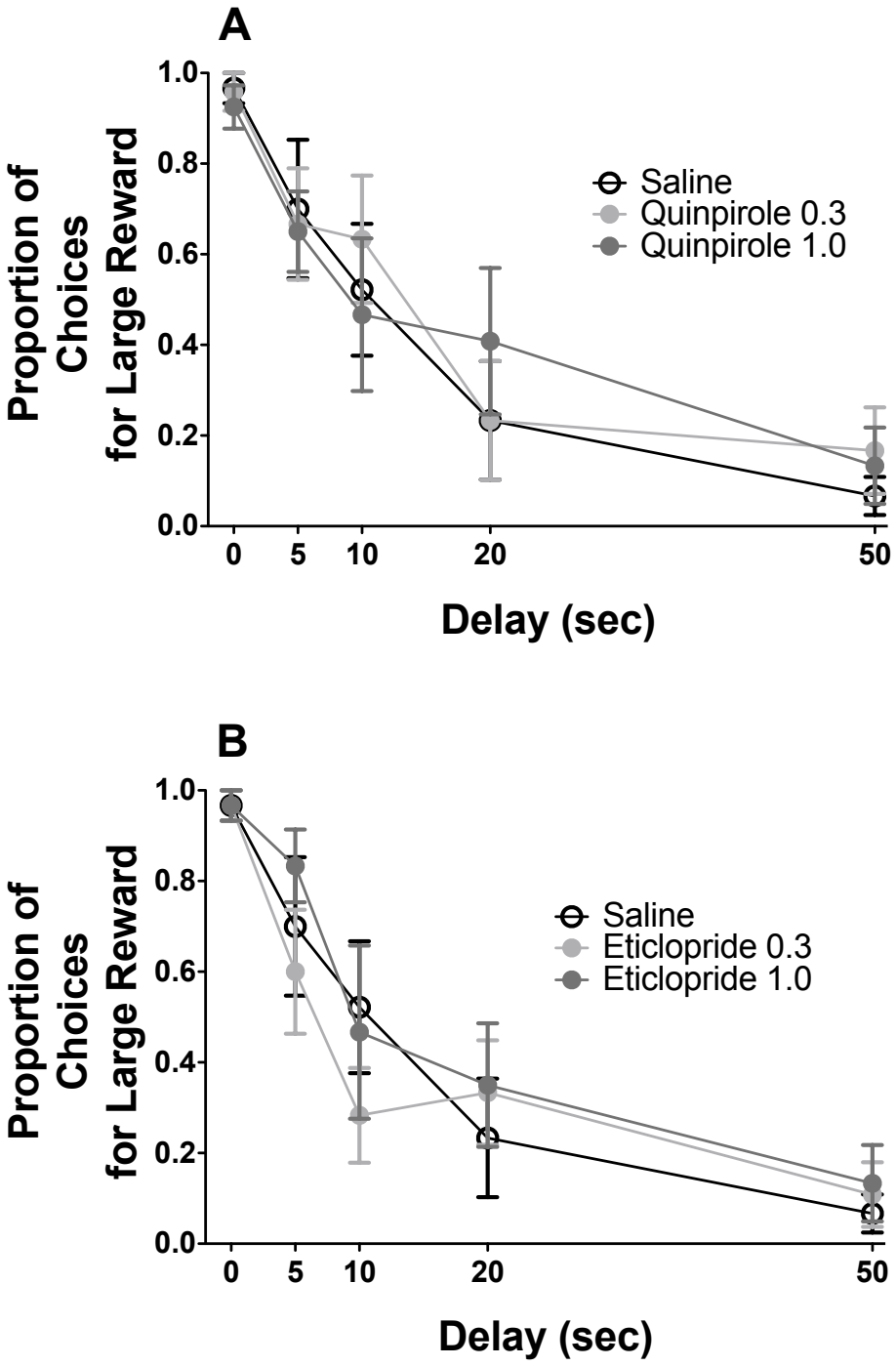


Figure 4.15. Mean (± SEM) proportion of choices for the large magnitude reinforcer as a function of the delay to receiving reinforcement following intra-NAcc infusions of quinpirole (Panel A) and eticlopride (Panel B).

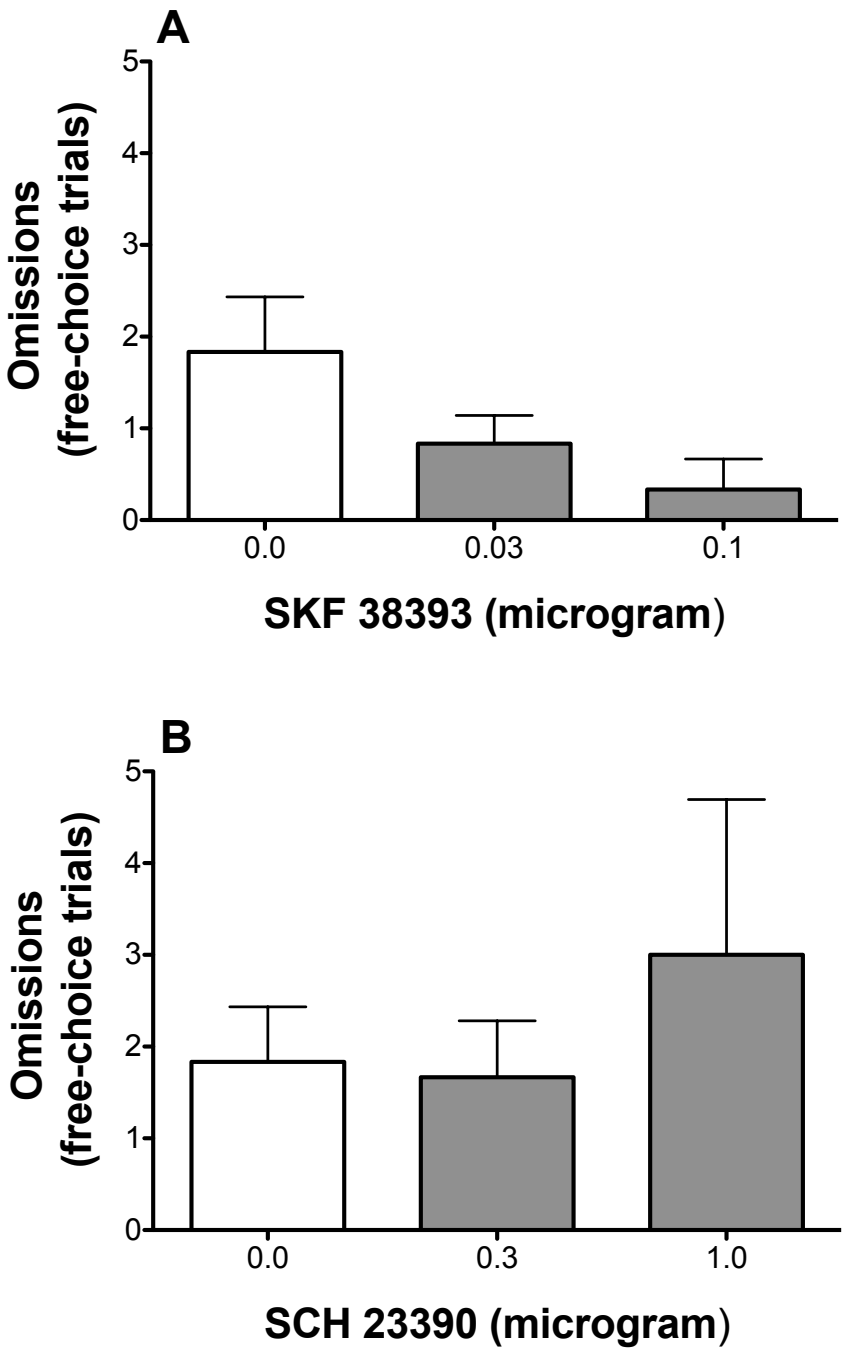


Figure 4.16. Mean (± SEM) omissions during free-choice trials following intra-NAcc infusions of SKF 38393 (Panel A) and SCH 23390 (Panel B).

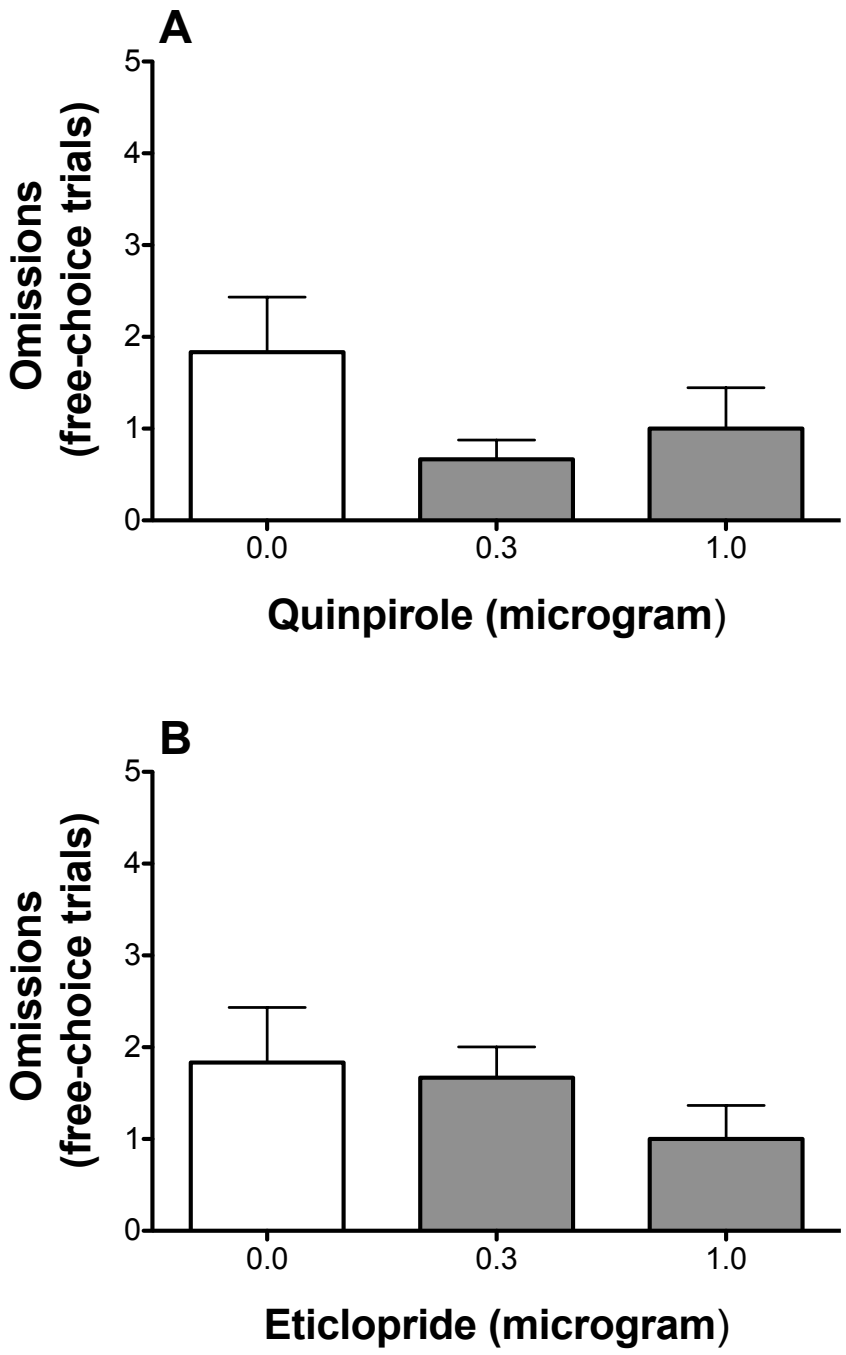


Figure 4.17. Mean (± SEM) omissions during free-choice trials following intra-NAcc infusions of quinpirole (Panel A) and eticlopride (Panel B).

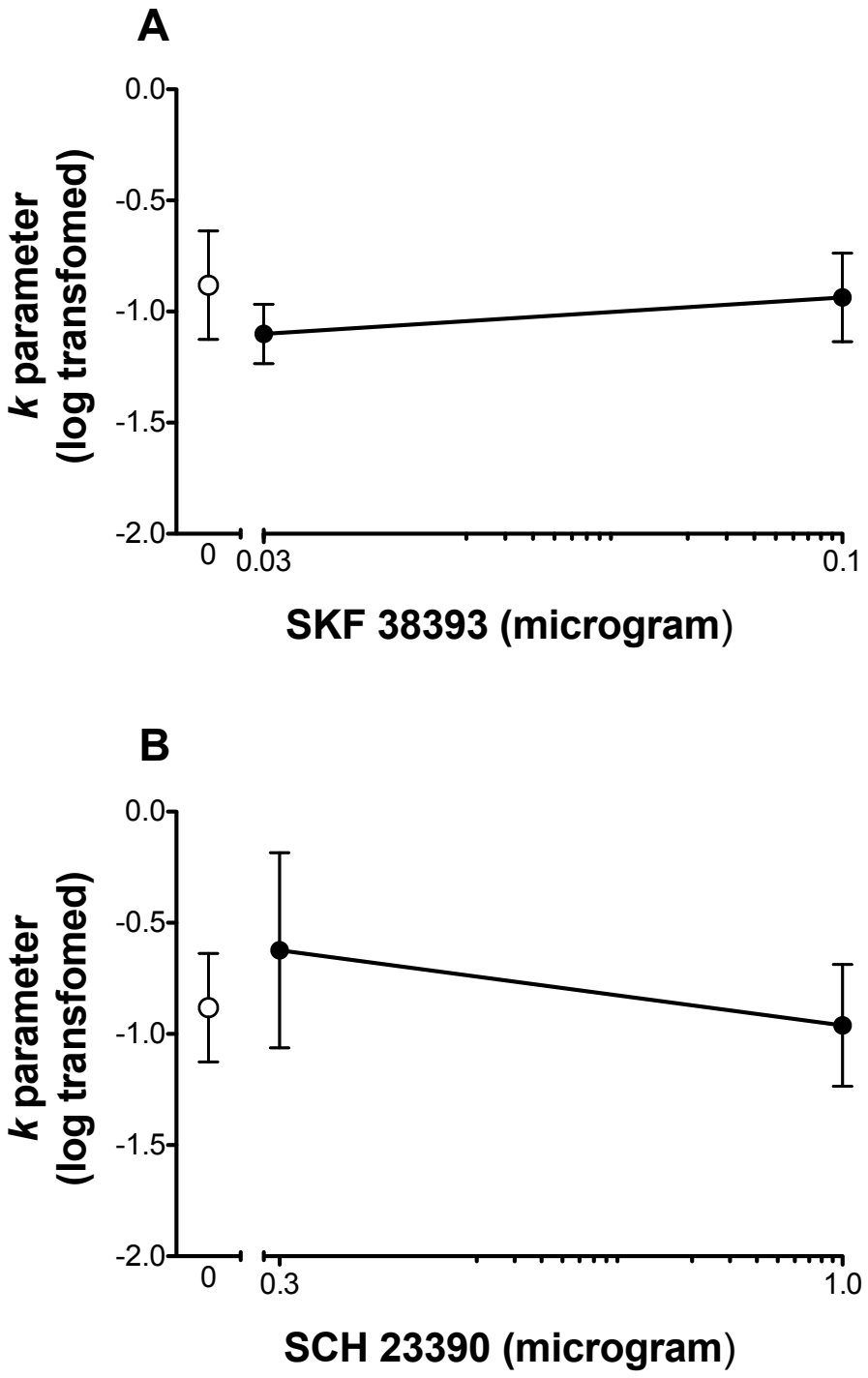


Figure 4.18. Mean (± SEM) *k* parameter estimates (log transformed) following intra-NAcc infusions of SKF 38393 (Panel A) and SCH 23390 (Panel B).

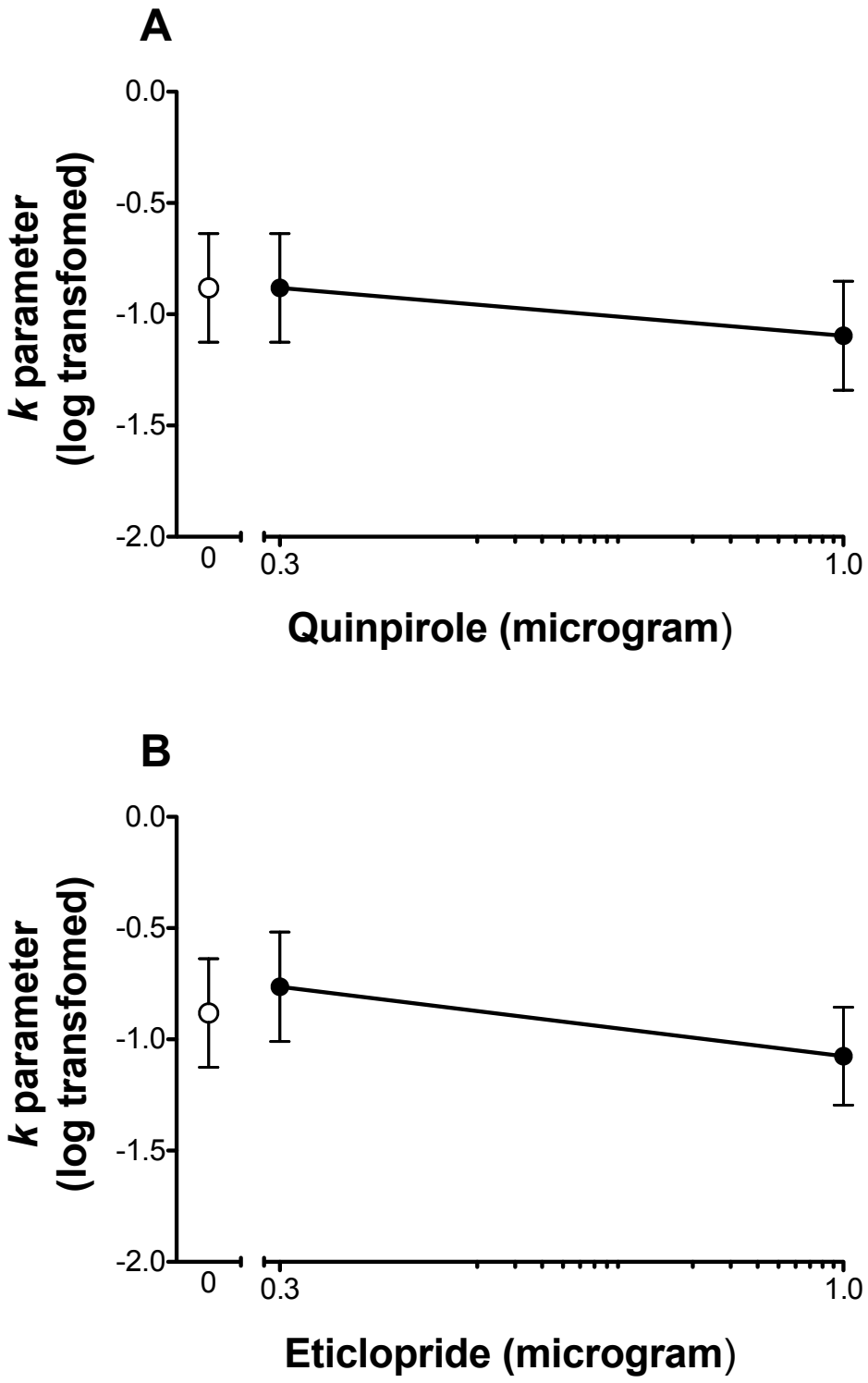


Figure 4.19. Mean (± SEM) *k* parameter estimates (log transformed) following intra-NAcc infusions of quinpirole (Panel A), and eticlopride (Panel B).

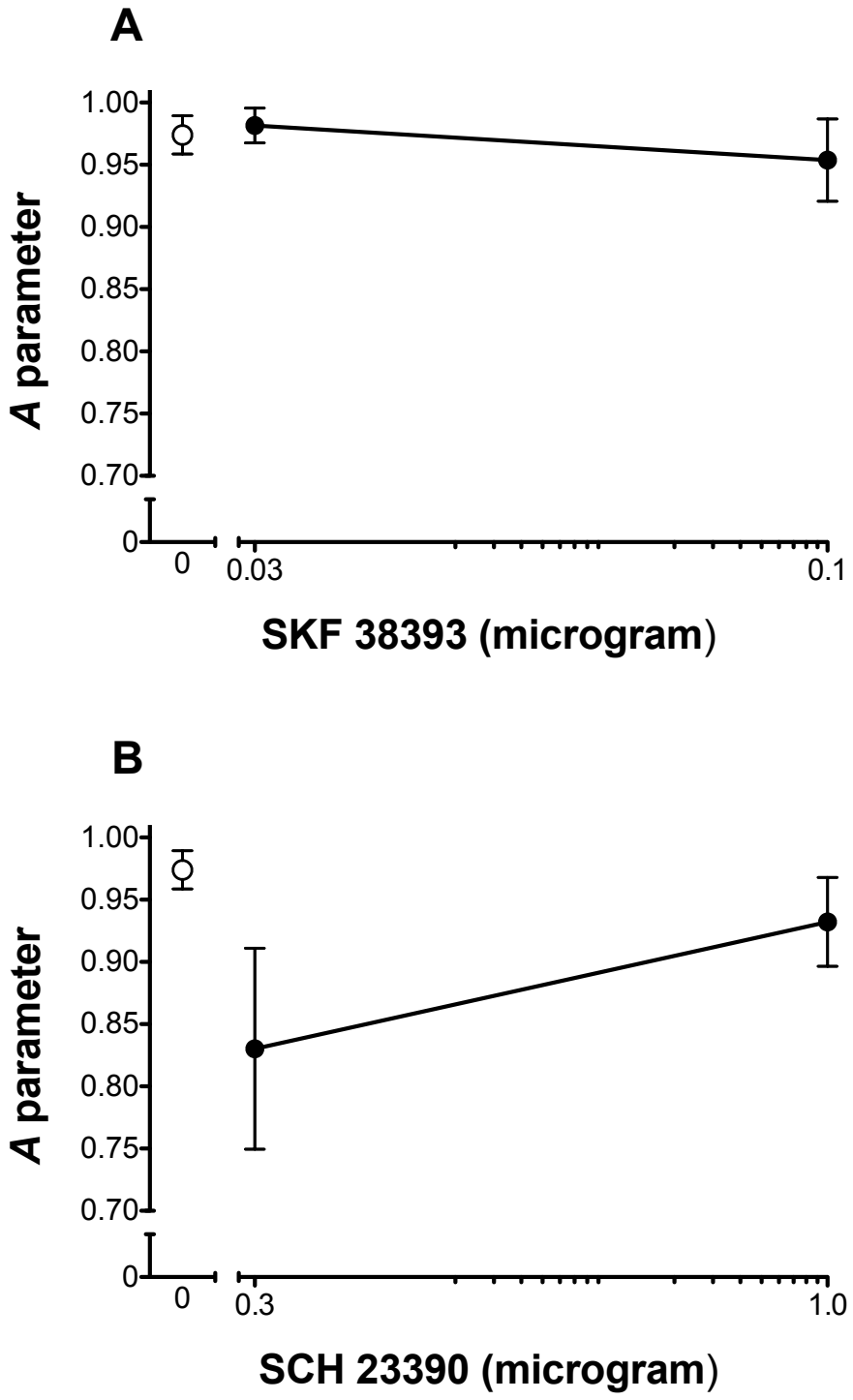


Figure 4.20. Mean (± SEM) *A* parameter estimates following intra-NAcc infusions of SKF 38393 (Panel A) and SCH 23390 (Panel B).

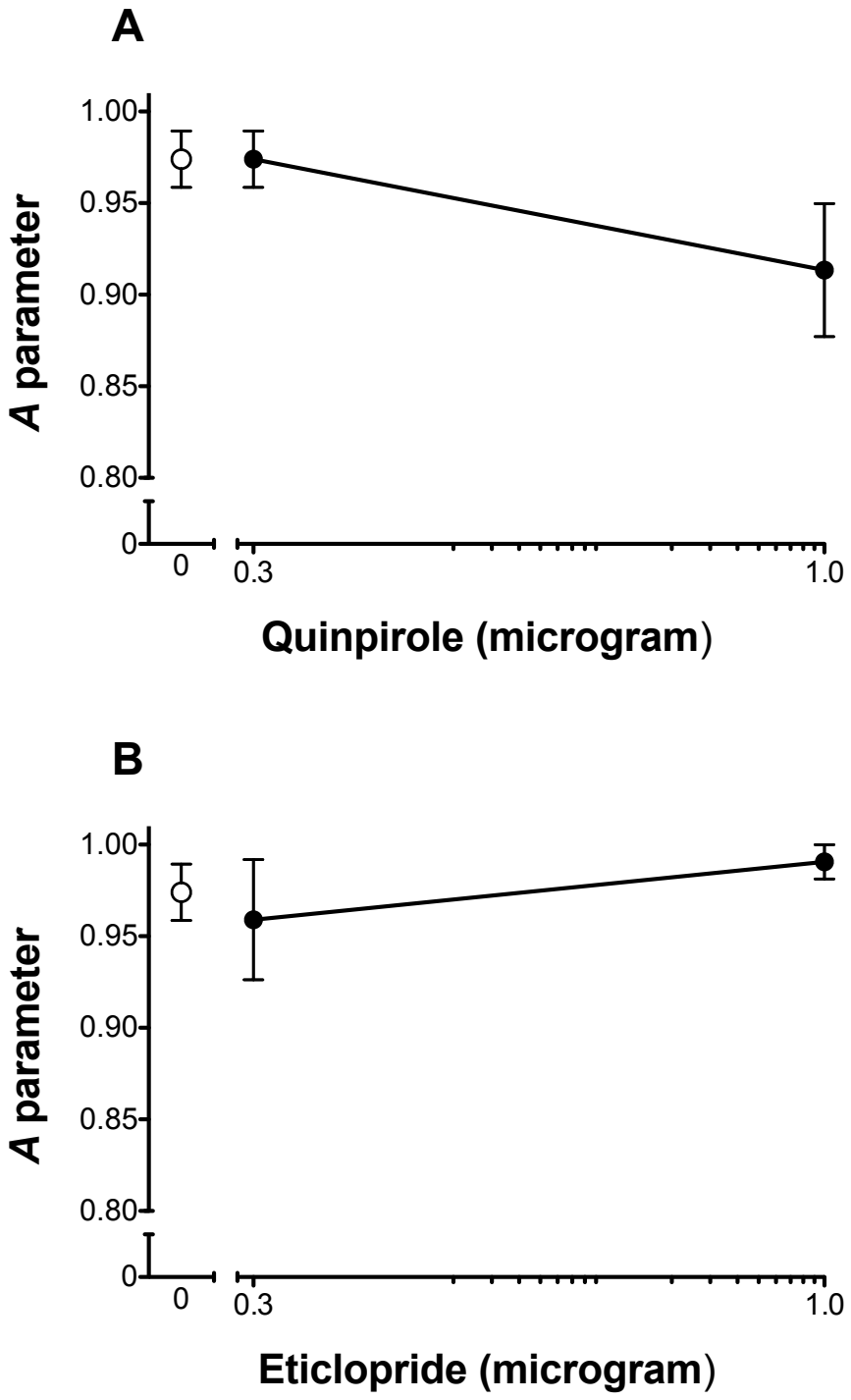


Figure 4.21. Mean (± SEM) *A* parameter estimates following intra-NAcc infusions of quinpirole (Panel A) and eticlopride (Panel B).

Chapter 5: General Discussion

The primary goal of the current set of experiments was to elucidate the role of the glutamatergic and dopaminergic systems in impulsive choice. The NAcc has been consistently linked to impulsive decision making (Bezzina et al., 2007; Cardinal et al., 2001; da Costa Araújo et al., 2009; Pothuzien et al., 2005; Valencia-Torres et al., 2012); however, studies examining the role of NAcc in impulsive choice have relied on excitotoxic lesions. Lesion studies do not indicate which specific neurotransmitter systems mediate this behavior. Therefore, the current experiments sought to determine if NAcc Glu and DA systems are a) altered in HiI and LoI animals, and b) to determine if NAcc Glu and DA receptors differentially alter impulsive choice. The results from these studies demonstrated that: 1) systemic administration of MK-801, but not CNQX, decreases impulsive choice (Experiment 1); 2) differences in discounting do not result from baseline differences in NAc NMDA receptor or DAT expression (Experiment 2); and 3) intra-NAcc infusions of Glu-selective and DA-selective ligands do not significantly alter impulsive choice (Experiment 3).

In the current experiments, the term “impulsive choice” has been used to describe performance in delay discounting. Although delay discounting is often described as a measure of impulsive choice (e.g., Ainslie, 1975; see Winstanley et al., 2010 for a review), some argue against this assertion. For example, Blanchard, Pearson, and Hayden (2013) show that monkeys often fail to associate postreward delays with their choices and systematically underestimate the delay to reinforcement. Blanchard et al. (2013) propose that discounting

does not necessarily reflect impulsivity, but may reflect other unrelated mental processes. Furthermore, Killeen (2011) postulates that animals do not discount future rewards; instead, the data observed in discounting experiments merely reflects decay in memory traces.

Despite these criticisms, studying delay discounting is important because performance in this task is often linked to maladaptive behaviors, such as pathological gambling (Petry, 2001b) and substance use disorders (Bickel et al., 1999; Coffey et al., 2003; Madden et al., 1997; Mitchell, 1999; Vuchinich & Simpson, 1998). As discussed in Chapter 1, animals showing increased sensitivity to delayed reinforcement are more likely to acquire psychostimulant self-administration at a faster rate (Perry et al., 2005, 2008a), to respond more for drug reinforcers (Diergaarde et al., 2008; Marusich & Bardo, 2009), and to be more susceptible to relapse-like behaviors (Diergaarde et al., 2008).

It should be noted that delay discounting is not the only measure of impulsivity that is linked to drug abuse. As with impulsive choice, the construct of impulsive action (i.e., behavioral disinhibition or motor impulsivity) has received considerable attention in the drug abuse field. Cocaine (Fillmore & Rush, 2002; Li, Milivojevic, Kemp, Hong, & Sinha, 2006) and methamphetamine (Monterosso, Aron, Cordova, Xu, & London, 2005) users display inhibitory deficits in a SSRT task relative to nonusers. Furthermore, cocaine users (Hester & Garavan, 2004; Kaufman, Ross, Stein, & Garavan, 2003; Verdejo-Garcia, Perales, & Perez-Garcia, 2007) and alcoholics (Noel et al., 2007) show increased inhibitory deficits on a go/no-go task compared to controls. Impulsive action is predictive of drug

abuse vulnerability, as rats that exhibit increased impulsivity in the 5CSRT task show escalation of cocaine self-administration (Dalley et al., 2007), compulsive cocaine self-administration (Belin, Mar, Dalley, Robbins, & Everitt, 2008), and reinstatement of cocaine self-administration (Economidou, Pelloux, Robbins, Dalley, & Everitt, 2009).

Like impulsive choice, motor impulsivity is altered by various drugs, and this effect is observed in humans and animals. Alcohol generally impairs inhibitory control in humans (de Wit, Crean, & Richards, 2000; Easdon, Izenberg, Armilo, Yu, & Alain, 2005; Fillmore & Vogel-Spott, 1999; Marczinski, Abroms, Van Selst, & Fillmore, 2005; Marczinski & Fillmore, 2003, 2005a, b; Mulvihill, Skilling, & Vogel-Sprott, 1997; but see Ortner, MacDonald, & Olmstead, 2003) and animals (Feola et al., 2000). Also, cocaine administration increases impulsive action in humans (Fillmore, Rush, & Hays, 2002) and animals (Paine & Olmstead, 2004; van Gaalen, Brueggeman, Bronius, Schoffelmeer, & Vanderschuren, 2006a; Winstanley et al., 2009).

Although impulsive choice and impulsive action are both linked to substance abuse, it should be emphasized that there is evidence that these facets of impulsivity are dissociable. In humans and animals, impulsive choice and impulsive action are not correlated (Broos et al., 2012; Marusich et al., 2011). Also, lesions to the subthalamic nucleus decreases impulsive choice (Winstanley, Baunez, Theobald, & Robbins, 2005) but increase impulsivity as assessed in the 5CSRT task (Baunez et al., 2001) and impair prepotent response inhibition (Weiner, Magaro, & Matell, 2008). Also, damage to OFC

alters delay discounting performance, albeit discrepancies have been reported in the literature (Mar et al., 2011; Mobini et al., 2002; Kheramin et al., 2002, 2004; Rudebeck et al., 2006; Winstanley et al., 2004b), whereas damage to OFC does not affect performance in the 5CSRT task (Chudasama et al., 2003). Furthermore, Experiment 2 showed that HiI and LoI rats had similar DAT densitiy within NAc, whereas a recent study found differential NAcSh DAT density in LoI rats relative to HiI rats performing a 5CSRT task (Jupp et al., 2013). Understanding the precise underlying neuromechanisms involved in distinct facets of impulsivity is important for providing effective pharmacotherapies for those who display different types of impulsive behavior. Results from Experiment 3 suggest that ifenprodil may be an effective treatment for reducing impulsive decision making. It is unknown if ifenprodil will reduce motor impulsivity, although there is evidence that blockade of NR2B subunit with Ro 63-1908 *increases* impulsive action (Burton & Fletcher, 2012; Higgims, Ballard, Huwyler, Kemp, & Gill, 2003). Thus, targeting NR2B subunits may not be an effective treatment for those who display increased motor impulsivity.

Although the current experiments focused on delay discounting, it is worth mentioning that other discounting procedures exist. Specifically, the probability discounting procedure has received some attention. This procedure is similar to delay discounting, but the odds against obtaining the large magnitude reinforcer increase (i.e., the probability of obtaining the reinforcer decreases). There is some dispute as to whether delay and probability discounting measure similar constructs of impulsivity. It has been proposed that delay and probability

discounting reflect a similar underlying process (Myerson & Green, 1995; Rachlin et al., 1991). In support of this proposal, the same mathematical functions (e.g., hyperbolic) can be used to model delay and probability discounting (Rachlin et al., 1991). Also, administration of amphetamine produces similar shifts in delay (van Gaalen et al., 2006b; Winstanley et al., 2003) and probability discounting (Floresco & Whelan, 2009; St Onge & Floresco, 2009). Furthermore, lesions to NAc increase the rate of discounting for delayed (Cardinal et al., 2001) and probabilistic reinforcement (Cardinal & Howes, 2005).

An important consideration is that similar shifts in delay and probability discounting following pharmacological manipulations does not necessarily mean that these tasks reflect the same process. Evidence suggests that delay and probability discounting involve distinct processes, with delay and probability discounting reflecting impulsive choice and risky decision making, respectively (Ainslie, 1975; Kahneman & Tversky, 1979). Although *increased* delay discounting is postulated to reflect impulsive choice (Ainslie, 1975), *decreased* probability discounting is proposed to reflect risky decision making (Kahneman & Tversky, 1979). Thus, drugs that decrease the rate of discounting of delayed and probabilistic reinforcement differentially alter impulsive behavior, with decreased delay discounting reflecting higher self control and decreased probability discounting reflecting increased risky decision making.

In line with this hypothesis, there is some support that delay and probability discounting are dissociable, as manipulating reinforcer magnitude differentially alters discounting of delayed and uncertain reinforcement (Green,

Myerson, & Ostaszewski, 1999), and forebrain depletion of 5-HT increases sensitivity to delayed reinforcement without altering sensitivity to probabilistic reinforcement (Mobini et al., 2000). In addition to the data collected in Experiment 1, a separate group of rats were administered MK-801 and CNQX before performing a probability discounting task. As in delay discounting, MK-801 (0.03 mg/kg) increased responding for the large, uncertain reinforcer, whereas CNQX (5.6 mg/kg) decreased responding. Overall, these results suggest that iGluRs differentially mediate impulsivity, with MK-801 decreasing impulsive choice but increasing risky decision making and CNQX increasing probability discounting without altering delay discounting. Future work will need to assess the effects of ifenprodil on risky decision making to determine if selective NR2B antagonists attenuate risky decision making. Moreover, perhaps probability discounting would be an alternative approach for examining the specific role of DA and Glu systems in impulsive decision making using the current autoradiographic and microinjection techniques.

One caveat to the current studies is that the delay to the large magnitude reinforcer increased across each block of trials. The rate of discounting can be influenced by the order in which delays/odds against are presented (e.g, ascending, descending, or mixed order; Fox et al., 2008; Robles and Vargas 2007, 2008; but see Slezak and Anderson 2009). Furthermore, drug effects can be dependent on the order in which delays are presented (Tanno, Maguire, Henson, & France, 2014). Specifically, Tanno et al. (2014) show that amphetamine and methylphenidate increase choice for the large, delayed

reinforcer when delays are presented in an ascending order, whereas a decrease in choice for the large reinforcer is observed when delays are presented in a descending order. One could argue that the increase in responding for the large magnitude reinforcer observed in Experiments 1 and 3 following NMDA and DA D2-like receptor blockade or DA D1-like receptor activation could reflect an increase in the persistence of choice behavior rather than a change in sensitivity to delay. Future work will need to randomize the order in which delays are presented in order to avoid this potential confound.

Another caveat to the current study relates to the upward shift in the discounting function following MK-801, ifenprodil, SKF 38393, and eticlopride administration. Interpretation of these findings is difficult because we cannot rule out the possibility that the upward shift in discounting was attributed to increased sensitivity to reinforcer magnitude. Indeed, a change in the *A* parameter (sensitivity to reinforcer magnitude) was observed following MK-801 administration in the delay discounting task in Experiment 1. Because the proportion of choices for the large magnitude reinforcer is close to a ceiling (near 1.0) when the delay to its delivery is set at 0 sec, an increase in responding for that reinforcer is difficult to observe following pharmacological manipulations. For example, certain drugs *decrease* responding for a large, delayed/uncertain reinforcer, even when the delay to its delivery is set at 0 sec (Cardinal et al., 2000; Koffarnus et al., 2011; Mendez et al., 2012; van Gaalen et al., 2006b; Winstanley et al., 2005).

Although promising, results from the current experiments are not fully conclusive about the specific role DA and Glu in NAcc, if any, in delay discounting and follow-up experiments are needed. Considering the complex interactions between Glu and monoamine neurotransmitters (DA and 5-HT) within the mesocorticolimbic pathway (see Tzschentke, 2001 for a review), future studies should examine how these interactions control impulsive choice. For example, there is evidence for DA:5-HT interactions to mediate impulsive choice, as DA depletions within NAc block impulsivity induced by a 5-HT_{1A} receptor agonist (Winstanley et al., 2005). Also, there is some evidence for Glu:5-HT interactions, as administration of a mGluR2/3 receptor agonist attenuates 5-HT_{2A}-induced impulsive choice (Wischof et al., 2011). These studies can help further our understanding of the role of the glutamatergic system in impulsive choice.

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Vita

Justin R Yates

Education

2011-Present	Ph.D. candidate, Behavioral Neuroscience and Psychopharmacology Program, Experimental Psychology, University of Kentucky, Lexington, KY
Degree Awarded December 2011	Master of Science in Experimental Psychology, University of Kentucky, Lexington, KY Thesis: *Using Preclinical Models to Assess the Role of Social Influences on Drug Abuse* Mentor: Michael T. Bardo, Ph.D.
Degree Awarded December 2008	Bachelor of Science in Psychology, Georgia College & State University, Milledgeville, GA

Professional Positions

Aug. 2009-Jun. 2010	Research Assistant, Psychology, University of Kentucky, Supervisor: Dr. Michael Bardo
Jan. 2011-May 2011	Teaching Assistant, Psychology, University of Kentucky, Supervisor: Dr. John Curtis
July 2012-Aug. 2013	Research Trainee Pharmaceutical Sciences, University of Kentucky, Supervisor: Dr. Linda Dwoskin
Aug. 2012-Dec. 2012	Part-time Lecturer, Psychological Science, Northern Kentucky University, Supervisor: Dr. Jeff Smith
Aug. 2013-May 2014	Full-time Lecturer Psychological Science, Northern Kentucky University, Supervisor: Dr. Jeff Smith
Aug. 2014-	Assistant Professor, Psychological Science, Northern Kentucky University

Awards, Fellowships, Grants

1. NIDA Predoctoral Traineeship, Department of Pharmaceutical Science and The National Institute of Drug Abuse, University of Kentucky, July 1, 2012-June 30, 2013 (T32 DA016176)

2. NIDA Women & Sex/Gender Junior Investigator Travel Award recipient, The College on Problems of Drug Dependence, 2013

Professional Affiliations

1. 2010, 2012 Midwestern Psychological Association
2. 2010-2013 Society for Quantitative Analysis of Behavior
3. 2010-2013 Bluegrass Chapter of the Society for Neuroscience
4. 2010 American Psychological Association (Division 28)
5. 2012 Delta Epsilon Iota Academic Honor Society
6. 2012 Omicron Delta Kappa

Research Experience

1. Graduate Student, Center for Drug Abuse Research Translation, July 2009-July 2013. Mentor: Dr. Michael T. Bardo, Psychology Department, University of Kentucky.

Service

1. Membership coordinator, Society for Quantitative Analysis of Behavior, 2010-2013

Published Publications

1. Gipson, C.D., **Yates, J.R.**, Beckmann, J.S., Marusich, J.A., Zentall, T.R., & Bardo, M.T. (2011). Social facilitation of d-amphetamine self-administration in rats. *Experimental and Clinical Psychopharmacology*, *19*, 409-419.

2. **Yates, J.R.**, Marusich, J.A., Gipson, C.D., Beckmann, J.S., & Bardo, M.T. (2012). High impulsivity in rats predicts amphetamine conditioned place preference. *Pharmacology Biochemistry & Behavior*, *100*, 370-376.

3. Gipson, C.D., Beckmann, J.S., Adams, Z.W., Marusich, J.A., Nesland, T.O., **Yates, J.R.**, Kelly, T.H., & Bardo, M.T. (2012). A translational behavioral model of mood-based impulsivity: Implications for substance abuse. *Drug and Alcohol Dependence*, *122*, 93-99.

4. **Yates, J.R.**, Darna, M., Gipson, C.D., Dwoskin, L.P., & Bardo, M.T. (2012). Isolation rearing as a preclinical model of attention/deficit-hyperactivity disorder. *Behavioural Brain Research*, *234*, 292-298.

5. **Yates, J.R.**, Beckmann, J.S., Meyer, A.C., & Bardo, M.T. (2013). Concurrent choice for social interaction and amphetamine using

conditioned place preference in rats: Effects of age and housing condition. *Drug and Alcohol Dependence, 129*, 240-246.

Manuscripts in Submission/Preparation

1. **Yates, J.R.**, Perry, J.L., Meyer, A.C., Gipson, C.D., Charnigo, R., & Bardo, M.T. (in revision). Role of medial prefrontal and orbitofrontal monoamine transporters and receptors in an adjusting delay discounting procedure. *Brain Research*.

2. **Yates, J.R.**, Beckmann, J.S., & Bardo, M. T. (in revision). Role of ionotropic glutamate receptors in delay and probability discounting. *Psychopharmacology*.

3. **Yates, J.R.**, Darna, M., Gipson, C.D., Dwoskin, L.P., & Bardo, M.T. (in preparation). Role of dopamine and serotonin transporters in an animal model of negative urgency. *Behavioural Brain Research.*

Scholarly Presentations

1. **Yates, J.R.**, & Bardo, M.T. Impulsivity as a Function of Amphetamine Conditioned Place Preference. Poster Presentation, Bluegrass Chapter of the Society of Neuroscience, Lexington, KY, March 17, 2010.

2. **Yates, J.R.**, & Bardo, M.T. The Effect of Impulsivity on Amphetamine Conditioned Place Preference. Poster Presentation, Center for Clinical & Translational Sciences, Lexington, KY, March 23, 2010.

3. Gipson, C.D., Beckmann, J.S., **Yates, J.R.**, & Bardo, M.T. Social Facilitation as a Preclinical Model of Drug Abuse. Oral Presentation, Midwestern Psychological Association, Chicago, IL, April 29, 2010.

4. **Yates, J.R.**, & Bardo, M.T. Impulsivity Predicts Amphetamine Conditioned Place Preference in Rats. Poster Presentation, Society for Quantitative Analyses of Behavior, San Antonio, TX, May 28, 2010.

5. Gipson, C.D., Perry, J.L., Meyer, A.C., **Yates, J.R.**, Beckmann, J.S., & Bardo, M.T. Role of Dopamine and Serotonin Receptors in Orbitofrontal Cortex on Impulsive Choice in Rats. Poster Presentation, Society for Neuroscience, San Diego, CA, November 14, 2010.

6. **Yates, J.R.**, & Bardo, M.T. The Effects of Amphetamine and Methylphenidate on Conditioned Place Preference in High and Low Impulsive Rats. Poster Presentation, Bluegrass Chapter of the Society of Neuroscience, Lexington, KY, March 31, 2011.

7. **Yates, J.R.**, & Bardo, M.T. Delay Discounting Predicts Differential Sensitivity to Amphetamine Reward, But not Methylphenidate Reward, in Rats. Poster Presentation, Center for Clinical & Translational Sciences, Lexington, KY, April 21, 2011.

8. **Yates, J.R.**, & Bardo, M.T. The Effect of Impulsive Choice on Locomotor Activity and Conditioned Place Preference in Rats Following Administration of Amphetamine or Methylphenidate. Poster Presentation, Society for Quantitative Analyses of Behavior, Denver, CO, May 26, 2011.

9. **Yates, J.R.**, & Bardo, M.T. Relationship between impulsivity and amphetamine conditioned place preference. Poster Presentation, The College on Problems of Drug Dependence, Hollywood, FL, June 23, 2011.

10. Darna, M., **Yates, J.R.**, Bardo, M.T., & Dwoskin, L.P. Individual differences in impulsive action and impulsive choice associated with dopamine and serotonin transporter function in rat medial prefrontal and orbitofrontal cortex. Poster Presentation. Society for Neuroscience, Washington, DC, November 14, 2011.

11. **Yates, J.R.**, Darna, M., Gipson, C.D., Dwoskin, L.P., & Bardo, M.T. Isolation rearing during development as a preclinical model of ADHD. Poster Presentation. Research Conference on Children at Risk, Lexington, KY, March 26, 2012.

12. **Yates, J.R.**, Beckmann, J.S., Meyer, A.C., & Bardo, M.T. Concurrent conditioned place preference for amphetamine vs. social interaction in adolescent rats. Center for Clinical & Translational Sciences, Lexington, KY, March 29, 2012.

13. Darna, M., **Yates, J.,** Bardo, M.T., & Dwoskin, L.P. Individual differences in impulsive action and impulsive choice are associated with dopamine and serotonin transporter function in rat orbitofrontal cortex. Bluegrass Chapter of the Society of Neuroscience, Lexington, KY, March 3o, 2012.

14. **Yates, J.R.**, Beckmann, J.S., & Bardo, M.T. Behavioral economic assessment of price and consumption of cocaine self-administration in high and low impulsive rats. Society for Quantitative Analyses of Behavior, Seattle, WA, May 25, 2012.

15. **Yates, J.R.**, Beckmann, J.S., Meyer, A.C., & Bardo, M.T. Concurrent choice between cues for social interaction and amphetamine in adolescent and adult rats: Effects of housing condition. Research Conference on Children at Risk, KY, April 5, 2013.

16. **Yates, J.R.**, Beckmann, J.S., & Bardo, M.T. Effects of ionotropic glutamate receptor blockade in delay and probability discounting. Blugrass Chapter of the Society of Neuroscience, Lexington, KY, April 8, 2013.

17. **Yates, J.R.**, Beckmann, J.S., & Bardo, M.T. Role of Ionotropic Glutamate Receptors in Delay and Probability Discounting. Oral Presentation, Midwestern Psychological Association, Chicago, IL, May 2, 2013.

18. **Yates, J.R.**, Jennings, F.C., Beckmann, J.S., Meyer, A.C., & Bardo, M.T. Concurrent choice between cues for social interaction and amphetamine in adolescent male and female rats. The College on Problems of Drug Dependence, San Diego, CA, June 17, 2013.

19. Weiss, V.G., **Yates, J.R.,** & Bardo, M.T. Using social cues for cocaine self-administration and cued reinstatement. Bluegrass Chapter of the Society of Neuroscience, Lexington, KY, March 27. 2014.

Justin Ryan Yates
Student's Signature

4/21/2014
Date