2019

Probability Discounting of Lewis and Fischer 344 rats: Strain Comparisons at Baseline and Following Acute Administration of d-Amphetamine

Jenny E. Ozga

West Virginia University, jeozga@mix.wvu.edu

Follow this and additional works at: <https://researchrepository.wvu.edu/etd>

Part of the [Animal Experimentation and Research Commons](#), [Animal Studies Commons](#), [Experimental Analysis of Behavior Commons](#), and the [Health Psychology Commons](#)

Recommended Citation

Ozga, Jenny E., "Probability Discounting of Lewis and Fischer 344 rats: Strain Comparisons at Baseline and Following Acute Administration of d-Amphetamine" (2019). *Graduate Theses, Dissertations, and Problem Reports*. 3948.

<https://researchrepository.wvu.edu/etd/3948>

This Dissertation is protected by copyright and/or related rights. It has been brought to you by the The Research Repository @ WVU with permission from the rights-holder(s). You are free to use this Dissertation in any way that is permitted by the copyright and related rights legislation that applies to your use. For other uses you must obtain permission from the rights-holder(s) directly, unless additional rights are indicated by a Creative Commons license in the record and/ or on the work itself. This Dissertation has been accepted for inclusion in WVU Graduate Theses, Dissertations, and Problem Reports collection by an authorized administrator of The Research Repository @ WVU. For more information, please contact researchrepository@mail.wvu.edu.

Probability Discounting of Lewis and Fischer 344 rats: Strain Comparisons at Baseline and

Following Acute Administration of *d*-Amphetamine

Jenny E. Ozga-Hess

Dissertation submitted
To the Eberly College of Arts and Sciences
at West Virginia University

in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Karen G. Anderson, Ph.D., Chair
Melissa D. Blank, Ph.D.
Regina A. Carroll, Ph.D.
David P. Siderovski, Ph.D.
Cole Vonder Haar, Ph.D.

Department of Psychology

Morgantown, West Virginia
2018

Keywords: probability discounting, uncertainty, risk, choice, rat, amphetamine
Copyright 2018 Jenny E. Ozga-Hess

ABSTRACT

Probability Discounting of Lewis and Fischer 344 rats: Strain Comparisons at Baseline and Following Acute Administration of *d*-Amphetamine

Jenny E. Ozga-Hess

Risky choice can be defined as choice for a larger, uncertain reinforcer over a smaller, certain reinforcer when choosing the smaller alternative maximizes reinforcement. Risky choice is studied using various procedures in the animal laboratory; one such procedure is called probability discounting. There are many variables that contribute to risky decision-making, including biological and pharmacological determinants. The present study assessed both of these variables by evaluating dose-response effects of *d*-amphetamine on risky choice of Lewis (LEW) and Fischer 344 (F344) rats. The probability-discounting procedure included discrete-trials choices between one food pellet delivered 100% of the time and three food pellets delivered following one of varying probabilities. The probability of three food pellets being delivered decreased systematically across blocks within each session. At baseline, risky choice did not differ between LEW and F344. However, choice for LEW became significantly less risky throughout extended training while choice for F344 remained relatively stable over time. *d*-Amphetamine significantly increased risky choice for both rat strains at low-to-moderate doses (0.1 and 0.3 mg/kg), although it did so at a lower dose for F344 (0.1 and 0.3 mg/kg) than LEW (0.3 mg/kg only), suggesting greater behavioral sensitivity to effects of *d*-amphetamine for F344. High doses of *d*-amphetamine (1.0 and 1.8 mg/kg) produced overall disruptions in choice for both strains, indicated by reductions in choice for the larger, uncertain alternative when the probability of delivery was relatively high and increases when the probability was relatively low. Results from the current study stand in contrast to previous reports investigating impulsive choice (i.e., choice involving temporal delays rather than uncertainty) of LEW and F344. Thus, the present work underscores the importance of considering risky and impulsive choice as two separate, but related, behavioral processes.

ACKNOWLEDGEMENTS

I would like to thank Dr. Karen G. Anderson, Dr. Melissa D. Blank, Dr. Cole Vonder Haar, Dr. David P. Siderovski, and Dr. Regina A. Carroll for serving on my dissertation committee and for offering valuable feedback throughout this project. I would like to specifically thank my advisor and mentor, Dr. Karen G. Anderson, for her everlasting support, encouragement, and guidance throughout this project and my graduate career. In addition, I thank Drs. Melissa D. Blank and Cole Vonder Haar for sharing their knowledge of statistics with me. Thank you to my lab-mates, Matt Eckard and Devin Galdieri, as well as Nicholas J. Felicione for always asking the tough questions and making me think critically. Thank you to undergraduate research assistants, Darien Beall and Ashley Richmond, for assisting with data collection. In terms of funding, I'd like to thank the Society for the Advancement of Behavior Analysis as well as the Behavioral and Biomedical Sciences research program for providing funding and other resources (e.g., graphical software) to assist with completion of this project. A very special thank you to my parents, John and Mary Ozga, and siblings, Joseph Ozga and Lindsay Mahan, who have always loved, encouraged, and supported me in every aspect of life. Finally, a very special thank you to my husband, Nicholas Hess, for providing a source of stress relief, making me laugh, and providing endless inspiration throughout the course of this project and my graduate career.

TABLE OF CONTENTS

	Page
LIST OF TABLES.....	v
LIST OF FIGURES.....	vi-vii
INTRODUCTION.....	1
METHOD.....	17
RESULTS.....	25
DISCUSSION.....	31
REFERENCES.....	41
TABLES.....	55
FIGURES.....	60
APPENDIX.....	71

LIST OF TABLES

	Page
Table 1.....	55
Statistical outcomes for all primary outcome measures comparing rat strains at baseline.	
Table 2.....	56
Sessions required to reach stability, indifference odds (IO), log-transformed discounting rates (log h), area under the curve (AUC), win-stay ratios, lose-shift ratios, and frequencies of free-choice omissions (Omit) at baseline for individual rats.	
Table 3.....	57
Statistical analyses for all primary outcome measures following acute d-AMP administration.	
Table 4.....	58
Area under the curve (AUC), discounting rates (log h), and indifference odds (IO) for individual rats following each dose of acute d-AMP.	
Table 5.....	59
Win-stay ratios (WS), lose-shift ratios (LS), and frequencies of free-choice omissions (Omit) for individual rats following each dose of acute d-AMP.	

LIST OF FIGURES

	Page
Figure 1.....	60
Average number of probability-discounting sessions required to reach baseline stability for LEW and F344.	
Figure 2.....	61
Mean percent choice for the large/risky lever (i.e., percent larger-reinforcer choice) as a function of the probability of larger-reinforcer delivery across successive blocks of trials for LEW and F344 across the last five baseline sessions.	
Figure 3.....	62
Mean indifference odds (IO; odds-against value where choice is for each reinforcer option with equal frequency) for LEW and F344 across the last five baseline sessions.	
Figure 4.....	63
Mean log h estimates for LEW and F344 across the last five baseline sessions.	
Figure 5.....	64
Mean AUC for LEW and F344 across the last five baseline sessions.	
Figure 6.....	65
Mean win-stay and lose-shift ratios for LEW and F344 across the last five baseline sessions.	
Figure 7.....	66
Mean percent choice for the large/risky lever (i.e., percent larger-reinforcer choice) as a function of decreasing probabilities of larger-reinforcer delivery across successive blocks of trials for LEW (left panel) and F344 (right panel) across all doses of acute d -AMP.	
Figure 8.....	67
Mean log h estimates for LEW and F344 across all doses of d -AMP.	
Figure 9.....	68
Mean indifference odds (IO) for LEW and F344 across all doses of d -AMP.	

Figure 10.....	69
Mean AUC for LEW and F344 across all doses of <i>d</i> -AMP.	
Figure 11.....	70
Mean win-stay (left) and lose-shift ratios (right) for LEW and F344 across all doses of <i>d</i> -AMP.	

Probability Discounting of Lewis and Fischer 344 rats: Strain Comparisons at Baseline and
Following Acute Administration of *d*-Amphetamine

Impulsivity is a multi-faceted construct that encompasses several distinct behaviors, including motor and choice impulsivity (see Evenden, 1999 for a description of impulsive behaviors). Behavioral paradigms evaluating choice impulsivity may include delayed and/or probabilistic consequences. In the case of choice impulsivity with delayed consequences, choice for a smaller, more immediate reward/reinforcer over a larger, delayed reward/reinforcer is defined as “impulsive.” In the case of choice impulsivity with probabilistic consequences, choice for a larger, uncertain reward/reinforcer over a smaller, certain reward/reinforcer is defined as “risky.” In general, greater impulsive choice in the delay paradigm predicts greater risky choice in the probability paradigm (Madden, Ewan, & Lagorio, 2007; Rachlin, 1990), and both are associated with various behavioral disorders, including substance use and abuse (e.g., Bickel & Marsch, 2001; Bickel et al., 2007; Reynolds, Richards, Horn, & Karraker, 2004), pathological gambling (Madden, Petry, & Johnson, 2009; Petry, 2001), and attention-deficit/hyperactivity disorder (ADHD; e.g., Dai, Harrow, Song, Rucklidge, & Grace, 2016; Drechsler, Rizzo, & Steinhausen, 2010; Yu & Sonuga-Barke, 2016). However, individuals who display greater impulsive choice do not necessarily display greater risky choice, suggesting that there is dissociation between the two behaviors (e.g., Yi, Chase, & Bickel, 2007). Fortunately, there is a large body of research on variables that influence impulsive choice (i.e., choice involving delayed reinforcement). However, risky choice (i.e., choice involving probabilistic reinforcement) is a relatively understudied aspect of impulsivity. Given that risky decision-making can reduce overall access to reinforcement (i.e., choice for a larger, uncertain reinforcer

may not result in reinforcement), which may negatively affect quality of life, understanding the biological and pharmacological bases of risky choice deserves further attention.

Delay- and Probability-Discounting Procedures

In general, impulsive choice is evaluated in the laboratory by using delay-discounting procedures. Delay-discounting procedures involve the presentation of discrete-trials choices between smaller, more immediate reinforcers and larger, delayed reinforcers. With non-human animal subjects, such as rats, choice may be between one food pellet delivered immediately versus three food pellets delivered after a delay (e.g., Anderson & Diller, 2010; Huskinson, Krebs, & Anderson, 2012). In general, when delays to larger-reinforcer delivery are relatively short, choice is nearly exclusive for the larger reinforcer, but as delays to larger-reinforcer delivery increase, choice switches to the smaller, more immediate reinforcer (e.g., Mazur, 1987). When individual choice trials begin after a fixed interval of time (e.g., every 100 s; e.g., Anderson & Diller, 2010; Huskinson et al., 2012), exclusive choice for the larger, delayed reinforcer will maximize reinforcement during a given session. Thus, any choice for the smaller, immediate reinforcer is considered maladaptive.

Delay discounting is described well by Mazur's (1987) hyperbolic discounting model (see Equation 1 below). In this model, V is the subjective value of outcome amount A (e.g., three food pellets), D is the delay to larger-reinforcer delivery, and k is a discounting parameter that varies freely to maximize model fit. Specifically, discounting refers to a change in subjective value based on the delay to the larger reinforcer, where subjective value declines as the delay increases. To obtain delay-discounting functions, subjective value is plotted as a function of the increasing delay to larger-reinforcer delivery. Relatively steeper discounting functions (i.e., larger k values) indicate greater delay discounting and greater impulsive choice (Mazur, 1987).

Importantly, Mazur's (1987) hyperbolic discounting model theorizes that the discounting rate decreases as a function of increasing delays to larger reinforcer delivery, accounting for preference reversals.

$$V = \frac{A}{1+kD} \quad (1)$$

Impulsive choice, evaluated using delay-discounting procedures, has been studied extensively in recent years. Given that impulsive choice is considered by many to be a hallmark of drug addiction (e.g., Alvors, Gregson, & Ross, 1993; Bickel, Koffarnus, Moody, & Wilson, 2014; Petry, Bickel, & Arnett, 1998; Stein et al., 2016), variables that influence delay discounting are of continued interest. However, due to the public-health relevance of risky choice to several behavioral disorders, this relatively understudied aspect of impulsivity warrants further consideration.

An example of risky choice is choosing \$500 with 40% chance of delivery versus choosing \$100 with 100% chance of delivery. There are several procedures for evaluating risky choice in the non-human animal laboratory, including the rat gambling task, risky decision-making task, and probability discounting (see Appendix for a further description of alternative procedures). Because delay discounting is considered the "gold standard" for evaluating impulsive choice (see Bickel et al., 2014 for a review), a significant advantage of using probability discounting to evaluate risky choice, rather than an alternative procedure, is that it is more analogous to delay discounting. In general, probability-discounting procedures involve the presentation of discrete-trials choices between smaller, certain reinforcers and larger, uncertain reinforcers. In experimental research using rats as subjects, choice may be between one food pellet delivered with 100% probability and four food pellets delivered with some lesser probability. In general, when the probability of larger-reinforcer delivery is relatively high,

choice is nearly exclusive for the larger reinforcer. As the probability of larger-reinforcer delivery decreases, choice switches to the smaller, certain option (e.g., Rachlin, Raineri, & Cross, 1991). In contrast to delay discounting, in which optimal choice is always for the larger, delayed reinforcer, optimal choice (i.e., choice that will maximize reinforcement) during probability-discounting procedures depends upon the probability associated with larger-reinforcer delivery (e.g., Cardinal & Howes, 2005; St. Onge & Floresco, 2009; St. Onge et al., 2010). The probability value at the maladaptive break-even point depends upon the magnitudes of both reinforcer options. For example, when choice is between one food pellet delivered with 100% probability and four food pellets delivered with one of varying probabilities, choice for the smaller, certain reinforcer is considered maladaptive when the probability of larger-reinforcer delivery is 50% or greater (e.g., St. Onge & Floresco, 2009; St. Onge et al., 2010). However, when the probability of larger-reinforcer delivery is less than 50%, choice for the larger, uncertain reinforcer is considered maladaptive (e.g., St. Onge & Floresco, 2009; St. Onge et al., 2010).

Similar to delay discounting, Mazur's (1987) hyperbolic discounting model describes choice during probability-discounting procedures well (Rachlin et al., 1991). In Equation 1, k is replaced with h (a free parameter) and D is replaced with θ , which is the odds against larger-reinforcer delivery. Odds against larger-reinforcer delivery are calculated using Equation 2, where p is the probability of larger-reinforcer delivery.

$$\theta = \frac{1-p}{p} \quad (2)$$

In this instance, discounting refers to a change in subjective value based on the odds against larger-reinforcer delivery, where subjective value declines as odds against larger-reinforcer delivery increase. Comparable to delay discounting, subjective value is graphed as a function of

increasing odds against larger-reinforcer delivery (or decreasing probability) to obtain probability-discounting functions. However, in contrast to delay discounting, steeper probability-discounting functions (i.e., larger h values) indicate more probability discounting and less risky choice (Rachlin et al., 1991). According to Rachlin et al. (1991), odds-against larger-reinforcer delivery functions in a similar manner to delays in Equation 1, and that the discounting rate during probability discounting decreases as a function of increasing odds against larger reinforcer delivery, accounting for preference reversals.

Evidence supporting that the same mathematical model describes delay and probability discounting suggests that they may reflect a single discounting process (e.g., Green & Myerson, 1996; Rachlin, Logue, Gibbon, & Frankel, 1986). In addition, it has been proposed that delays influence probability discounting indirectly, given that choice for an uncertain reinforcer may not result in reinforcer delivery (e.g., Adriani & Laviola, 2006). Not receiving reinforcement on some trials results in a delay to reinforcement delivery (e.g., Adriani & Laviola, 2006). Alternatively, probability may influence delay discounting indirectly, in that longer delays may be associated with subjective uncertainty of reinforcer delivery (e.g., Cardinal, 2006; Rotter, 1954). However, aside from being described well by the same quantitative model (Mazur, 1987), delay and probability discounting appear to be distinct processes (see Green & Myerson, 2004 for a review). For example, when the magnitude of the larger reinforcer is increased, delay discounting decreases (i.e., impulsive choice decreases), but probability discounting either increases (i.e., risky choice decreases) or remains unchanged (Christensen, Parker, Silberberg, & Hursh, 1998; Green, Myerson, & Ostaszewski, 1999; Myerson, Green, & Morris, 2011; Terrell et al., 2014). In addition, when Hinvest and Anderson (2010) evaluated real versus hypothetical monetary rewards with human subjects, delivery of real rewards reduced delay discounting

relative to delivery of hypothetical rewards, but had no effect on probability discounting. Thus, although there is a large body of research evaluating delay discounting, probability discounting should continue to be studied as a separate process.

Dependent Measures. When delays to or odds against larger-reinforcer delivery are altered systematically (i.e., either increased or decreased) within sessions, the primary dependent measure is percent larger-reinforcer choice at each delay duration or odds-against value (e.g., Cardinal & Howes, 2005; Evenden & Ryan, 1996; 1999). Percent larger-reinforcer choice is plotted as a function of increasing delay duration or odds against to obtain delay or probability-discounting curves, respectively. From these curves, the hyperbolic discounting model shown in Equation 1 (Mazur, 1987) can be fit to the data to obtain discounting functions, and discounting rates (k or h parameters from Equation 1), as well as indifference points, can be estimated from delay or probability-discounting functions, respectively (e.g., Huskinson, Krebs, & Anderson, 2012; Mobini, Chiang, Ho, Bradshaw, & Szabadi, 2000). In general, larger discounting rates (k or h values) indicate steeper discounting (i.e., more impulsive choice and less risky choice).

An indifference point is defined as the delay duration or odds-against value where choice is for each reinforcer option with equal frequency (i.e., percent larger-reinforcer choice is 50%; Mazur, 1987). Generally, for both delay- and probability-discounting functions, a smaller indifference point indicates greater discounting (i.e., more impulsive choice and less risky choice) and a larger indifference point indicates less discounting (i.e., less impulsive choice and more risky choice). Finally, area under the discounting curve (AUC) can be calculated using the method proposed by Myerson, Green, & Warusawitharana (2001). Using AUC as a dependent measure avoids some potential problems associated with using a theoretically driven model of discounting, such as obtaining data from individual subjects that are fit poorly by the hyperbolic

model (Myerson et al., 2001). In general, a smaller AUC for delay and probability discounting indicates greater discounting relative to a larger AUC (i.e., more impulsive choice and less risky choice; Myerson et al., 2001).

An additional measure for assessing probability discounting is win-stay/lose-shift analysis (see Data Analysis section for a full description). To conduct this analysis, individual choice trials are evaluated based on the choice and outcome of the preceding trial (i.e., reinforcement or no reinforcement). This analysis helps to determine whether behavior perseverates on the larger, uncertain alternative following reinforcer delivery on that alternative during the preceding trial (i.e., a “win”), and if choice switches to the smaller, certain alternative when a reinforcer is not delivered on the larger, uncertain alternative on the preceding trial (i.e., a “loss”). Win-stay performance is indicative of sensitivity to reward, similar to “preference pulses”—brief periods of heightened preference for the response option last associated with reinforcer delivery—that are observed during free-operant concurrent-schedule arrangements (e.g., Davison & Baum, 2002). In contrast, lose-shift performance suggests a negative-feedback function with larger ratios being indicative of greater loss aversion (i.e., more switching to the smaller, certain alternative following a “loss;” Stopper & Floresco, 2011; Stopper, Green, & Floresco, 2014).

Neurological Contributions to Discounting

In addition to environmental variables such as those discussed above (e.g., reinforcer magnitude), biological variables also influence choice during delay- and probability-discounting procedures. In particular, monoaminergic signaling in brain regions such as the prefrontal cortex (PFC), the nucleus accumbens (NuAc), the striatum, and the hippocampus may contribute differentially to such task performance (see Cardinal, 2006 for a review). Although the majority

of work aimed at isolating the neurological mechanisms by which discounting is affected has focused locally rather than taking a widespread approach, it is important to note that all of the regions discussed below communicate with one another and thus, influencing neurotransmitter signaling in one area almost certainly leads to downstream effects on alternative regions (e.g., Jenni et al., 2017; St Onge et al., 2012; Stopper & Floresco, 2014).

Dopaminergic Signaling. Given that dopamine (DA) efflux in the PFC is associated with choice during delay- and probability-discounting procedures (Floresco, 2013; St Onge et al., 2012; Winstanley, Theobald, Dalley, Cardinal, & Robbins, 2006), involvement of discrete sub-regions of the PFC have been identified, including the medial PFC (mPFC; St Onge & Floresco, 2010; Stopper et al., 2014; Yates et al., 2014) and the orbitofrontal cortex (OFC; Abela & Chudasama, 2013; Ishii et al., 2015; St Onge and Floresco, 2010; Yates et al., 2014). In regard to the mPFC, when DA D2-receptor agonists are administered directly via microinfusion, probability discounting decreases (i.e., risky choice increases), yet delay discounting remains unaffected (St Onge, Abhari, & Floresco, 2011; Yates et al., 2014). In contrast, DA D2-receptor antagonists impair decision making on probability-discounting tasks—increasing choice for the larger, risky option at low probabilities of larger reinforcer delivery and increasing choice for the smaller, certain option at high probabilities of larger reinforcer delivery (St Onge et al., 2011). However, these same D2-receptor antagonists increase impulsive choice on delay-discounting tasks (Yates et al., 2014). In contrast to effects of drugs targeting D2 receptors, local injections of D1 antagonists and agonists increase or decrease probability discounting (i.e., reduce or increase risky choice, respectively), respectively (St. Onge et al., 2011) while neither affect delay discounting. Together, results following local mPFC injections of D1- and D2-like drugs suggest

important, yet dissociable, roles for D1 and D2 receptors in choice during delay- and probability-discounting procedures.

In contrast to the mPFC, DA transmission in the OFC appears to be less involved in both types of discounting assessments. When DA is depleted in the OFC, or when D1 or D2 drugs (both agonists and antagonists) are infused locally into the OFC, choice is unaffected across delay- and probability-discounting procedures (Mai & Hauber, 2015; Mai et al., 2015; Yates et al., 2014). However, following lesions to the OFC, probability discounting of male Long-Evans rats increases while delay discounting is unaffected compared to rats with sham lesions, suggesting an important role for the OFC in choice during probability-discounting procedures (Abela & Chudasama, 2013). Thus, although DA transmission in the OFC may not contribute to probability discounting specifically (Mai & Hauber, 2015; Mai et al., 2015), the OFC remains a vital contributor to choice during such procedures.

To further parse OFC sub-region effects on discounting, Stopper et al. (2014) reversibly inactivated the medial sub-region of the OFC with baclofen and muscimol (both gamma-aminobutyric acid (GABA) agonists), which led to a reduction in probability discounting (i.e., more risky choice), but no effect on delay discounting (Stopper et al., 2014). In contrast, when the lateral OFC was inactivated, delay discounting was affected differentially based on baseline discounting as well as the presence of delay cues (i.e., greater delay discounting decreased and less discounting was unaffected when the delay was un-cued whereas less discounting was increased and greater discounting was unaffected when the delay was cued; Zeeb, Floresco, & Winstanley, 2010), but probability discounting was unaffected (St. Onge & Floresco, 2010). Together, it seems as though the OFC plays an important role in both types of discounting but may do so via different mechanisms.

In addition to influence from the PFC and its sub-regions, the NuAc also plays a vital role in performance on delay- and probability-discounting tasks. When DA is depleted in the NuAc, probability discounting is not affected (Mai & Hauber, 2012), although local infusions of DAergic compounds into the NuAc do affect choice during both types of procedures (Orsini et al., 2017; Stopper et al., 2013; Yates & Bardo, 2017). In regard to delay discounting, acute local injections of a non-selective DA indirect agonist into the NuAc result in alterations of choice that are dependent upon the way in which delays are presented (i.e., increased impulsive choice when delays are presented in an ascending sequence and reduced impulsive choice when presented in a descending sequence; Orsini et al., 2017). However, it is unclear from the study by Orsini et al. (2017) whether effects of the DA indirect agonist in the NuAc on delay discounting were due to specific DA receptor subtypes. Thus, Yates and Bardo (2017) administered a selective D1 agonist, a D1 antagonist, a D2 agonist, or a D2 antagonist directly into the NuAc to parse receptor-specific effects. Out of the compounds tested, the D1 antagonist was the only one to produce a significant effect (i.e., increased impulsive choice) on delay discounting (Yates & Bardo, 2017), suggesting that D1, but not D2, receptors in the NuAc contribute to delay discounting.

In regard to probability discounting, Stopper et al. (2013) administered a selective D1 antagonist, a D1 agonist, a D2 antagonist, a D2 agonist, a D2/D3 agonist, or a D3 agonist directly into the NuAc to evaluate receptor-specific effects. The D1 antagonist increased probability discounting (i.e., reduced risky choice) whereas the D1 agonist optimized decision making (i.e., increased risky choice when the probability of larger-reinforcer delivery was high and reduced risky choice when the probability was low; Stopper et al., 2013). In contrast to the influence of D1 transmission on probability discounting, the D2 antagonist, D2 agonist, and D2/D3 agonist

had no effect on choice (Stopper et al., 2013), suggesting the D1, but not D2, receptors in the NuAc contribute to probability discounting. Together, results following local injections imply that DA transmission in the NuAc contributes to choice during delay- and probability-discounting procedures and in particular, D1 activation plays a prominent role in both assessments.

When divided into shell and core sub-regions, DAergic transmission in the NuAc core affects choice during delay- and probability-discounting procedures (Mai et al., 2015; Moschak & Carelli, 2017; Yates & Bardo, 2017), while it appears that transmission in the shell may not (Mai et al., 2015; Mai & Hauber, 2015). Following lesions to the NuAc core, delay discounting increased for male Wistar rats (i.e., greater impulsive choice; Pothuizen, Jongen-Relo, Feldon, & Yee, 2005) whereas identical lesions increased probability discounting in male Long-Evans rats (i.e., less risky choice; Cardinal & Howes, 2005; Stopper & Floresco, 2011). In contrast, lesions to the NuAc shell did not affect behavior on either discounting task in male Wistar rats (Pothuizen et al., 2005) and DA receptor blockade in the NuAc shell of male Lister-hood rats had no effect on probability discounting (Mai et al., 2015). Together, results suggest that the NuAc core, but not the NuAc shell, is involved in delay and probability discounting.

In addition to the PFC and NuAc, ventral hippocampal lesions increase delay discounting of male Long-Evans rats (e.g., Abela & Chudasama, 2013; Cheung & Cardinal, 2005) while having no effect on probability discounting (Abela & Chudasama, 2013). Similarly, DAergic lesions to the dorsolateral striatum are associated with increased delay discounting in male Sprague-Dawley rats (e.g., greater impulsive choice; Tedford, Persons, & Napier, 2015) but similar lesions do not affect probability discounting in male Wistar rats (Yang & Liao, 2015). Collectively, results from studying region-specific effects on choice suggest that biology may

contribute differentially to delay and probability discounting, which supports the view that delay and probability discounting are distinct processes. Importantly, differential contributions from the PFC, NuAc, hippocampus, and striatum during delay and probability discounting may influence how additional variables, such as drugs, affect discounting.

Serotonergic Signaling. Although the majority of pharmacological manipulations during discounting procedures have focused on DA, there has been some work suggesting that serotonin (5-HT) transmission is also involved in discounting. For example, when rats were exposed to an L-typtophan depleted diet, probability discounting was reduced (i.e., greater risky choice) compared to rats that had a normal diet (Koot et al., 2011), suggesting that 5-HT is involved in risk-taking. However, assessment after sacrifice suggested that rats with a depleted diet experienced less 5-HT synthesis as well as less DA turnover compared to rats with a normal diet. Therefore, effects of the depleted diet on discounting may have been an effect of DA rather than 5-HT per se. Indeed, when 5-HT was depleted centrally via pharmacological manipulation, delay discounting increased (i.e., greater impulsive choice) while probability discounting was unaffected for female Wister rats (Mobini et al., 2000), suggesting that 5-HT may play a role in delay, but not probability, discounting. However, in contrast, Ishii, Ohara, Tobler, Tsutsui, and Iijima (2015) suggest that effects of 5-HT on probability discounting may be receptor- and region-specific. Specifically, probability discounting decreases following acute local injections of a 5-HT_{1A} antagonist into the OFC, but is unaffected following acute local injections of a 5-HT_{2A} antagonist (Ishii et al., 2015). Results from Ishii et al. (2015) suggest a role for 5-HT_{1A} in the OFC, but that 5-HT_{2A} in the OFC may not influence probability discounting. Given the limited evidence regarding 5-HT transmission and discounting, it is currently unclear whether 5-

HT signaling in the mPFC, NuAc, hippocampus, and/or striatum contributes to choice during discounting procedures.

Noradrenergic Signaling. Similar to 5-HT, the potential role of norepinephrine (NE) in discounting is less clear than that of DA. In regard to delay discounting, acute inhibition of global NE reuptake has no effect on choice (Paterson, Wetzler, Hackett, & Hanania, 2012; Yates et al., 2014) while chronic inhibition during adolescence decreases delay discounting of rats during adulthood (Sun, Cocker, Zeeb, & Winstanley, 2012). In regard to probability discounting, acute inhibition of global NE reuptake increases risky choice—an effect that is attenuated by global NE receptor blockade (Yang, Pan, & Li, 2016). However, Montes, Stopper, and Floresco (2015) suggest that effects of NE reuptake inhibition on probability discounting may be baseline-dependent—more probability discounting at baseline is decreased while less probability discounting is unaffected. Given the limited work that has been done on NE and discounting, it is currently unclear whether NE plays a significant role in choice during such procedures. In addition, the work that has been conducted thus far has included only systemic drug administration, which makes it ambiguous whether NE signaling in the brain regions described above (or others) play a prominent role in choice during discounting procedures.

Lewis and Fischer 344 Rats

Two rat strains that may contribute to understanding biological contributions to choice impulsivity are Lewis (LEW) and Fischer 344 (F344) rats. It has been suggested that LEW and F344 are a valuable model of genetic vulnerability to drug addiction among other behavioral disorders that include an impulse-control component (see Cadoni, 2016 for a review). LEW and F344 differ substantially in various monoaminergic systems, including DA, 5-HT, and NE. In regard to DA, LEW have fewer DA transporters in the striatum and NuAc, fewer DA D₃

receptors in the NuAc shell, and fewer DA D₂ receptors in the striatum and NuAc core relative to F344 (Flores, Wood, Barbeau, Quirion, & Srivastava, 1998). For 5-HT, LEW have lower basal 5-HT levels in the NuAc core and PFC, as well as fewer 5-HT receptors in the PFC and hippocampus relative to F344 (Selim & Bradberry, 1996). Although there is limited evidence regarding NE system function in LEW and F344, Herradon, Ezquerro, Morales, Franklin, Silos-Santiago, and Alguacil (2006) suggest that, compared to LEW, NE receptors are lower in the hippocampus and higher in the hypothalamus of F344.

Given the importance of the NuAc core, PFC, hippocampus, and striatum in delay discounting (e.g., Abela & Chudasama, 2014; Basar et al., 2010; Besson et al., 2010; Cheung & Cardinal, 2005; Dalley et al., 2007; Moreno et al., 2013; Pothuizen et al., 2005), differences in monoaminergic systems in these regions between LEW and F344 are consistent with greater delay discounting (i.e., greater impulsive choice) in LEW compared to F344 (Anderson & Diller, 2010; Anderson & Woolverton, 2005; Huskinson & Anderson, 2010; Huskinson et al., 2012; Madden, Smith, Brewer, Pinkston, & Johnson, 2008; Stein, Pinkston, Brewer, Francisco, & Madden, 2012, but also see Richards et al., 2013 and Wilhelm & Mitchell, 2009 for exceptions). However, it is unclear whether biological differences between LEW and F344 will also affect probability discounting.

Effects of *d*-Amphetamine (*d*-AMP) on Discounting

d-AMP is a non-selective DA indirect agonist that acts on the central nervous system by stimulating pre-synaptic DA release while simultaneously blocking DA transporters (e.g., Lieberman & Tasman, 2006, p. 176) and stimulating release of 5-HT and NE (e.g., Holmes & Rutledge, 1976; Kankaanpää, Meririnne, Lillsunde, & Seppälä, 1998; Kuroki, Ichikawa, Dai, & Meltzer, 1996). Although *d*-AMP acts primarily on the DA system, Winstanley, Dalley,

Theobald, and Robbins (2003) and Winstanley, Theobald, Dalley, and Robbins (2005) suggest that effects of *d*-AMP on 5-HT release is a vital component of its effects on delay discounting, in which global 5-HT depletion or 5-HT_{1A} stimulation prior to *d*-AMP administration attenuates effects of *d*-AMP. Thus, 5-HT may play an important role in effects of *d*-AMP on delay discounting, but it is unclear whether 5-HT has a similar effect for probability discounting. In addition, there is no evidence to designate whether NE contributes to *d*-AMP's effects on either type of choice. Due to differential contributions (or lack thereof) of 5-HT and NE to delay and probability discounting generally, it is possible that effects of *d*-AMP on delay and probability discounting will differ. In addition, because LEW and F344 differ in DA, 5-HT, and NE receptor densities in various brain regions, it is possible that effects of *d*-AMP on discounting will differ between rat strains.

In general, effects of *d*-AMP on delay discounting appear to be baseline dependent (see Bickel, Quisenberry, & Snider, 2016 for a review). That is, when delay discounting is greater at baseline, *d*-AMP reduces delay discounting (e.g., Huskinson et al., 2012; Krebs & Anderson, 2012; Perry, Stairs, & Bardo, 2008; Wooters & Bardo, 2011), and either increases or has no effect on delay discounting that is lower at baseline (e.g., Huskinson et al., 2012; Krebs & Anderson, 2012; Perry et al., 2008; Wooters & Bardo, 2011). Delay discounting is greater for LEW relative to F344 prior to any environmental manipulation(s) (e.g., Anderson & Diller, 2010; Anderson & Woolverton, 2005; Huskinson & Anderson, 2012; Huskinson et al., 2012). As evidence of baseline dependency, acute *d*-AMP administered via intraperitoneal injection reduces delay discounting for LEW but does not affect delay discounting for F344 (Huskinson et al., 2012). However, differences in 5-HT and/or NE transmission between LEW and F344 may contribute to previously observed strain differences in delay discounting (e.g., Anderson &

Diller, 2010; Anderson & Woolverton, 2005; Huskinson & Anderson, 2010; Huskinson et al., 2010; Madden et al., 2008; Stein et al., 2012), as well as effects of *d*-AMP on delay discounting of LEW and F344 (Huskinson et al., 2012; Winstanley et al., 2003; 2005), but may not influence probability discounting.

In three separate evaluations of probability discounting using male Long-Evans and Lister-hooded rats, *d*-AMP consistently reduced probability discounting when odds against larger-reinforcer delivery were presented in a descending sequence (i.e., increased choice for the larger, risky alternative; Mai et al., 2015; St. Onge & Floresco, 2009; St. Onge, Chiu, & Floresco, 2010). However, when odds against larger-reinforcer delivery were presented in an ascending sequence, *d*-AMP increased probability discounting (St. Onge et al., 2010). Although baseline choice did not differ between rats that experienced ascending and descending probability sequences, differential effects of *d*-AMP on probability discounting based on probability presentation may be evidence of baseline dependency. In fact, Kaminski and Ator (2001) suggest that effects of *d*-AMP on probability discounting may be baseline dependent, in which greater probability discounting decreases and less probability discounting increases or remains unchanged for individual male Long-Evans rats following acute intraperitoneal injection of *d*-AMP. However, research is lacking in terms of potential interactions between biology and *d*-AMP. Therefore, evaluating effects of *d*-AMP on probability discounting in genetically distinct rat strains, such as LEW and F344, may prove beneficial.

Statement of the Problem

Prior research supports a role of biology in delay and probability discounting (i.e., impulsive and risky choice, respectively). Two rat strains that may contribute to understanding biological contributions to discounting are LEW and F344, which differ in DA, 5-HT, and NE

transmission. Delay discounting is also greater (i.e., more impulsive choice) for LEW relative to F344 prior to environmental manipulation(s). However, it is unclear whether strain differences between LEW and F344 that are apparent during delay discounting will also emerge when assessing probability discounting. Research suggests that DA is involved in both, delay and probability discounting, but research on 5-HT and NE involvement is mixed. Given that differences in 5-HT and NE between LEW and F344 may contribute to delay discounting, it is possible that strain differences observed with delay discounting will be diminished or reversed when assessing probability discounting.

Furthermore, effects of *d*-AMP on delay discounting appear to be dependent upon baseline choice and/or biology in LEW and F344. Specifically, acute *d*-AMP reduces delay discounting of LEW and increases or has no effect on delay discounting of F344. There is some evidence that suggests effects of *d*-AMP on probability discounting may also be baseline dependent. Based on this prior research, two outcomes were hypothesized: (1) probability discounting would be greater for F344 relative to LEW at baseline (i.e., more risky choice for LEW relative to F344); (2) effects of *d*-AMP on probability discounting of LEW and F344 would be baseline dependent, in that *d*-AMP would increase probability discounting for LEW (i.e., reduce risky choice) and reduce probability discounting for F344.

Method

Subjects

Eight experimentally naïve male LEW and eight experimentally naïve male F344 rats served as subjects. All rats were housed individually in controlled environmental conditions (temperature, 24°C; 12-h reverse light/dark cycle), with continuous access to water in home cages. Sessions were conducted at approximately the same time each day, five days per week

(Monday-Friday). Rats were fed approximately 15 g of food approximately 30 min following sessions, resulting in approximately 22 h of food restriction.

Apparatus

Sessions were conducted in eight standard operant-conditioning chambers for rats, each enclosed in a melamine sound-attenuating cubicle (Med Associates, VT). Each chamber contained a working area of 30.5 cm by 24.5 cm by 21.0 cm, a grid floor, and a 45-mg pellet dispenser with a pellet receptacle centered between two retractable response levers. Levers were 11.5 cm apart from each other and required at least 0.25 N of force for a response to be recorded. Levels are 4.8 cm wide, protrude 1.9 cm into the chamber, and were elevated 8 cm from the grid floor. Two 28-V stimulus lights, 2.5 cm in diameter, were placed approximately 7 cm above each lever. Each chamber had a 28 V houselight on the wall opposite to the working wall, and a ventilation fan to circulate air and to mask extraneous noise. Data collection and programmed consequences were controlled by a personal computer equipped with Med-PC software (Med Associates, VT).

Procedure

Lever-press training. Both levers were extended into the chamber and food pellets were delivered on a variable-time (VT) fixed-ratio (FR) 1 conjoint schedule of reinforcement. Each lever-press training session terminated following 60 food-pellet deliveries. After five sessions, if lever pressing was not acquired, it was shaped by successive approximations. After lever-press acquisition, an alternating FR 1 schedule of reinforcement went into effect. During alternating FR 1 sessions, one lever was extended into the chamber with a cue light illuminating over it. A press on this lever resulted in the delivery of one food pellet. The FR 1 contingency and cue light alternated between the two levers after every five food-pellet deliveries. Alternating FR 1

sessions terminated following 40 food-pellet deliveries, and continued until lever pressing was consistent on both levers.

Probability training procedure. Prior to starting the probability-discounting procedure (described below), a probability training procedure was put into effect to familiarize behavior with the probabilistic nature of the full procedure. During probability training, 90 trials were presented per session and each trial began every 40 s, resulting in varying ITIs. During each trial, one lever (randomly determined) was extended into the chamber and a response on that lever resulted in the delivery of one food pellet with 50% probability. Probability training was in effect for at least five sessions and continued until there were fewer than 10 omitted trials for three consecutive sessions. After meeting this criterion, the full probability-discounting procedure went into effect for the remainder of the experiment.

Probability-discounting procedure. All probability-discounting sessions began with a 10-min blackout period, followed by five blocks of 20 trials each. The start of each block was signaled by five 0.5-s flashes of the houselight, followed by 12 forced-exposure trials. During each forced-exposure trial, one random lever was extended into the chamber with the cue light above it illuminated. After one response on the extended lever, either one or three food pellets were delivered, either with 100% probability (one food pellet) or with one of varying probabilities (three food pellets), depending on the reinforcer magnitude and probability associated with the lever. The houselight flashed for 0.1 s as each food pellet was delivered. Rat strains were counterbalanced, such that half LEW and half F344 received one food pellet by pressing the right lever and half of each strain received one food pellet by pressing the left lever. Levers correlated with each reinforcer magnitude (one or three food pellets) remained constant for individual rats throughout the experiment. After food pellet(s) were delivered, the lever

retracted and a 20-s inter-trial interval (ITI) began. Lever presentation during forced-exposure trials was sampled at random with replacement, with the constraints that the same lever not be presented on more than two consecutive trials and that each lever be presented six times during a single block. In addition, the probability of larger-reinforcer delivery during forced-exposure trials was dependent across the trials in a block. For example, if the probability of larger-reinforcer delivery is 33.3% for a given block of trials, the larger reinforcer was delivered on two, and only two (randomly selected), out of the six forced-exposure trials.

Forced-exposure trials were followed by eight free-choice trials, in which both levers were extended into the chamber, with cue lights illuminating over each, and choice was recorded. The probability of larger-reinforcer delivery was independent during free-choice trials, in which the probability of delivery on any given trial was the same regardless of the outcome of the preceding trial. After one response on either lever, cue lights turned off, levers retracted, and one or three food pellets were delivered either with 100% probability (one food pellet) or with one of varying probabilities (three food pellets), dependent upon which lever was pressed. The houselight flashed for 0.1 s as each food pellet was delivered. After food pellet(s) were delivered, a 20-s ITI began. If a response did not occur within 10 s of the onset of a trial for either type (i.e., forced or free), it was recorded as an omission. If an omission occurred, the houselight and cue light(s) turned off, lever(s) retracted, and a 20-s ITI began. Sessions were terminated after 100 total trials (60 forced-exposure and 40 free-choice), or 60 min, whichever occurred first. Any sessions with more than 20 omissions during free-choice trials were excluded from data analyses.

Baseline assessment. Baseline probability discounting for individual rats was established by reducing the probability of larger-reinforcer delivery (i.e., increasing the odds against larger-

reinforcer delivery) within each session, across successive blocks of trials. During the first block of trials, an FR 1 contingency was in effect for presses on both levers, with both reinforcer magnitudes (one or three food pellets) delivered with 100% probability ($\theta = 0.0$). The probability of larger-reinforcer delivery decreased across blocks (i.e., the odds against larger-reinforcer delivery increased across blocks) according to the sequence: 100% ($\theta = 0.0$), 66.7% ($\theta = 0.5$), 33.3% ($\theta = 2.0$), 16.7% ($\theta = 5.0$), and 8.3% ($\theta = 11.0$; Cardinal & Howes, 2005).

A minimum of 20 sessions were conducted to obtain baseline probability-discounting curves for individual rats and continued until choice was stable. To evaluate stability, visual inspection and two-way analysis of variance (ANOVA) were used according to the following criteria across the last five baseline sessions: no increasing or decreasing trends in total percent choice for the larger-reinforcer during free-choice trials, an average of at least 80% choice (seven out of eight free-choice trials) for the larger reinforcer during the 100%-probability block, the presence of a main effect of trial block, and the absence of a main effect of session as well as the absence of an interaction between session and trial block.

Acute d-AMP administration. After stable baseline probability discounting was established for individual rats, acute effects of *d*-AMP on probability discounting were evaluated. *d*-AMP and its vehicle control (saline) were administered via intraperitoneal injection immediately before sessions in 0.0, 0.1, 0.3, 1.0, and 1.7 mg/kg doses. Control sessions were on Mondays and Thursdays, and drug or vehicle administrations occurred on Tuesdays and Fridays, given that responding during the 100%-probability block was at least 80% and total percent larger-reinforcer choice was within the range of the last five baseline sessions during the most recent control session. Saline was administered at least twice prior to *d*-AMP administration to evaluate behavioral interference due to injection procedures alone. All doses were administered

in a decreasing then increasing sequence, and each dose was administered at least twice.

Additional administrations occurred if there is substantial variability in choice between the two initial administrations.

Drugs. Each dose of *d*-AMP (Sigma-Aldrich) was delivered in a 0.9% saline vehicle at a concentration of 1.0 mg/mL. Doses were delivered in a volume of 1.0 mL/kg.

Data Analysis

Dependent Measures.

Sessions to stability. Number of sessions required to reach baseline stability was calculated and compared across rat strains. All probability-discounting sessions that occurred prior to the first saline injection were considered part of the baseline phase.

Percent larger-reinforcer choice. The primary dependent variable was percent larger-reinforcer choice, and was calculated per block by dividing the number of free-choice responses on the lever associated with the larger, uncertain reinforcer, by the total number of free-choice responses made in a single block. To maximize reinforcement during a given session, choice should be for the smaller, certain reinforcer when the probability of larger-reinforcer delivery is less than 33.3% and should be for the larger, probabilistic reinforcer when the probability of larger-reinforcer delivery is greater than 33.3%. Thus, choice for the larger, uncertain alternative was considered optimal or maladaptive based upon the probability associated with it. Percent larger-reinforcer choice was plotted as a function of the increasing odds against larger-reinforcer delivery (i.e., decreasing probability of larger-reinforcer delivery) to obtain probability-discounting curves.

Discounting rate (h). Mazur's (1987) hyperbolic-discounting model was fit to mean percent larger-reinforcer choice data for individual rats (see Equation 1). Mean percent larger-

reinforcer choice during the 100% probability block was used as an estimate of the A parameter and estimates of h were interpolated from model fits.

Indifference odds (IO). IOs were interpolated by fitting Mazur's (1987) hyperbolic-discounting model (see Equation 1) to mean percent larger-reinforcer choice data for individual rats. IOs were defined as the odds against larger-reinforcer delivery in which choice was for each reinforcer option with equal frequency (i.e., percent larger-reinforcer choice was 50%). In general, larger IO values indicate more risky choice, and smaller IO values indicate less risky choice.

Area under the curve (AUC). From probability-discounting curves, AUC was calculated for individual rats according to the formula described by Myerson et al. (2001). The calculation consisted of adding the area of the trapezoids that were shaped when vertical lines were drawn from each odds-against value to the corresponding percent larger-reinforcer choice obtained at that odds-against value. Once summed, the area of the trapezoids was divided by the whole area of the graph. AUCs range from 0.0 (exclusive choice for the smaller, certain reinforcer) to 1.0 (exclusive choice for the larger, uncertain reinforcer). In general, smaller AUCs indicate less risky choice, and larger AUCs indicate more risky choice.

Win-stay/Lose-shift ratios. To evaluate reinforcer sensitivity and negative feedback, win-stay and lose-shift analyses were conducted. Individual trials within each session were evaluated according to the choice (i.e., smaller, certain or larger, uncertain) and outcome (i.e., reinforcer or no reinforcer delivered) of each preceding trial. Win-stay trials were analyzed as a proportion, in which the number of choices for the larger, uncertain alternative following a "win" on the preceding trial was divided by the total number of free-choice trials that resulted in a "win" on the larger, uncertain alternative. Similarly, lose-shift trials were analyzed as a proportion, in

which the number of choices for the smaller, certain alternative following a “loss” on the preceding trial was divided by the total number of free-choice trials that resulted in a “loss” on the larger, uncertain alternative. Smaller win-stay ratios indicate relatively lower reinforcer sensitivity while smaller lose-shift ratios indicate relatively lower loss aversion.

Omitted free-choice trials. Frequencies of free-choice omissions were analyzed as a secondary outcome measure. Omitted trials were counted when a response was not made within 10 s of free-choice trial initiation (signaled by illumination of the houselight, cue lights, and lever extension).

Statistical analyses. At baseline, repeated-measures analysis of variance (ANOVA) was used to examine effects of rat strain (between-subjects factor) and block in session (within-subjects factor) on percent larger-reinforcer choice. For sessions to reach stability, AUC, h estimates, IOs, win-stay ratios, and lose-shift ratios, independent samples t -tests were used to examine potential effects of rat strain. After acute d -AMP administration, mixed ANOVAs were used to examine percent larger-reinforcer choice, h estimates, IOs, AUC, win-stay ratios, and lose-shift ratios (i.e., percent larger-reinforcer choice during the first block of trials). ANOVAs included rat strain as the between-subjects variable, and various doses of d -AMP as within-subjects variables. Percent larger-reinforcer choice data also included block in session as an additional within-subjects factor. Huynh-Feldt corrections were used to adjust for violations of the sphericity assumption as needed (Huynh & Feldt, 1976). For significant main effects and/or interactions, Tukey’s Honestly Significant Difference (HSD) post-hoc tests were used to make pairwise comparisons. When homogeneity of variance was violated, $\log_{10}$ transformations were performed prior to analyses. Given that data regarding frequency of free-choice omissions violated homogeneity of variance following such transformation, non-parametric tests were

performed for this dependent measure. For within-subjects effects (drug doses), Friedman tests were used, and for between-subjects effects (rat strain), Mann-Whitney U tests were used. Significant non-parametric tests were followed up with Wilcoxon signed-rank post-hoc tests using Bonferroni corrections. For all statistical analysis, significance was defined as $p < .05$.

Results

Baseline

Statistical analyses for all primary outcome measures at baseline are shown in Table 1.

Sessions to Stability. All probability-discounting sessions that took place before the first saline injection were included in the baseline phase. Shown in Figure 1, there were no significant differences between strains regarding sessions required to reach baseline stability. LEW required a mean of 28.63 ($SEM = 2.33$) sessions while F344 required a mean of 30.38 ($SEM = 3.70$) sessions.

Percent larger-reinforcer choice. Figure 2 shows percent larger-reinforcer choice as a function of decreasing probabilities of larger-reinforcer delivery across blocks (corresponding to increasing odds-against larger-reinforcer delivery) for the last five baseline sessions. A significant main effect of trial block indicates that probabilistic discounting did occur, in which choice was for the larger reinforcer at relatively high probabilities of delivery (i.e., 100% and 66.7% blocks) and for the smaller reinforcer at relatively low probabilities of larger-reinforcer delivery (i.e., 16.7% and 8.5% blocks). Also shown in Figure 2, and supported by the absence of a significant main effect of rat strain and interaction between rat strain and trial block, there were no significant differences between strains in terms of percent larger-reinforcer choice at any probability value.

Indifference odds (IO). IOs for individual subjects are shown in Table 2, while mean IOs across rat strains are displayed in Table 2 and Figure 3. There were no significant differences in IOs between strains. Notably, obtained IO values approached the IO value that was considered optimal during the current study (i.e., $IO = 2.0$).

Discounting rate (h). Given that homogeneity of variance was violated for raw h estimates, they were transformed prior to further analysis. Log h estimates for individual subjects are shown in Table 2, while mean log h estimates across rat strains are displayed in Table 2 and Figure 3. There were no significant differences in discounting rates (log h) between strains at baseline.

Area under the curve (AUC). AUC for individual subjects are shown in Table 2, while mean AUCs across rat strains are displayed in Table 2 and Figure 5. There were no significant differences in AUC between strains at baseline.

Win-stay ratios. Win-stay ratios for individual rats are shown in Table 2, while mean win-stay ratios across rat strains are shown in Table 2 and Figure 6. There were no differences between strains in terms of win-stay ratios, suggesting that there were no differences between LEW and F344 in regard to reinforcer sensitivity.

Lose-shift ratios. Lose-shift ratios for individual rats are shown in Table 2, while mean win-stay ratios across rat strains are shown in Table 2 and Figure 6. LEW has significantly larger lose-shift ratios as compared to F344, indicating greater loss aversion for LEW.

Omitted free-choice trials. Frequencies of free-choice omissions for individual rats as well as the mean frequency of omissions across rat strains are shown in Table 2. Frequencies of omitted trials during baseline were notably low for all rats, ranging from an average of 0.0 to 2.4 free-choice omissions per session (out of 40). A significant Mann-Whitney U test for between-

subjects effects revealed that, on average, F344 omitted a greater number of free-choice trials at baseline than LEW, $Z = -2.21$, $p = 0.027$.

Acute *d*-AMP

Statistical analyses for all primary outcome measures following acute *d*-AMP are shown in Table 3. Given the relatively small sample of rats that responded following 1.8 mg/kg, two separate mixed ANOVAs were conducted for each dependent measure—one that included doses 0.0 (saline) – 1.0 mg/kg (low-to-moderate dose ANOVA) and one that included doses 0.0 (saline) and 1.8 mg/kg only (high dose ANOVA).

Percent larger-reinforcer choice. Figure 7 shows percent larger-reinforcer choice as a function of decreasing probabilities of larger-reinforcer delivery at each dose of acute *d*-AMP. For the low-to-moderate dose ANOVA, post-hoc tests following the detection of a three-way interaction (dose by strain by trial block) revealed that under control (no-drug) conditions, percent larger-reinforcer choice was significantly higher for F344 ($M = 72.74$, $SEM = 11.88$) as compared to LEW ($M = 51.56$, $SEM = 11.11$) during the 33.3% probability block, indicating more risky choice for F344. This strain difference stands in contrast to the absence of differences at baseline. Further investigation revealed that choice became less risky throughout extended training for LEW while choice for F344 remained relatively stable over time, $F(4, 56) = 3.25$, $p = .031$. Specifically, percent larger-reinforcer choice for LEW decreased significantly during later probability blocks, from a mean of 29.18% ($SEM = 6.57$) at baseline to a mean of 19.13% ($SEM = 4.24$) during control sessions and from a mean of 16.88% ($SEM = 3.50$) at baseline to a mean of 5.62% ($SEM = 2.49$) during control sessions for the 16.7% and 8.3% probability blocks, respectively.

Low-to-moderate doses of *d*-AMP (0.1 and 0.3 mg/kg) increased risky choice for F344, indicated by an increase in larger-reinforcer choice during the 33.3%, 16.7%, and 8.5% probability blocks. For LEW, *d*-AMP produced a similar effect on percent larger-reinforcer choice at the 0.3 mg/kg dose (i.e., significant increases during the 33.3%, 16.7%, and 8.5% probability blocks), but had no effect on choice following 0.1 mg/kg. Following 1.0 mg/kg, *d*-AMP produced an overall disruption in choice (i.e., more maladaptive choice) for both rat strains, indicated by simultaneous reductions in percent larger-reinforcer choice during the 100% and 66.7% probability blocks and increases during the 16.7% and 8.5% probability blocks following 1.0 mg/kg *d*-AMP. For the high dose ANOVA, a significant dose by block interaction was observed. Collapsed across rat strains, percent larger-reinforcer choice was reduced during the 100% ($M = 99.23$, $SEM = 0.60$ versus $M = 70.54$, $SEM = 11.06$) and 66.7% ($M = 98.32$, $SEM = 0.65$ versus $M = 64.88$, $SEM = 10.00$) probability blocks and increased during the 16.7% ($M = 20.44$, $SEM = 5.74$ versus $M = 60.12$, $SEM = 9.88$) and 8.5% ($M = 4.69$, $SEM = 3.19$ versus $M = 54.61$, $SEM = 4.97$) blocks as compared to saline, revealing an overall disruption in choice.

Discounting rate (*h*). Given that homogeneity of variance was violated and *h* estimates were “0.0” for some rats following 1.0 and 1.8 mg/kg doses of *d*-AMP, a numeric constant was added to all *h* estimates prior to logarithmic transformation. The constant was calculated as one-half that of the minimum non-zero *h* estimate. For 1.0 mg/kg, the constant was 0.015 and for 1.8 mg/kg, the constant was 0.025, effectively shifting curves to the right. Log *h* estimates for individual subjects across doses of acute *d*-AMP are shown in Table 4, while mean log *h* estimates are displayed in Table 4 and Figure 8. For the low-to-moderate dose ANOVA, following the detection of a two-way interaction between drug dose and rat strain, post-hoc tests revealed that there were no significant differences in log *h* for either rat strain following saline relative

to control conditions, suggesting that choice was unaffected by the injection procedures alone. In addition, there were no differences between strains during control or saline sessions. Log h estimates were reduced for LEW following 1.0 mg/kg d -AMP while a similar effect was observed for F344 following 0.3 and 1.0 mg/kg doses relative to saline. At 1.0 mg/kg, log h estimates were significantly lower for F344 than LEW, suggesting greater sensitivity to d -AMP for F344. For the high dose ANOVA, a significant main effect of dose was observed such that, collapsed across rat strain, log h estimates were significantly reduced following 1.8 mg/kg ($M = -0.86$, $SEM = 0.15$) relative to saline ($M = -0.09$, $SEM = 0.05$). Together, significant reductions in log h suggest that discounting was reduced following acute d -AMP, indicating greater choice for the larger, uncertain alternative.

Indifference odds (IO). IOs for individual subjects across doses of acute d -AMP are shown in Table 4, while mean IOs across rat strains are displayed in Table 4 and Figure 9. IOs could not be interpolated following individual doses of d -AMP for several rats given that percent larger-reinforcer choice did not drop below 50% during several drug-administration sessions (i.e., there was no point of indifference) and are as follows: 0.1 mg/kg ($n = 1$ F344); 0.3 mg/kg ($n = 4$ F344; $n = 1$ LEW); 1.0 mg/kg ($n = 7$ F344; $n = 3$ LEW), and 1.8 mg/kg ($n = 6$ F344; $n = 6$ LEW). Given the relatively small sample sizes for both rat strains following 1.0 and 1.8 mg/kg d -AMP, ANOVA was performed including 0.1 and 0.3 mg/kg only. Under control (no-drug) conditions, there were no differences in IOs between LEW and F344. In addition, there were no significant differences in IOs following saline or control conditions, suggesting that choice was unaffected by the injection procedures alone. Still, saline was used for subsequent pair-wise comparisons across doses. Following the detection of a main effect of drug dose, collapsed across rat strains, post-hoc tests revealed that 0.3 mg/kg d -AMP only ($M = 2.72$, $SEM = 0.32$)

increased mean IOs relative to saline ($M = 1.38$, $SEM = 0.20$), which corresponds with increases in percent larger-reinforcer choice during later probability blocks at this dose for both rat strains.

Area under the curve (AUC). AUC values for individual subjects across doses of acute *d*-AMP are shown in Table 4, while mean AUCs across rat strains are displayed in Table 4 and Figure 10. Under control (no-drug) conditions, there were no differences in AUCs between LEW and F344. In addition, there were no significant differences in AUCs following saline or control conditions for either rat strain, suggesting that choice was unaffected by the injection procedures alone. For the low-to-moderate dose ANOVA, following the detection of a two-way interaction between drug dose and rat strain, post-hoc tests revealed that acute *d*-AMP dose dependently increased mean AUC relative to saline for F344 at 0.1, 0.3, and 1.0 mg/kg doses. For LEW, acute *d*-AMP increased mean AUC at the 0.3 and 1.0 mg/kg doses only. Following 0.1 and 0.3 mg/kg, AUC was significantly larger for F344 than LEW, suggesting greater sensitivity to *d*-AMP for F344. The high dose ANOVA revealed that 1.8 mg/kg *d*-AMP had no effect on AUC of either rat strain.

Win-stay ratios. Win-stay ratios for individual subjects across doses of acute *d*-AMP are shown in Table 5, while mean win-stay ratios across rat strains are displayed in Table 5 and Figure 11 (left panel). Following the detection of a main effect of dose, collapsed across strains, 1.0 mg/kg *d*-AMP reduced sensitivity to reinforcer delivery, indicated by a significant reduction in win-stay ratios ($M = 0.64$, $SEM = 0.05$) relative to saline ($M = 0.88$, $SEM = 0.02$). The high dose ANOVA revealed that, collapsed across rat strains, win-stay ratios were significantly reduced following 1.8 mg/kg ($M = 0.64$, $SEM = 0.06$) relative to saline ($M = 0.86$, $SEM = 0.03$).

Lose-shift ratios. Lose-shift ratios for individual subjects across doses of acute *d*-AMP are shown in Table 5, while mean lose-shift ratios across rat strains are displayed in Table 5 and

Figure 11 (right panel). No dose of *d*-AMP produced a significant effect on loss aversion, indicated by no change in lose-shift ratios relative to saline for either rat strain.

Omitted free-choice trials. Table 5 shows frequency of free-choice omissions for individual rats as well as means across rat strains across all doses of *d*-AMP. A Friedman nonparametric test for within-subjects effects revealed a significant effect of drug dose on number of omitted trials, $\chi^2 = 58.84$, $p < .001$. Post-hoc analyses using Wilcoxon signed-rank tests with Bonferroni corrections were applied, resulting in a significant level set at $p < .0125$. Collapsed across rat strain, *d*-AMP produced a dose-dependent increase in number of omitted trials, with significantly more omissions occurring following 1.0 ($M = 8.68$, $SEM = 2.52$) and 1.8 mg/kg *d*-AMP ($M = 21.91$, $SEM = 2.93$) relative to saline ($M = 0.44$, $SEM = 0.18$). Significant Mann-Whitney U tests for between-subjects effects revealed that F344 omitted a greater number of trials than LEW following saline vehicle and 1.0 mg/kg *d*-AMP. Although 1.8 mg/kg *d*-AMP produced omitted trials that exceeded the 20-trial cutoff for data inclusion for more F344 ($n = 5$) than LEW ($n = 1$), this difference was not statistically significant, $\chi^2(1) = 4.27$, $p = .119$.

Discussion

The current study was designed to evaluate whether strain differences in choice between LEW and F344 during delay-discounting procedures would maintain when assessing probability discounting. At baseline, discounting was observed for both strains, in which choice was for the smaller, certain reinforcer at relatively low probabilities of larger-reinforcer delivery and for the larger, uncertain reinforcer at relatively high probabilities of delivery. However, there were no differences in choice between the two rat strains in terms of percent larger-reinforcer choice, log h estimates (i.e., discounting rates), IOs, or AUC. This finding stands in contrast to prior work assessing delay discounting of LEW and F344, in which choice for LEW is consistently more

impulsive than that for F344 across several delay-discounting assessments (Anderson and Diller 2010; Anderson and Woolverton 2005; Huskinson and Anderson 2012; Huskinson et al. 2012; Madden et al. 2008; Stein et al. 2012).

To further assess within-session choice patterns in relation to “wins” and “losses,” win-stay and lose-shift ratios were calculated. At baseline, F344 had significantly smaller lose-shift ratios compared to LEW, meaning that F344 switched to the smaller, certain alternative following a “loss” on the larger, uncertain alternative significantly less often than LEW. Mean lose-shift ratios for LEW are comparable to those reported in prior work (range = 0.25 to 0.40; Montes et al., 2015; Stopper et al., 2013; 2014), suggesting that F344 may be more risk-prone relative to LEW. Indeed, when comparing risk-based decision-making using a rodent analog of the Balloon Analog Risk Task (Jentsch et al., 2010), choice for F344 was significantly more risky than that for LEW, Wistar-Furth, Brown Norway, and Spontaneously Hypertensive rats (Ashenurst et al., 2012). Evidence for F344 being relatively risk-prone is not only shown by significantly smaller lose-shift ratios compared to LEW, but also in percent larger-reinforcer choice data in the present study. Although percent larger-reinforcer choice for LEW and F344 did not differ during the baseline assessment (prior to the first saline injection), choice for LEW became significantly less risky throughout the duration of the experiment, indicated by significant reductions in percent larger-reinforcer choice during the 16.7% and 8.3% probability blocks between baseline and control (no-drug) sessions, while choice for the larger, uncertain reinforcer at low probabilities of delivery for F344 remained relatively high and stable across time. Evidence for shifting choice patterns during longitudinal testing (i.e., 105 sessions) on delay-discounting procedures has been reported with LEW and F344 (Aparicio et al., 2015), suggesting that choice impulsivity is not a static property of behavior but rather may change as a

function of exposure to environmental contingencies. Although none have investigated this question in relation to probability discounting, the current study provides evidence for shifting choice patterns during continued testing for LEW despite the establishment of baseline stability.

Following baseline assessments, dose-dependent effects of acute *d*-AMP on probabilistic discounting of LEW and F344 were characterized. *d*-AMP increased risky choice at low to moderate doses for both strains (0.1 – 0.3 mg/kg), indicated by significant increases in percent larger-reinforcer choice during relatively low probabilities of larger-reinforcer delivery (33.3%, 16.7%, and 8.3%), increases in IOs, increases in AUC, and reductions in log *h* estimates, although it did so at a lower dose for F344 (0.1 and 0.3 mg/kg) as compared to LEW (0.3 mg/kg only). At high doses (1.0 – 1.8 mg/kg), *d*-AMP produced an overall disruption in choice for both strains, indicated by reductions in percent larger-reinforcer choice during relatively high probabilities of delivery (100% and 66.7%), enhanced frequency of omitted trials, and reduced sensitivity to reinforcer delivery (i.e., significant reductions in win-stay ratios). Such effects on frequencies of omitted trials at high doses may be indicative of enhanced stereotypical behavior (e.g., pacing, rocking, etc.).

Prior work with LEW and F344 suggests that effects of *d*-AMP on delay discounting may be biology- and/or baseline-dependent (Huskinson et al., 2012). That is, *d*-AMP reduces delay discounting of LEW (i.e., the more impulsive strain) while simultaneously increasing or having no effect on delay discounting of F344 (i.e., the less impulsive strain). Although *d*-AMP affected probabilistic discounting at a lower dose for F344 as compared to LEW in the present study, in general, *d*-AMP produced similar effects on choice of both rat strains and such effects are consistent with prior reports assessing effects of *d*-AMP on probability discounting of male

Long-Evans and Lister-hooded rats (Mai et al., 2015; St Onge & Floresco, 2009; St Onge et al., 2010).

Delay and Probability Discounting

Together, results from baseline and acute *d*-AMP administration lend additional support for the notion that probabilistic and delay discounting represent different constructs, although they share several commonalities (e.g., Madden et al., 2007; Rachin, 1990; also see review by Green and Myerson, 2013). Notably, the current study expands upon the literature regarding differences in delay and probability discounting by characterizing choice of LEW and F344—two rat strains that have been suggested as ideal animal models for studying impulse control—when outcomes involve uncertainty rather than delays (Cadoni, 2016).

Measurement Comparisons. The present experiment utilized summary outcome measures that are used commonly for assessing delay discounting, including AUC, IOs, and discounting rates (*h* parameters) to facilitate comparison against delay-discounting assessments with LEW and F344. In contrast to delay discounting, several of these measures may not be appropriate for assessing choice during probability-discounting procedures or, at the very least, warrant alternative interpretation. Given that optimal choice during probability-discounting procedures changes as a function of environmental contingencies (in this case, probabilities of larger-reinforcer delivery), dependent measures that collapse across probability blocks may not be valid summary measures of choice patterns. However, these are appropriate measures for assessing delay discounting given that optimal choice remains static regardless of what delay duration is associated with larger-reinforcer delivery.

AUC is considered to be an attractive complement to discounting measures given its atheoretical nature (Myerson et al., 2001). In general, larger AUCs are indicative of more larger-

reinforcer choice, corresponding with less impulsive choice during delay-discounting procedures. Thus, an AUC of 1.0 (on a scale from 0.0 to 1.0) indicates optimal choice during delay discounting (i.e., exclusive choice for the larger, delayed reinforcer). However, this is not the case for probability-discounting procedures, in which larger-reinforcer choice during low probabilities of larger-reinforcer delivery is considered maladaptive. Thus, using a blanket statement such as, “larger AUC values indicate more risky choice” is inappropriate and does not reflect the changing contingencies present within sessions. However, this does not necessarily negate the use of AUC for assessing choice during probability-discounting procedures. Instead, an AUC of 0.5 (on a scale from 0.0 to 1.0) may indicate optimal choice with the caveat that choice follows the appropriate pattern—nearly exclusive for the larger reinforcer at high probabilities of delivery and for the smaller reinforcer at low probabilities of delivery. However, an AUC of 0.5 may also exist if choice follows the opposite pattern and thus, AUC may not be appropriate as a sole measure of choice during probability-discounting procedures and its interpretation should be supplemented by percent larger-reinforcer choice data.

Similar to AUC, interpretation of IOs during probability-discounting procedures should be approached with caution. In general, longer indifference points (longer delay durations) are indicative of more percent larger-reinforcer choice and in turn, less impulsive choice during delay-discounting procedures. However, during probability discounting, indifference at an odds-against value that corresponds with the break-even point (33.3% during the present study) is considered optimal, indifference at a smaller odds-against value is considered risk-averse, and indifference at a larger odds-against value is considered risk-prone. Still, indifference points may not always be an appropriate, or feasible, measure for assessment of choice during either type of procedure. In the current study, this is indicated by the failure to interpolate IOs following

moderate to high (0.3 – 1.8 mg/kg) doses of *d*-AMP given that percent larger-reinforcer choice did not drop below 50% following administration of such doses. Similar effects have been observed during delay-discounting and probability-discounting procedures (e.g., Huskinson et al., 2012; Mai et al., 2015; St. Onge & Floresco, 2009; St. Onge, Chiu, & Floresco, 2010). Thus, similar to AUC, IOs should not be used as a sole measure of choice during either type of discounting procedure, but rather as a supplementary measure to percent larger-reinforcer choice data. For the same reasons as those provided for AUC and IOs, assessment of discounting rates (*h* estimates) during probability discounting should also be given careful consideration. Taken together, researchers should use particular dependent measures with caution and remain aware that specific measures come with underlying assumptions about the overall nature of choice and what is defined as optimal choice during a given procedure.

Limitations and Future Directions

Results from the current study must be considered in light of some important considerations. First, a probability-discounting procedural variation was used that has not been reported in the literature previously. During typical delay-discounting assessments, and those conducted with LEW and F344 in particular, choice occurs between one food pellet delivered immediately and three food pellets delivered after a temporal delay (e.g., Evenden & Ryan, 1996; Huskinson et al., 2012). Characteristically, during probability-discounting procedures, choice is between one food pellet delivered 100% of the time and four food pellets delivered with varying probabilities (e.g., Cardinal & Howes, 2005). Based on such reinforcer magnitudes during probability-discounting procedures (one and four pellets), probabilities of larger-reinforcer delivery are extracted to create an optimal switchover point within sessions. Specifically, the probability values used during these procedures are usually 100, 75, 50, 25, and

12.5%, which creates a situation where optimal choice is for the larger, uncertain reinforcer during the 100% and 75% probability blocks, 50% serves as an optimal switchover point, and optimal choice is for the smaller, certain reinforcer during the 25% and 12.5% probability blocks. However, in an attempt to match choice alternatives to those used during delay-discounting procedures with LEW and F344 (e.g., Anderson & Diller, 2010; Huskinson & Anderson, 2012; Huskinson et al., 2012; Turturici et al., 2018), choice between one and three food pellets was used during the current study. Given that a one-versus-three-pellet procedure was used, probability values were adjusted to account for changes in larger-reinforcer magnitude and were 100, 66.7, 33.3, 16.7, and 8.3%. Similar to one-versus-four-pellet procedures, choice was considered optimal when it was for the larger, uncertain reinforcer during the first two probability blocks (100% and 66.7%), 33.3% served as an optimal switch-over point, and optimal choice was for the smaller, certain reinforcer during the 16.7% and 8.3% probability blocks.

Although it seems as though the ratios between reinforcer magnitudes and probability values for one-versus-four-pellet and one-versus-three-pellet procedures are functionally equivalent, and altering larger-reinforcer magnitude has been shown to have no effect on probability discounting of humans (Green et al., 1999), it is possible that using one- and three-pellet alternatives affected results from the present study. Indeed, given that choice for F344 is significantly more risky than LEW on an alternative measure of risk-based decision-making, the Balloon Analog Risk Task (Ashenhurst et al., 2012), it is possible that the probabilistic-discounting task used during the present study was not sensitive enough to detect differences in choice between the two strains. The current study should be replicated systematically using the one-versus-four-pellet probabilistic-discounting procedure as well as additional alternative

measures of risk-based decision making such as the rodent gambling task (Zeeb et al., 2009) and/or the risky decision-making task (Simon et al., 2009).

In addition to procedural variations, the mechanisms by which *d*-AMP affected probability discounting in the current study are unknown. In addition to its action at the DA transporter, *d*-AMP's effects on probability discounting may be due to its action at specific DA receptor subtypes. When SCH23390 (a D1 antagonist) or eticlopride (a D2 antagonist) was administered to rats prior to *d*-AMP administration, effects of *d*-AMP on probability discounting were attenuated (St Onge & Floresco, 2009). In contrast, pretreatment with nafadotride (a D3 antagonist) or L745,870 (a D4 antagonist) potentiated or did not influence effects of *d*-AMP, respectively, suggesting that effects of *d*-AMP on probability discounting are mediated by its action at D1 and D2, but not D3 or D4, receptors. Given that LEW and F344 differ in D2-receptor and DA-transporter densities in brain regions that have been suggested to be critical for risk-based decision making, such as the NuAc core (Flores et al., 1998; Mai et al., 2015; Selim & Bradberry, 1996), it is likely that such biological differences influenced *d*-AMP's effects on probability discounting in the current study. In particular, *d*-AMP reduced probability discounting (i.e., increased risky choice) at a lower dose for F344 (0.1 mg/kg) relative to LEW (0.3 mg/kg), and enhanced frequency of omitted trials to a greater extent for F344 (1.8 mg/kg), which is likely due to F344's relatively abundant D2-receptor and DA-transporter densities.

Given that *d*-AMP not only increases DA transmission, but also affects 5-HT and NE, as well as other neurotransmitter systems (see review by Faraone, 2018), it is unclear from the present study whether effects of *d*-AMP on probability discounting were due to its effects on DA per se. For example, although *d*-AMP acts primarily on the DA system, Winstanley, Dalley, Theobald, and Robbins (2003) suggest that effects of *d*-AMP on 5-HT release are a vital

component of its effects on delay discounting. To our knowledge, there are no studies that have investigated 5-HT or NE receptor antagonism in relation to attenuating *d*-AMP's effects on probability discounting of rats. Future research would benefit from evaluating whether 5-HTergic and/or noradrenergic antagonists attenuate effects of *d*-AMP on probability discounting to further elucidate the mechanisms by which *d*-AMP affects such behavior. This will be especially important for identifying the mechanisms behind F344's relatively greater sensitivity to *d*-AMP given that F344 have more 5-HT and NE receptors in various brain regions as compared to LEW (Herradon et al., 2006; Selim & Bradberry, 1996).

Although delay and probability discounting have been studied primarily as separate processes, many argue that considering them in isolation may not represent real-world situations in which choice reflects components of both processes (e.g., Blackburn & El-Deredy, 2013; Cox & Dallery, 2016; Vanderveldt et al., 2015). Consider the example of choosing to smoke cigarettes now for immediate reinforcement as opposed to abstaining for health benefits in the future. In this example, abstaining from smoking cigarettes does not guarantee a healthy future and thus is not only delayed, but also includes a probabilistic component. More recently, researchers have developed methods for studying delay and probability discounting together in the same empirical framework (e.g., Blackburn & El-Deredy, 2013; Cox & Dallery, 2016; Kelsey & Niraula, 2013; Vanderveldt et al., 2015). Although the majority of these combined procedures have been developed for use with human subjects (e.g., Blackburn & El-Deredy, 2013; Cox & Dallery, 2016; Vanderveldt et al., 2015), one procedure conducted with rats includes choice between a reinforcer delivered immediately 50% of the time (e.g., one food pellet) and the same reinforcer magnitude delivered 100% of the time following increasing temporal delays (Kelsey & Niraula, 2013). Limitations to this procedure include the lack of a

reinforcer-magnitude manipulation, however, future research would benefit from continuing along this trajectory to enhance translatability from animal models to human choice patterns when alternatives include both, delays and uncertainty.

Summary and Conclusions

Although baseline probability discounting did not differ between LEW and F344 in the present study, choice for LEW became significantly less risky throughout extended training while choice for F344 remained relatively stable over time. In addition, lose-shift ratios were significantly smaller for F344 as compared to LEW. This means that F344 switched to the smaller, certain alternative following a “loss” on the larger, uncertain alternative significantly less often than LEW, suggesting that F344 may be more risk-prone relative to LEW. It is possible that the probability-discounting procedure used in the current study was not sensitive enough to capture global differences in risky choice between LEW and F344 and future research would benefit from designs that compare these two rat strains on alternative measures of risk-based decision making such as those described in the Appendix.

Administration of acute *d*-AMP resulted in significant increases in risky choice at low-to-moderate doses (0.1 and 0.3 mg/kg) as well as overall disruptions in choice at high doses (1.0 and 1.8 mg/kg) for both rat strains, although it did so at a lower dose for F344 as compared to LEW. Such differences in dose-dependent effects may be a result of underlying differences in DAergic regulation between rat strains given that *d*-AMP’s primary neurochemical target is to increase extracellular DA. However, given that *d*-AMP also affects alternative neurotransmitter systems, such as 5-HT and NE, it will be important to continue disentangling the mechanisms by which *d*-AMP affects probability discounting.

References

- Abela, A.R., & Chudasama, Y. (2013). Dissociable contributions of the ventral hippocampus and orbitofrontal cortex to decision-making with a delayed or uncertain outcome. *European Journal of Neuroscience*, 37, 640-647.
- Abela, A.R., & Chudasama, Y. (2014). Noradrenergic alpha2A-receptor stimulation in the ventral hippocampus reduces impulsive decision-making. *Psychopharmacology*, 231, 521-531.
- Adriani, W., & Laviola, G. (2006). Delay aversion but preference for large and rare rewards in two choice tasks: Implications for the measurement of self-control parameters. *BMC Neuroscience*, 7, 52.
- Alvos, L., Gregson, R.A.M., & Ross, M.W. (1993). Future time perspective in current and previous injecting drug users. *Drug and Alcohol Dependence*, 31, 193-197.
- Anderson, K.G., & Diller, J.W. (2010). Effects of acute and repeated nicotine administration on delay discounting in Lewis and Fischer 344 rats. *Behavioural Pharmacology*, 21, 754-764.
- Anderson, K.G., & Woolverton, W.L. (2005). Effects of clomipramine on self-control choice in Lewis and Fischer 344 rats. *Pharmacology Biochemistry and Behavior*, 80, 387-393.
- Aparicio, C.F., Elcoro, M., & Alonso-Alvarez, B. (2015). A long-term study of the impulsive choices of Lewis and Fischer 344 rats. *Learning Behavior*, 43, 251-271.
- Ashenhurst, J.R., Seaman, M., & Jentsch, J.D. (2012). Responding in a test of decision-making under risk is under moderate genetic control in the rat. *Alcoholism: Clinical and Experimental Research*, 36, 941-949.

- Basar, K., Sesia, T., Groenewegen, H., Steinbusch, H.W., Visser-Vandewalle, V., & Temel, Y. (2010). Nucleus accumbens and impulsivity. *Progress in Neurobiology*, 92, 533-557.
- Besson, M., Belin, D., McNamara, R., . . . , & Dalley, J.W. (2010). Dissociable control of impulsivity in rats by dopamine d2/3 receptors in the core and shell subregions of the nucleus accumbens. *Neuropsychopharmacology*, 35, 560-569.
- Bickel, W.K., Koffarnus, M.N., Moody, L., & Wilson, A.G. (2014). The behavioral- and neuro-economic process of temporal discounting: A candidate behavioral marker of addiction. *Neuropharmacology*, 76, 518-527.
- Bickel, W.K., & Marsch, L.A. (2001). Toward a behavioral economic understanding of drug dependence: Delay discounting processes. *Addiction*, 96, 73-86.
- Bickel, W.K., Miller, M.L., Yi, R., Kowal, B.P., Lindquist, D.M., & Pitcock, J.A. (2007). Behavioral and neuroeconomics of drug addiction: Competing neural systems and temporal discounting processes. *Drug and Alcohol Dependence*, 90, S85-S91.
- Bickel, W.K., Quisenberry, A.J., & Snider, S.E. (2016). Dose impulsivity change rate dependently following stimulant administration? A translational selective review and re-analysis. *Psychopharmacology*, 233, 1-18.
- Blackburn, M., & El-Deredy, W. (2013). The future is risky: Discounting of delayed and uncertain outcomes. *Behavioural Processes*, 94, 9-18.
- Cadoni, C. (2016). Fischer 344 and Lewis rat strains as a model of genetic vulnerability to drug addiction. *Frontiers in Neuroscience*, 10, 1-22.
- Cardinal, R.N. (2006). Neural systems implicated in delayed and probabilistic reinforcement. *Neural Networks*, 19, 1277-1301.

- Cardinal, R.N., & Howes, N.J. (2005). Effects of lesions of the nucleus accumbens core on choice between small certain rewards and large uncertain rewards in rats. *BMC Neuroscience*, 6, 37.
- Cheung, T.H.C., Cardinal, R.N. (2005). Hippocampal lesions facilitate instrumental learning with delayed reinforcement but induce impulsive choice in rats. *BMC Neuroscience*, 6, 36.
- Christensen, J., Parker, S., Silberberg, A., & Hursh, S. (1998). Trade-offs in choice between risk and delay depend on monetary amounts. *Journal of the Experimental Analysis of Behavior*, 69, 123-139.
- Cox, D.J., & Dallery, J. (2016). Effects of delay and probability combinations on discounting in humans. *Behavioural Processes*, 131, 15-23.
- Dai, Z., Harrow, S.E., Song, X., Rucklidge, J.J., & Grade, R.C. (2016). Gambling, delay, and probability discounting in adults with and without ADHD. *Journal of Attentional Disorders*, 20, 968-978.
- Dalley, J.W., Fryer, T.D., Brichard, L., . . . , & Robbins, T.W. (2007). Nucleus accumbens d2/3 receptors predict train impulsivity and cocaine reinforcement. *Science*, 315, 1267-1270.
- Davison, M., & Baum, W.M. (2002). Choice in a variable environment: Effects of blackout duration and extinction between components. *Journal of the Experimental Analysis of Behavior*, 77, 65-89.
- Drechsler, R., Rizzo, P., & Steinhausen, H.C. (2010). Decision making with uncertain reinforcement in children with attention deficit/hyperactivity disorder (ADHD). *Child Neuropsychology*, 16, 145-161.
- Evenden, J.L. (1999). Varieties of impulsivity. *Psychopharmacology*, 146, 348-361.

- Evenden, J.L., & Ryan, C.N. (1996). The pharmacology of impulsive behaviour in rats: The effects of drugs on response choice with varying delays of reinforcement. *Psychopharmacology*, 128, 161-170.
- Evenden, J.L., & Ryan, C.N. (1999). The pharmacology of impulsive behaviour in rats VI: The effects of ethanol and selective serotonergic drugs on response choice with varying delays of reinforcement. *Psychopharmacology*, 146, 413-421.
- Faraone, S.V. (2018). The pharmacology of amphetamine and methylphenidate: relevance to the neurobiology of attention-deficit/hyperactivity disorder and other psychiatric comorbidities. *Neuroscience and Biobehavioral Reviews*, 87, 255-270.
- Flores, G., Wood, G.K., Barbeau, D., Quirion, R., & Srivastava, L.K. (1998). Lewis and Fischer rats: A comparison of dopamine transporter and receptor levels. *Brain Research*, 814, 34-40.
- Floresco, S.B. (2013). Prefrontal dopamine and behavioral flexibility: shifting from an “inverted-U” toward a family of functions. *Frontiers in Neuroscience*, 7, 62.
- Green, L., & Myerson, J. (1996). Exponential versus hyperbolic discounting of delayed outcomes: Risk and waiting time. *American Zoologist*, 36, 496-505.
- Green, L., & Myerson, J. (2004). A discounting framework for choice with delayed and probabilistic rewards. *Psychological Bulletin*, 130, 769-792.
- Green, L., & Myerson, J. (2013). How many impulsivities? A discounting perspective. *Journal of the Experimental Analysis of Behavior*, 99, 3-13.
- Green, L., Myerson, J., & Ostaszewski, P. (1999). Amount of reward has opposite effects on the discounting of delayed and probabilistic outcomes. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 25, 418-427.

- Griffiths, M. (1995). The role of subjective mood states in the maintenance of fruit machine gambling behaviour. *Journal of Gambling Studies*, 11, 123-135.
- Herradon, G., Ezquerro, L., Morales, L., Franklin, B., Silos-Santiago, I., & Alguacil, L.F. (2006). Lewis and Fischer 344 strain differences in alpha2-adrenoceptors and tyrosine hydroxylase expression. *Life Sciences*, 78, 862-868.
- Hinvest, N.S., & Anderson, I.M. (2010). The effects of real versus hypothetical reward on delay and probability discounting. *Quantitative Journal of Experimental Psychology*, 63, 1072-1084.
- Holmes, J.C., & Rutledge, C.O. (1976). Effects of the *d*- and *l*-isomers of amphetamine on uptake, release, and catabolism of norepinephrine, dopamine and 5-hydroxytryptamine in several regions of rat brain. *Biochemical Pharmacology*, 25, 447-451.
- Huskinson, S.L., & Anderson, K.G. (2012). Effects of acute and chronic administration of diazepam on delay discounting in Lewis and Fischer 344 rats. *Behavioural Pharmacology*, 23, 315-330.
- Huskinson, S.L., Krebs, C.A., & Anderson, K.G. (2012). Strain differences in delay discounting between Lewis and Fischer 344 rats at baseline and following acute and chronic administration of *d*-amphetamine. *Pharmacology Biochemistry and Behavior*, 101, 403-416.
- Huynh, H., & Feldt, L.S. (1976). Estimation of the box correction for degrees of freedom from sample data in randomized block and split-plot designs. *Journal of Educational Statistics*, 1, 69-82.

- Ishii, H., Ohara, S., Tobler, P.N., Tsutsui, K., & Iijima, T. (2015). Dopaminergic and serotonergic modulation of anterior insular and orbitofrontal cortex function in risky decision making. *Neuroscience Research*, 92, 53-61.
- Jentsch, J.D., Woods, J.A., Groman, S.M., & Seu, E. (2010). Behavioral characteristics and neural mechanisms mediating performance in a rodent version of the Balloon Analog Risk Task. *Neuropsychopharmacology*, 35(8), 1797-1806.
- Kaminski, B.J., & Ator, N.A. (2001). Behavioral and pharmacological variables affecting risky choice in rats. *Journal of the Experimental Analysis of Behavior*, 75, 275-297.
- Kankaanpää, A., Meririnne, E., Lillsunde, P., & Seppälä, T. (1998). The acute effects of amphetamine derivatives on extracellular serotonin and dopamine levels in rat nucleus accumbens. *Pharmacology Biochemistry and Behavior*, 59, 1003-1009.
- Kelsey, J.E., & Niraula, A. (2013). Effects of acute and sub-chronic nicotine on impulsive choice in rats in a probabilistic delay-discounting task. *Psychopharmacology (Berl)*, 227, 385-392.
- Koot, S., Zoratto, F., Cassano, T., . . . , & Adriani, W. (2012). Compromised decision-making and increased gambling proneness following dietary serotonin depletion in rats. *Neuropharmacology*, 62, 1640-1650.
- Krebs, C.A., & Anderson, K.G. (2012). Preference reversals and effects of *d*-amphetamine on delay discounting in rats. *Behavioural Pharmacology*, 23, 228-240.
- Kuroki, T., Ichikawa, J., Dai, J., & Meltzer, H.Y. (1998). R(+)-8-OH-DPAT, a 5-HT_{1A} receptor agonist, inhibits amphetamine-induced serotonin and dopamine release in rat medial prefrontal cortex. *Brain Research*, 743, 357-361.

- Li, Y., Zuo, Y., Yu, P., Ping, X., & Cui, C. (2015). Role of basolateral amygdala dopamine D2 receptors in impulsive choice in acute cocaine-treated rats. *Behavior and Brain Research*, 287, 187-195.
- Lieberman, J.A., & Tasman, A. (2006). Psychostimulants. In *Handbook of Psychiatric Drugs* (pp. 176). West Sussex, England: John Wiley and Sons Limited.
- Madden, G.J., Ewan, E.E., & Lagorio, C.H. (2007). Toward an animal model of gambling: Delay discounting and the allure of unpredictable outcomes. *Journal of Gambling Studies*, 23, 63-83.
- Madden, G.J., Petry, N.M., & Johnson, P.S. (2009). Pathological gamblers discount probabilistic rewards less steeply than matched controls. *Experimental and Clinical Psychopharmacology*, 17, 283-290.
- Madden, G.J., Smith, N.G., Brewer, A.T., Pinkston, J.W., & Johnson, P.S. (2008). Steady-state assessment of impulsive choice in Lewis and Fischer 344 rats: between-condition delay manipulations. *Journal of the Experimental Analysis of Behavior*, 90, 333-344.
- Mai, B., & Hauber, W. (2015). Orbitofrontal or accumbens dopamine depletion does not affect risk-based decision making in rats. *Cognitive, Affective, & Behavioral Neuroscience*, 15, 507-522.
- Mai, B., Sommer, S., & Hauber, W. (2015). Dopamine D1/D2 receptor activity in the nucleus accumbens core but not in the nucleus accumbens shell and orbitofrontal cortex modulates risk-based decision making. *International Journal of Neuropsychopharmacology*, 18, 1-9.
- Mazur, J.E. (1987). An adjusting procedure for studying delayed reinforcement. In M.L. Commons, J.E. Mazur, J.A. Nevin, & H. Rachlin (Eds.). *Quantitative analyses of*

- behavior, vol. 5: The effect of delay and of intervening events on reinforcement value* (pp. 55-73). Hillsdale, NJ: Erlbaum.
- Mobini, S., Chiang, T.-J., Ho, M.-Y., Bradshaw, C.M., & Szabadi, E. (2000). Effects of central 5-hydroxytryptamine depletion on sensitivity to delayed and probabilistic reinforcement. *Psychopharmacology*, 152, 390-397.
- Montes, D.R., Stopper, C.M., & Floresco, S.B. (2015). Noradrenergic modulation of risk/reward decision making. *Psychopharmacology (Berl)*, 232, 2681-2696.
- Moreno, M., Economidou, D., Mar, A.C., . . . , & Dalley, J.W. (2013). Divergent effects of d2/3 receptor activation in the nucleus accumbens core and shell on impulsivity and locomotor activity in high and low impulsive rats. *Psychopharmacology*, 228, 19-30.
- Moschak, T.M., & Carelli, R.M. (2017). Impulsive rats exhibit blunted dopamine release dynamics during a delay discounting task independent of cocaine history. *eNeuro*, 4(2), pii.
- Myerson, J., Green, L., & Morris, J. (2011). Modeling the effect of reward amount on probability discounting. *Journal of the Experimental Analysis of Behavior*, 95, 175-187.
- Myerson, J., Green, L., & Warusawitharana, M. (2001). Area under the curve as a measure of discounting. *Journal of the Experimental Analysis of Behavior*, 76, 235-243.
- Orsini, C.A., Mitchell, M.R., Heshmati, S.C., . . . , & Setlow, B. (2017). Effects of nucleus accumbens amphetamine administration on performance in a delay discounting task. *Behavior and Brain Research*, 15, 130-136.
- Paterson, N.E., Wetzler, C., Hackett, A., & Hanania, T. (2012). Impulsive action and impulsive choice are mediated by distinct neuropharmacological substrates in rat. *International Journal of Neuropsychopharmacology*, 15(10), 1473-1487.

- Perry, J.L., Stairs, D.J., & Bardo, M.T. (2008). Impulsive choice and environmental enrichment: effects of *d*-amphetamine and methylphenidate. *Behavioural Brain Research*, 193, 48-54.
- Petry, N.M. (2001). Pathological gamblers, with and without substance use disorders, discount delayed rewards at high rates. *Journal of Abnormal Psychology*, 110, 482-487.
- Petry, N.M., Bickel, W.K., & Arnett, M. (1998). Shortened time horizons and insensitivity to future consequences in heroin addicts. *Addiction*, 93, 729-738.
- Pothuizen, H.H., Jongen-Relo, A.L., Feldon, J., & Yee, B.K. (2005). Double dissociation of the effects of selective nucleus accumbens core and shell lesions on impulsive-choice behavior and salience learning in rats. *European Journal of Neuroscience*, 22, 2605-2616.
- Rachlin, H. (1990). Why do people gamble and keep gambling despite heavy losses? *Psychological Science*, 1, 294-297.
- Rachlin, H., Logue, A.W., Gibbon, J., & Frankel, M. (1986). Cognition and behavior in studies of choice. *Psychological Review*, 93, 33-55.
- Rachlin, H., Raineri, A., & Cross, D. (1991). Subjective probability and delay. *Journal of the Experimental Analysis of Behavior*, 55, 233-244.
- Reynolds, B., Richards, J.B., Horn, K., & Karraker, K. (2004). Delay discounting and probability discounting as related to cigarette smoking status in adults. *Behavioural Processes*, 65, 35-42.
- Richards, J.B., Lloyd, D.R., Kuehlewind, B., Militello, L., Paredes, M., Woods, L.S., & Palmer, A.A. (2013). Strong genetic influences on measures of behavioral regulation among inbred rat strains. *Genes Brain and Behavior*, 12, 490-502.
- Rotter, J.B. (1954). *Social learning and clinical psychology*. Englewood Cliffs, NJ: Prentice-Hall.

- Selim, M., & Bradberry, C.W. (1996). Effect of ethanol on extracellular 5-HT and glutamate in the nucleus accumbens and prefrontal cortex: Comparison between the Lewis and Fischer 344 rats strains. *Brain Research*, 716, 157-164.
- Simon, N.W., Gilbert, R.J., Mayse, J.D., Bizon, J.L., & Setlow, B. (2009). Balancing risk and reward: A rat model of risky decision-making. *Neuropsychopharmacology*, 34, 2208-2217.
- St. Onge, J.R., Abhari, H., & Floresco, S.B. (2011). Dissociable contributions by prefrontal D1 and D2 receptors to risk-based decision making. *Journal of Neuroscience*, 31, 8625-8633.
- St. Onge, J.R., Ahn, S., Phillips, A.G., & Floresco, S.B. (2012). Dynamic fluctuations in dopamine efflux in the prefrontal cortex and nucleus accumbens during risk-based decision making. *Journal of Neuroscience*, 32, 16880-16891.
- St. Onge, J.R., Chui, Y.C., & Floresco, S.B. (2010). Differential effects of dopaminergic manipulations on risky choice. *Psychopharmacology*, 211, 209-221.
- St. Onge, J.R., & Floresco, S.B. (2009). Dopaminergic modulation of risk-based decision making. *Neuropsychopharmacology*, 34, 681-697.
- St. Onge, J.R., & Floresco, S.B. (2010). Prefrontal cortical contribution to risk-based decision making. *Cerebral Cortex*, 20, 1816-1828.
- Stein, J.S., Pinkston, J.W., Brewer, A.T., Francisco, M.T., & Madden, G.J. (2012). Delay discounting in Lewis and Fischer 344 rats: steady-state and rapid-determination adjusting-amount procedures. *Journal of the Experimental Analysis of Behavior*, 97, 305-321.

Stein, J.S., Wilson, A.G., Koffarnus, M.N., Daniel, T.O., Epstein, L.H., & Bickel, W.K. (2016).

Unstuck in time: Episodic future thinking reduces delay discounting and cigarette smoking. *Psychopharmacology*, 233, 3771-3778.

Stopper, C.M., & Floresco, S.B. (2011). Contributions of the nucleus accumbens and its subregions to different aspects of risk-based decision making. *Cognitive Affective and Behavioral Neuroscience*, 11, 97-112.

Stopper, C.M., Green, E.B., & Floresco, S.B. (2014). Selective involvement by the medial orbitofrontal cortex in biasing risky, but not impulsive, choice. *Cerebral Cortex*, 24, 154-162.

Stopper, C.M., Khayambashi, S., & Floresco, S.B. (2013). Receptor-specific modulation of risk-based decision making by nucleus accumbens dopamine. *Neuropsychopharmacology*, 38, 715-728.

Sun, H., Cocker, P.J., Zeeb, F.D., & Winstanley, C.A. (2012). Chronic atomoxetine treatment during adolescence decreases impulsive choice, but not impulsive action, in adult rats and alters markers of synaptic plasticity in the orbitofrontal cortex. *Psychopharmacology*, 219(2), 285-301.

Tedford, S.E., Persons, A.L., & Napier, T.C. (2015). Dopaminergic lesions of the dorsolateral striatum in rats increase delay discounting in an impulsive choice task. *Plos One*, 10, e0122063.

Terrell, H.K., Derenne, A., & Weatherly, J.N. (2014). Analyses of probability discounting of different outcomes across different methods of measurement. *American Journal of Psychology*, 127, 215-231.

- Turturici, M., Ozga, J.E., & Anderson, K.G. (2018). Pair housing alters delay discounting in Lewis and Fischer 344 rats. *The Psychological Record*, 68, 61-70.
- Vanderveldt, A., Green, L., & Myerson, J. (2015). Discounting of monetary rewards that are both delayed and probabilistic: delay and probability combine multiplicatively, not additively. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 41, 148-162.
- Wilhelm, C.J., & Mitchell, S.H. (2009). Strain differences in delay discounting using inbred rats. *Genes Brain and Behavior*, 8, 426-434.
- Winstanley, C.A., & Clark, L. (2016). Translational models of gambling-related decision making. *Current Topics in Behavioral Neuroscience*, 28, 93-120.
- Winstanley, C.A., Dalley, J.W., Theobald, D.E., & Robbins, T.W. (2003). Global 5-HT depletion attenuates the ability of amphetamine to decrease impulsive choice on a delay-discounting task in rats. *Psychopharmacology*, 170, 320-331.
- Winstanley, C.A., Theobald, D.E., Dalley, J.W., Cardinal, R.N., & Robbins, T.W. (2006). Double dissociation between serotonergic and dopaminergic modulation of medial prefrontal and orbitofrontal cortex during a test of impulsive choice. *Cerebral Cortex*, 16(1), 106-114.
- Winstanley, C.A., Theobald, D.E., Dalley, J.W., & Robbins, T.W. (2005). Interactions between serotonin and dopamine in the control of impulsive choice in rats: therapeutic implications for impulsive control disorders. *Neuropsychopharmacology*, 30(4), 669-682.
- Wooters, T.E., & Bardo, M.T. (2011). Methylphenidate and fluphenazine, but not amphetamine, differentially affect impulsive choice in spontaneously hypertensive, Wistar-Kyoto and Sprague-Dawley rats. *Brain Research*, 1396, 45-53.

- Yang, J.-H., & Liao, R.-M. (2015). Dissociable contribution of nucleus accumbens and dorsolateral striatum to the acquisition of risk choice behavior in the rat. *Neurobiology of Learning and Memory*, 126, 67-77.
- Yang, F.N., Pan, J.S., & Li, X. (2016). Beta-adrenoreceptor blockade abolished atomoxetine-induced risk-taking. *Physiology and Behavior*, 153, 125-132.
- Yates, J.R., & Bardo, M.T. (2017). Effects of intra-accumbal administration of dopamine and ionotropic glutamate receptor drugs on delay discounting performance in rats. *Behavioral Neuroscience*, 131(5), 392-405.
- Yates, J.R., Perry, J.L., Meyer, A.C., Gipson, C.D., Charnigo, R., & Bardo, M.T. (2014). Role of medial prefrontal and orbitofrontal monoamine transporters and receptors in performance in an adjusting delay discounting procedure. *Brain Research*, 1574, 26-36.
- Yi, R., Chase, W.D., & Bickel, W.K. (2007). Probability discounting among cigarette smokers and nonsmokers: Molecular analysis discerns group differences. *Behavioural Pharmacology*, 18, 633-639.
- Young, J.S. (1981). Discrete-trial choice in pigeons: Effects of reinforcer magnitude. *Journal of the Experimental Analysis of Behavior*, 35, 23-29.
- Yu, X., & Sonuga-Barke, E. (2016). Childhood ADHD and delayed reinforcement: A direct comparison of performance on hypothetical and real-time delay tasks. *Journal of Attentional Disorders*. [Epub ahead of print].
- Zeeb, F.D., Robbins, T.W., & Winstanley, C.A. (2009). Serotonergic and dopaminergic modulation of gambling behavior as assessed using a novel rat gambling task. *Neuropsychopharmacology*, 34, 2329-2343.

Zeeb, F.D., Floresco, S.B., & Winstanley, C.A. (2010). Contributions of the orbitofrontal cortex to impulsive choice: Interactions with basal levels of impulsivity, dopamine signaling, and reward-related cues. *Psychopharmacology*, 211, 87-98.

Table 1.

Statistical outcomes for all primary outcome measures comparing rat strains at baseline.

	<i>t</i>	<i>p</i>	Cohen's <i>d</i>
Session to stability ^a	-0.40	0.70	0.20
Indifference odds ^a	-0.97	0.35	0.49
Log <i>h</i> ^a	0.58	0.57	0.29
Area under the curve ^a	-0.56	0.59	0.28
Win-stay ratio ^a	-0.51	0.62	0.25
Lose-shift ratio ^a	2.20	0.05	1.11
	<i>F</i>	<i>p</i>	Partial η^2
Percent larger-reinforcer choice			
Strain ^a	0.28	0.60	0.02
Block ^b	158.82	<.001	0.92
Block x Strain ^b	1.21	0.31	0.08

Note: bolded values denote statistical significance, $p < .05$.^a df = 14; ^b df = (4, 56)

Table 2.

Sessions required to reach stability, indifference odds (IO), log-transformed discounting rates (log h), area under the curve (AUC), win-stay ratios, lose-shift ratios, and frequencies of free-choice omissions (Omit) at baseline for individual rats.

Subject ID	Stability	IO	Log h	AUC	Win-stay	Lose-shift	Omit
LEW							
PDL1	25	2.04	-0.31	0.54	0.86	0.33	0.00
PDL2	31	2.36	-0.37	0.57	0.79	0.29	0.00
PDL3	24	2.03	-0.31	0.52	0.81	0.20	0.00
PDL4	40	0.74	0.13	0.27	0.75	0.16	0.00
PDL5	28	2.27	-0.36	0.55	0.90	0.26	0.00
PDL6	36	1.36	-0.13	0.39	0.82	0.35	0.00
PDL7	21	1.23	-0.09	0.38	0.92	0.18	0.00
PDL8	24	1.81	-0.26	0.49	0.83	0.44	0.00
Mean	28.63	1.73	-0.21	0.46	0.83	0.27	0.00
SEM	2.33	0.20	0.06	0.04	0.02	0.03	0.00
F344							
PDF1	41	2.47	-0.39	0.57	0.96	0.12	0.00
PDF2	47	2.48	-0.39	0.56	0.73	0.16	0.00
PDF3	35	2.68	-0.43	0.59	0.95	0.07	2.20
PDF4	20	3.77	-0.58	0.69	0.84	0.31	0.00
PDF5	26	0.97	0.01	0.31	0.93	0.16	0.40
PDF6	20	2.00	-0.30	0.51	0.76	0.26	0.20
PDF7	34	1.93	-0.28	0.51	0.88	0.13	0.00
PDF8	20	0.67	0.18	0.25	0.77	0.22	2.40
Mean	30.38	2.12	-0.27	0.50	0.85	0.18	0.65
SEM	3.70	0.35	0.09	0.05	0.03	0.03	0.36

Statistical analyses for all primary outcome measures following acute d-AMP administration.

ANOVA including 0.0 (saline) - 1.0 mg/kg d-AMP															
	%LRC			IO*			Log h			AUC			WS		
	F	p	Partial η ²	F	p	Partial η ²	F	p	Partial η ²	F	p	Partial η ²	F	p	Partial η ²
Strain ^a	1.47	0.247	0.10	0.41	0.540	0.04	7.00	0.020	0.35	2.56	0.130	0.16	0.44	0.519	0.03
Dose ^b	11.26	<.001	0.46	10.55	<.001	0.54	39.78	<.001	0.75	19.45	<.001	0.60	17.19	<.001	0.57
Dose X Strain ^b	4.61	0.008	0.26	2.14	0.120	0.19	3.61	0.017	0.22	5.32	0.002	0.29	1.93	0.174	0.13
Block ^c	152.62	<.001	0.92												
Dose X Block ^d	28.63	<.001	0.69												
Strain X Block ^e	4.44	0.010	0.26												
Dose X Strain X Block ^d	4.15	<.001	0.24												
ANOVA including 0.0 (saline) and 1.8 mg/kg d-AMP															
	%LRC			IO			Log h			AUC			WS		
	F	p	Partial η ²	F	p	Partial η ²	F	p	Partial η ²	F	p	Partial η ²	F	p	Partial η ²
Strain ^e	2.63	0.144	0.25	N/A	N/A	N/A	0.16	0.707	0.03	0.74	0.415	0.09	0.49	0.502	0.06
Dose ^e	0.12	0.742	0.12	N/A	N/A	N/A	31.35	0.001	0.84	1.72	0.226	0.18	20.55	0.002	0.72
Dose X Strain ^e	1.94	0.201	0.20	N/A	N/A	N/A	2.36	0.175	0.28	0.51	0.497	0.06	1.53	0.251	0.16
Block ^f	43.00	<.001	0.84												
Dose X Block ^f	34.73	<.001	0.81												
Strain X Block ^f	0.14	0.961	0.02												
Dose X Strain X Block ^f	2.85	0.040	0.26												

Note: Bolded values indicate statistical significance, $p < .05$.
*ANOVA for IOs includes 0.0 - 0.3 mg/kg d-AMP only
^a df = 1, 13; ^b df = 3, 39; ^c df = 4, 52; ^d df = 12, 156; ^e df = 1, 8; ^f df = 4, 32

Table 4.

Area under the curve (AUC), discounting rates (log h), and indifference odds (IO) for individual rats following each dose of acute d-AMP.

Dose:	Saline			0.1 mg/kg			0.3 mg/kg			1.0 mg/kg			1.8 mg/kg		
Subject ID	AUC	Log h	IO	AUC	Log h	IO	AUC	Log h	IO	AUC	Log h	IO	AUC	Log h	IO
LEW															
PDL1	0.52	-0.31	2.03	0.64	-0.52	3.38	0.66	-0.52	3.36	0.56	-0.65	2.93	0.27	-0.87	N/A
PDL2	0.55	-0.41	2.34	0.41	-0.19	1.47	0.39	-0.17	1.13	0.70	-0.90	5.52	0.70	-1.12	N/A
PDL3	0.50	-0.32	1.91	0.37	-0.11	1.29	0.70	-0.60	3.93	0.72	-1.35	N/A	0.53	-0.61	2.26
PDL4	0.38	-0.12	1.31	0.33	-0.07	1.17	0.36	-0.15	1.40	0.73	-0.87	N/A	0.84	-1.07	N/A
PDL5	0.23	0.18	0.66	0.29	0.01	0.97	0.43	-0.22	1.68	0.44	-0.08	1.14	0.43	-0.12	1.20
PDL6	0.33	-0.05	1.06	0.38	-0.12	1.32	0.52	-0.33	2.12	0.61	-0.87	4.16	0.07	-0.61	N/A
PDL7	0.25	0.19	0.65	0.25	0.12	0.76	0.49	-0.30	1.99	0.52	-0.90	2.19	0.39	-1.60	N/A
PDL8	0.26	0.23	0.59	0.40	-0.22	1.12	0.86	-1.10	N/A	0.90	-1.82	N/A	N/A	N/A	N/A
Mean	0.38	-0.08	1.32	0.38	-0.14	1.44	0.55	-0.42	2.23	0.65	-0.93	3.19	0.46	-0.86	1.73
SEM	0.05	0.09	0.25	0.04	0.07	0.29	0.06	0.11	0.39	0.05	0.19	0.76	0.10	0.19	0.53
F344															
PDF1	0.49	-0.27	1.85	0.86	-1.05	N/A	0.93	-1.40	N/A	0.67	-1.82	1.74	N/A	N/A	N/A
PDF2	0.41	-0.16	1.45	0.51	-0.30	1.99	0.68	-0.62	4.14	0.38	-1.82	N/A	N/A	N/A	N/A
PDF3	0.42	-0.21	1.61	0.48	-0.20	1.60	0.60	-0.42	2.62	N/A	N/A	N/A	N/A	N/A	N/A
PDF4	0.50	-0.31	2.05	0.67	-0.52	3.36	0.98	-2.00	N/A	0.74	-1.07	N/A	0.63	-0.49	3.32
PDF5	0.29	0.03	0.93	0.35	-0.02	1.06	0.54	-0.51	2.17	0.60	-1.26	N/A	N/A	N/A	N/A
PDF6	0.42	-0.21	1.62	0.47	-0.28	1.89	0.88	-1.30	N/A	0.49	-1.82	N/A	0.42	-0.55	0.97
PDF7	0.22	0.27	0.53	0.49	-0.24	1.74	0.73	-0.59	3.88	0.40	-1.35	N/A	N/A	N/A	N/A
PDF8	0.34	-0.04	1.08	0.63	-0.47	2.98	0.88	-1.05	N/A	0.84	-0.98	N/A	0.77	-1.60	N/A
Mean	0.39	-0.11	1.39	0.56	-0.38	2.09	0.78	-0.98	3.20	0.59	-1.45	1.74	0.61	-0.88	2.15
SEM	0.03	0.07	0.18	0.06	0.11	0.30	0.06	0.20	0.48	0.07	0.19	N/A	0.10	0.44	1.17

Table 5.

Win-stay ratios (WS), lose-shift ratios (LS), and frequencies of free-choice omissions (Omit) for individual rats following each dose of acute d-AMP.

Dose:	Saline			0.1 mg/kg			0.3 mg/kg			1.0 mg/kg			1.8 mg/kg		
Subject ID	WS	LS	Omit	WS	LS	Omit	WS	LS	Omit	WS	LS	Omit	WS	LS	Om
LEW															
PDL1	0.86	0.21	0.0	0.92	0.16	0.0	0.93	0.10	0.0	0.81	0.12	0.3	0.49	0.63	6.3
PDL2	0.75	0.10	0.0	0.81	0.30	0.0	0.63	0.21	0.0	0.74	0.34	0.0	0.69	0.14	7.3
PDL3	0.97	0.10	0.5	0.92	0.07	0.0	0.95	0.05	0.3	0.68	0.26	2.3	0.55	0.10	9.3
PDL4	0.83	0.28	0.0	0.78	0.00	0.0	0.91	0.30	0.0	0.76	0.34	1.0	0.77	0.30	9.8
PDL5	0.96	0.13	0.0	0.98	0.00	0.0	0.97	0.00	0.0	0.79	0.58	2.8	0.82	0.56	22.1
PDL6	0.79	0.18	0.0	0.83	0.45	0.0	0.85	0.23	0.0	0.52	0.57	3.4	0.33	1.00	9.0
PDL7	0.95	0.17	0.0	1.00	0.17	0.3	0.97	0.17	0.7	0.64	0.00	9.3	0.43	0.25	25.7
PDL8	0.83	0.18	2.0	0.61	0.15	11.3	0.87	0.22	0.3	0.73	0.13	5.6	N/A	N/A	39.4
Mean	0.87	0.17	0.31	0.86	0.16	1.46	0.88	0.16	0.16	0.71	0.29	3.08	0.58	0.43	16.1
SEM	0.03	0.02	0.25	0.04	0.05	1.41	0.04	0.04	0.09	0.03	0.07	1.10	0.06	0.11	4.19
F344															
PDF1	0.96	0.10	1.0	0.95	0.03	0.3	0.98	0.07	0.5	0.77	0.00	15.5	N/A	N/A	39.0
PDF2	0.82	0.34	0.7	0.75	0.13	7.8	0.74	0.21	2.8	0.00	0.33	22.0	N/A	N/A	34.0
PDF3	0.93	0.05	0.3	0.85	0.18	6.5	1.00	0.21	0.7	N/A	N/A	36.0	N/A	N/A	33.7
PDF4	0.86	0.16	0.0	0.87	0.27	0.0	0.89	0.09	0.0	0.66	0.30	1.0	0.75	0.31	18.7
PDF5	0.95	0.08	0.0	0.94	0.06	0.2	0.90	0.20	0.0	0.63	0.32	8.8	N/A	N/A	36.0
PDF6	0.84	0.15	0.3	0.86	0.18	0.0	0.89	0.24	0.0	0.72	0.14	20.2	0.66	0.05	20.3
PDF7	0.89	0.19	0.0	0.92	0.11	0.0	0.94	0.17	0.3	0.38	0.38	8.8	N/A	N/A	20.7
PDF8	0.83	0.44	2.3	0.77	0.54	1.0	0.87	0.20	0.0	0.78	0.19	2.0	0.69	0.29	18.4
Mean	0.89	0.19	0.56	0.87	0.19	1.96	0.90	0.17	0.53	0.56	0.24	14.28	0.70	0.21	27.7
SEM	0.02	0.05	0.27	0.03	0.06	1.14	0.03	0.02	0.33	0.10	0.05	4.13	0.02	0.05	3.11

Note: "WS" corresponds to win-stay ratios, "LS" corresponds to lose-shift ratios, and "Omit" corresponds to frequency of omitted trials.

Figure 1. Average number of probability-discounting sessions required to reach baseline stability for LEW and F344.

Figure 2. Mean percent choice for the large/risky lever (i.e., percent larger-reinforcer choice) as a function of the probability of larger-reinforcer delivery across successive blocks of trials for LEW and F344 across the last five baseline sessions.

Figure 3. Mean indifference odds (IO; odds-against value where choice is for each reinforcer option with equal frequency) for LEW and F344 across the last five baseline sessions. See Equation 2 for calculation of odds-against values based on probabilities of larger-reinforcer delivery.

Figure 4. Mean log h estimates for LEW and F344 across the last five baseline sessions. Note the inverted y-axis scale.

Figure 5. Mean AUC for LEW and F344 across the last five baseline sessions.

Figure 6. Mean win-stay and lose-shift ratios for LEW and F344 across the last five baseline sessions. Asterisks represent a statistically significant difference between rat strains ($p < .05$).

Figure 7. Mean percent choice for the large/risky lever (i.e., percent larger-reinforcer choice) as a function of decreasing probabilities of larger-reinforcer delivery across successive blocks of trials for LEW (left panel) and F344 (right panel) across all doses of acute *d*-AMP. Due to increased frequency of free-choice omissions at higher doses, data were excluded for some rats and sample sizes for these doses are included in the legends. Asterisks represent a statistically significant difference from saline for each rat strain separately (p 's < .05).

Figure 8. Mean log h estimates for LEW and F344 across all doses of d -AMP. “C” corresponds to control (no-drug) sessions and “S” corresponds to saline vehicle. Estimates were interpolated based on Mazur’s (1987) hyperbolic discounting model fits. Due to increased frequency of free-choice omissions at higher doses, data were excluded for some rats; sample sizes are as follows—1.0 mg/kg: $n = 8$ LEW and $n = 7$ F344; 1.8 mg/kg: $n = 7$ LEW and $n = 3$ F344. Asterisks represent a statistically significant difference from saline; Pound symbols represent a statistically significance between rat strains at a given dose (p ’s $< .05$).

Figure 9. Mean indifference odds (IO) for LEW and F344 across all doses of *d*-AMP. “C” corresponds to control (no-drug) sessions and “S” corresponds to saline vehicle. Indifference odds were interpolated based on Mazur’s (1987) hyperbolic discounting model fits. Due to never reaching a point of indifference following some doses as well as increased frequencies of omitted trials at higher doses, data were excluded for some rats; sample sizes are as follows—0.1 mg/kg: $n = 8$ LEW and $n = 7$ F344; 0.3 mg/kg: $n = 7$ LEW and $n = 4$ F344; 1.0 mg/kg: $n = 5$ LEW and $n = 1$ F344; 1.8 mg/kg: $n = 2$ LEW and $n = 2$ F344. Asterisks represent a statistically significant difference from saline (p ’s < .05).

Figure 10. Mean AUC for LEW and F344 across all doses of *d*-AMP. “C” corresponds to control (no-drug) sessions and “S” corresponds to saline vehicle. Due to increased frequency of free-choice omissions at higher doses, data were excluded for some rats; sample sizes are as follows—1.0 mg/kg: $n = 8$ LEW and $n = 7$ F344; 1.8 mg/kg: $n = 7$ LEW and $n = 3$ F344. Asterisks represent a statistically significant difference from saline within each rat strain; Pound symbols represent a statistically significance between rat strains at a given dose (p 's $< .05$).

Figure 11. Mean win-stay (left) and lose-shift ratios (right) for LEW and F344 across all doses of *d*-AMP. “C” corresponds to control (no-drug) sessions and “S” corresponds to saline vehicle. Due to increased frequency of free-choice omissions at higher doses, data were excluded for some rats; sample sizes are as follows—1.0 mg/kg: $n = 8$ LEW and $n = 7$ F344; 1.8 mg/kg: $n = 7$ LEW and $n = 3$ F344. Asterisks represent a statistically significant difference from saline (p 's < .05).

Appendix

Procedures for Evaluating Risky Choice

Risk-based decision-making is a conceptual framework from which procedures are designed to assess gambling-like behavior. There are various procedures for evaluating risky choice in non-human animals, including the rat gambling task (rGT), risky decision-making task (RDT), and probabilistic discounting (PD). Developed by Zeeb, Robbins, and Winstanley (2009), the rGT incorporates reinforcement and punishment contingencies simultaneously, which allows for evaluation of both “wins” and “losses” associated with risky choice. In general, discrete-trials choices are presented between four reinforcer/punisher options, e.g. one food pellet with 90% probability, two food pellets with 80% probability, three food pellets with 50% probability, and four food pellets with 40% probability (see Winstanley & Clark, 2016 for a review of the rGT). A response on any operandum that does not produce food during a given trial initiates a fixed-interval time-out duration, in which longer time-out durations are associated with smaller probabilities of reinforcer delivery (i.e., bigger “losses”). A response on any operandum that does produce food during a given trial results in food delivery (i.e., “win”). Overall reinforcement is maximized in the rGT by perseverating on the smaller, less-risky operanda and reinforcement is minimized by perseveration on the larger, more-risky operanda. Thus, greater risky behavior is evidenced by greater choice for larger, riskier options (e.g., four food pellets with 40% probability of delivery) relative to choice for smaller, less risky options (e.g., two food pellets with 20% probability of delivery). Others have expanded this procedure by including alternative, perhaps more salient, punishment contingencies.

The risky decision-making task (RDT), developed by Simon, Gilbert, Mayse, Bizon, and Setlow (2009), incorporates simultaneous reinforcement and punishment contingencies, in a

similar manner to the rGT. However, during the RDT, discrete-trials choices are presented between two reinforcer/punisher options, e.g. one food pellet with 100% probability of food delivery and 0% probability of electric shock versus three food pellets with a 100% probability of food delivery and a probability of electric shock greater than 0%. In general, choice for the larger reinforcer associated with a given probability of electric shock is considered risky relative to choice for the smaller reinforcer associated with no shock delivery. However, in contrast to the rGT, reinforcement is maximized in the RDT by choosing the larger, risky option regardless of shock presentation. Thus, the RDT may not be an adequate analog of gambling-like behavior, given that all trials result in reinforcement (i.e., “win”).

Finally, PD, first developed by Young (1991) incorporates simultaneous reinforcement and punishment contingencies, similar to the rGT and RDT. However, during probabilistic discounting, discrete-trials choices are presented between two reinforcer/punisher options, e.g. one food pellet with 100% probability of delivery versus three food pellets with a probability of delivery less than 100%. In general, choice for the larger, uncertain option is considered risky relative to choice for the smaller, certain option. However, in contrast to the rGT and RDT, probabilistic-discounting tasks do not incorporate explicit punishment contingencies following a “loss” on the larger, risky alternative. Instead, a fixed inter-trial interval (ITI) separates the time between a response on the larger, risky operandum and the start of the next trial. This ITI can be conceptualized as a brief “time-out” period, which may act as a punisher during probabilistic-discounting procedures. Also in contrast to the rGT and RDT, optimal performance during probabilistic-discounting tasks changes with reinforcer probability. That is, when the probability of larger-reinforcer delivery is high, optimal choice is for the larger, uncertain reinforcer; as the

probability of larger-reinforcer delivery decreases, optimal choice is for the smaller, certain reinforcer.

Overall, there are several procedures for evaluating risky decision-making in the laboratory, and choice of a given procedure depends upon the behavior of interest. As discussed by Winstanley and Clark (2016), gambling serves as an umbrella term for various tasks. For example, some forms of gambling are associated with outcomes with pure chance (e.g., slot machines, lotteries) while others may involve some level of skill (e.g., betting on sports, poker). Further, the types of games involving gambling that appeal to gamblers may depend, in part, on individual differences, such that some may gamble as a form of negative reinforcement while others gamble to gain access to positive reinforcers (Griffiths, 1995; Stewart et al., 2008). Thus, it is important to continue exploring behavior in relation to the various types of gambling procedures discussed above.

.