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CHANGING NONHUMAN IMPULSIVE CHOICE

by

C. Renee Renda

A dissertation proposal submitted in partial fulfillment
of the requirements for the degree

of

DOCTOR OF PHILOSOPHY

in

Psychology

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ABSTRACT

Changing Nonhuman Impulsive Choice

by

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Utah State University, 2018

Major Professor: Gregory J. Madden, Ph.D.

Department: Psychology

Impulsive choice describes the preference for smaller, sooner over larger, later rewards. The process thought to underlie impulsive choice is excessive delay discounting, which characterizes the rapid devaluation of a reward as a function of the delay until its receipt. Strong, positive correlations have been observed between excessive delay discounting and several problematic behaviors (e.g., substance dependence, gambling). Excessive delay discounting may be a transdiagnostic process, and interventions designed to reduce discounting may reduce the maladaptive behaviors with which it correlates. The research described in Chapters 2-5 explores two methods to change nonhuman impulsive choice. The first method took its lead from a study in which working-memory training reduced delay discounting in human stimulant-dependent individuals. Using a back-translational approach, Chapter 2 evaluated the cross-species generality of this finding. Although working-memory training improved working-memory performance, it did not influence nonhuman impulsive choice. The experiments described in Chapters 3-5 used a

training regimen involving prolonged exposure to immediate or delayed food reinforcers (immediacy- and delay-exposure training, respectively). Previous research has shown that delay-exposed rats make fewer impulsive choices than immediacy-exposed rats. Chapter 3 sought to determine the duration of this effect. Replicating prior findings, there was a significant between-group difference in impulsive choice immediately following training. This effect remained significant after a 120-day test-retest interval. In Chapter 3, and in previous reports, it is unclear whether delay-exposure training reduces impulsive choice, or if immediacy-exposure training increases impulsive choice. To address this limitation, Chapter 4 assessed within-subject changes in impulsive choice and compared the effects of delay- and immediacy-exposure training on impulsive choice to developmental reductions in impulsivity. The results from this experiment suggest that delay-exposure training reduces impulsive choice and that immediacy-exposure training does not increase it. All prior studies of delay- and immediacy-exposure training have evaluated its effects after at least 90 training sessions (approximately 9,600 training trials). Chapter 5 demonstrated that the delay-exposure training effect can be obtained in fewer sessions than has been previously employed. Finally, Chapter 6 provides a summary of all four papers.

(174 pages)

PUBLIC ABSTRACT

Changing Nonhuman Impulsive Choice

C. Renee Renda

Preference for smaller-sooner over larger-later rewards characterizes one type of impulsivity—impulsive choice. Impulsive choice is related to a number of maladaptive behaviors including substance abuse, pathological gambling, and poor health behaviors. As such, interventions designed to reduce impulsive choice may have therapeutic benefits. The purpose of this dissertation was to explore two methods to change nonhuman impulsive choice. In doing so, we hope to provide a baseline that future research can use to assess variables that are less amenable to human research (e.g., drug self-administration following reductions in impulsive choice). In Chapter 2, we failed to reduce nonhuman impulsive choice using working-memory training, a finding both inconsistent and consistent with the extant human literature. Chapters 3-5 sought to better understand a training regimen that generates large between-group differences in nonhuman impulsive choice—delay- and immediacy-exposure training. The results from Chapters 3 and 4 suggest that prolonged exposure to delayed food rewards produces large and long-lasting reductions in impulsive choice. Chapter 5 showed that the delay-exposure training effect can be obtained in fewer sessions than has previously been employed. A better understanding of the effects of delay-exposure training on nonhuman impulsive choice may have implications for the design and implementation of a human analog.

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C. Renee Renda

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CHAPTER 1

INTRODUCTION

Impulsivity is a broad construct that encompasses several problem behaviors such as risk taking and sensation seeking, tendencies to act prematurely or with little forethought, and impulsive choice (for review, see Evenden, 1999). Impulsive choice describes the propensity to choose smaller-sooner rewards (SSRs) in lieu of larger-later rewards (LLRs; e.g., Ainslie, 1974). Several human and nonhuman studies have demonstrated that the subjective value of a reinforcer decreases as a function of the delay to its receipt (e.g., Green, Myerson, Shah, Estle, & Holt, 2007; Madden, Bickel, & Jacobs, 1999; Mazur, 1987; Rachlin, Raineri, & Cross, 1991). This phenomenon is termed “delay discounting,” and excessive delay discounting (i.e., rapid devaluation of delayed rewards) is one process thought to underlie impulsive choice.

Over the past two decades, delay discounting has received considerable attention. Figure 1-1 (adapted from Madden & Bickel, 2010) shows the number of articles published each year in the PubMed database from 1980 to 2016 with the keyword “delay discounting.” It is impossible to point to any one event as the causal factor for the increase in delay-discounting research. Rachlin et al. (1991) provided a convenient task used to quantify delay discounting in humans, and Myerson and Green (1995) demonstrated orderly hyperbolic discounting functions in individual participants. Chapman and Elstein (1995) extended the study of discounting to health outcomes, and Madden, Petry, Badger, and Bickel (1997) reported a positive relationship between excessive delay discounting and substance abuse. Since then, several studies have

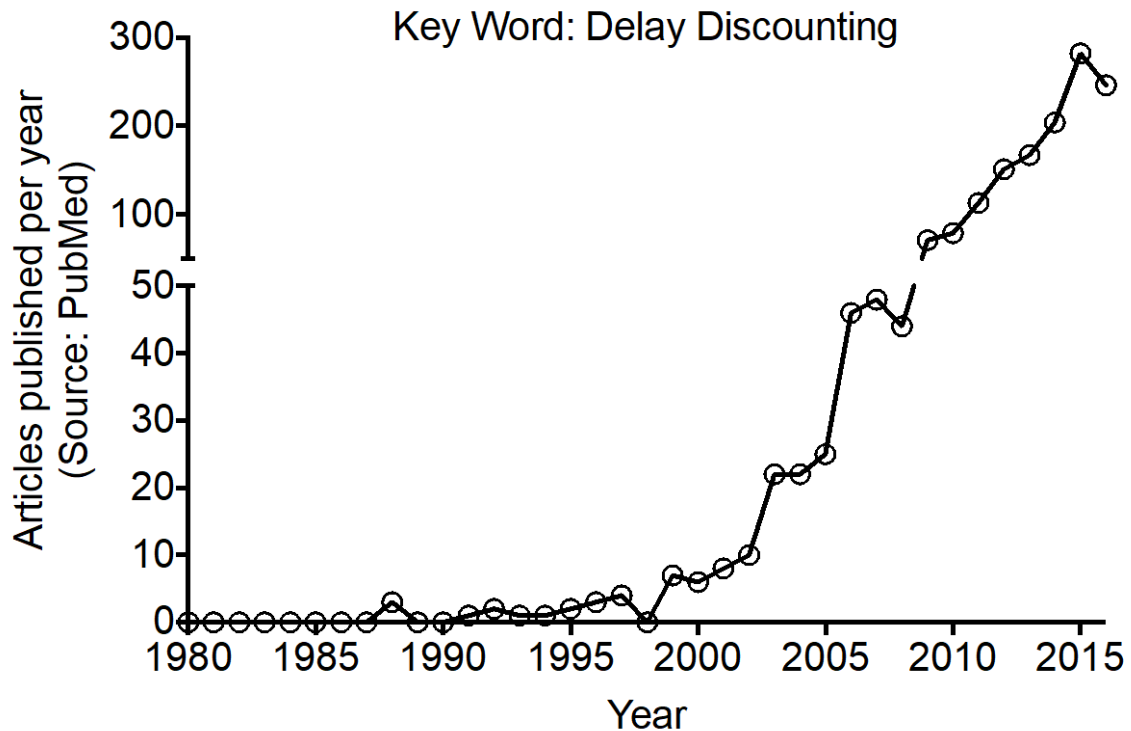


Figure 1-1. Articles published per year in the PubMed database with the keyword “delay discounting.” Figure adapted from *Impulsivity: The Behavioral and Neurological Science of Discounting* (p. 4), by G. J. Madden and W. K. Bickel, 2010, Washington, DC: American Psychological Association. Copyright 2010 by the American Psychological Association. Permission to adapt one figure from a book chapter was not required by the American Psychological Association; see Appendix A.

examined delay discounting and how it relates to a myriad of maladaptive behaviors (for meta-analyses, see Amlung, Vedelago, Acker, Balodis, & MacKillop, 2017; MacKillop et al., 2011). In humans, excessive delay discounting is observed with nearly all types of substance use (e.g., Heil, Johnson, Higgins, & Bickel, 2006; Madden, et al., 1997; Vuchinich & Simpson, 1998). Similar relationships have also been reported in the nonhuman literature (though these findings are not without exceptions; for review, see Stein & Madden, 2013). For example, nonhuman impulsive choice predicts the acquisition (e.g., Zlebnik & Carroll, 2015) and escalation (Anker, Perry, Gliddon, &

Carroll, 2009) of cocaine self-administration, demand for cocaine (Koffarnus & Woods, 2013) and nicotine (Diergaarde et al., 2008), and maintenance of methamphetamine responding (Marusich & Bardo, 2009). Excessive delay discounting in humans is also correlated with pathological gambling (e.g., Alessi & Petry, 2003; Petry, 2001), obesity (e.g., Bickel et al., 2014; Jarmolowicz et al., 2014), internet addiction (Saville, Gisbert, Kopp, & Telesco, 2010), failure to engage in preventative health care (e.g., weekly exercise, routine dental and physician visits, wearing sunscreen; Bradford, 2010; Daugherty & Brase, 2010), and risky behaviors (e.g., Chesson et al., 2006; Odum, Madden, Badger, & Bickel, 2000).

Given that excessive delay discounting is a common process underlying many problem behaviors, it may be a transdisease process (i.e., a neurobehavioral process operating across two or more maladaptive behaviors; Bickel, Jarmolowicz, Mueller, Koffarnus, & Gatchalian, 2012; Bickel & Mueller, 2009). This view suggests that therapeutically reducing discounting may be an effective intervention for a wide range of addictions and other behavioral maladies.

A variety of behavioral approaches have been successful at reducing delay discounting in humans (for reviews, see Gray & MacKillop, 2015; Koffarnus, Jarmolowicz, Mueller, & Bickel, 2013). For example, Bickel, Yi, Landes, Hill, & Baxter (2011) showed that stimulant-dependent individuals that completed a commercially-available working-memory training (WMT) program discounted delayed money less steeply than a control group that completed sham training (i.e., these individuals were given the correct answers, and thus did not need to engage working memory). Other

strategies to change human delay discounting include episodic future thinking (e.g., Lin & Epstein, 2014; Peters & Büchel, 2010), reframing the intertemporal choice (e.g., DeHart & Odum, 2015; Magen, Dweck, & Gross, 2008), and contingency management for substance use (e.g., Landes, Christensen, & Bickel, 2012; Yi et al., 2008).

Reductions in nonhuman impulsive choice have also been observed (e.g., Mazur & Logue, 1978; Smith, Marshall, & Kirkpatrick, 2015; Stein et al., 2013; Stein, Renda, Hinnenkamp, & Madden, 2015). For example, Stein et al. (2013) exposed two groups of weanling Long Evans rats to 120 training sessions in which lever pressing produced either immediate (i.e., immediacy-exposure [IE] training) or delayed (i.e., delay-exposure [DE] training) food reinforcers. Immediately following training, impulsive choice was evaluated using a within-session increasing-delay procedure (Evenden & Ryan, 1996). Results showed that DE rats made significantly fewer impulsive choices than IE rats (see also Stein et al., 2015) and that this between-group difference remained at follow-up tests conducted approximately 66 (Stein et al., 2013) and 48 (Stein et al., 2015) days after the initial assessment was completed. Taken together, the human and nonhuman literature provide evidence that impulsive choice can be changed.

The purpose of this dissertation was to explore two methods to change nonhuman impulsive choice. The first method was based on the human study conducted by Bickel et al. (2011) in which stimulant-dependent individuals that completed a commercially-available WMT program discounted delayed money less steeply than a control group that completed sham training. Using a back-translational approach, the experiment described in Chapter 2 evaluated the cross-species generality of the WMT effect. The experiments

in Chapters 3-5 sought to better understand the effects of DE/IE training. Chapter 3 was designed to evaluate the durability of the DE-training effect. Chapter 4 compared the effects of DE/IE training on impulsive choice relative to maturational changes in impulsivity. In Chapter 5, DE/IE training duration was parametrically manipulated to determine if a more efficient training regimen can be employed. Finally, Chapter 6 provides a summary of Chapters 2-5.

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CHAPTER 2
WORKING-MEMORY TRAINING: THE EFFECTS ON DELAY
DISCOUNTING IN MALE LONG EVANS RATS¹

Abstract

Delay discounting describes the devaluation of a reward as the delay to the receipt of the reward increases. Because steep delay discounting is robustly correlated with a number of behavioral problems (e.g., substance dependence, gambling) and some evidence suggests steep discounting precedes and predicts drug taking in humans and rats, this study sought to experimentally reduce rats' delay discounting. Human stimulant-dependent participants given working-memory training reportedly decreased their rates of discounting relative to a sham-training group (Bickel et al., 2011). To evaluate the cross-species generality of this effect, 38 male Long-Evans rats, matched on pre-training delay-discounting rates, were randomly assigned to receive 140 sessions of working-memory training or sham training (which required no memory of the sample stimulus). Large between-group differences in working memory were observed after training; however, post-training delay-discounting rates were undifferentiated across groups. Potential explanations for these findings are discussed.

¹ Chapter 2 of this dissertation was adapted from "Working-memory training: The effects on delay discounting in male long evans rats," by C. R. Renda, J. S. Stein, and G. J. Madden, 2015, *Journal of the Experimental Analysis of Behavior*, 103, 50-61. Permission to reprint this material was granted by John Wiley & Sons, and the corresponding license agreement and permission-to-use letter is provided in Appendix B.

Introduction

Steeply discounting the value of delayed rewards is correlated with substance-dependence (MacKillop et al., 2011), pathological gambling (Petry & Casarella, 1999), obesity (Weller, Cook, Avsar, & Cox, 2008), and risky behaviors (Chesson et al., 2006; Odum, Madden, Badger, & Bickel, 2000). In addition, evidence from human longitudinal studies (Audrain-McGovern et al., 2009; Brody et al., 2014; Khurana et al., 2013; Kim-Spoon, McCullough, Bickel, Farley, & Longo, 2014) and animal studies (Koffarnus & Woods, 2013; Perry, Larson, German, Madden, & Carroll, 2005; Perry, Nelson, & Carroll, 2008) suggest that steeply discounting delayed rewards is predictive of drug taking. Given these findings, Bickel, Jarmolowicz, Mueller, Koffarnus, and Gatchalian (2012) have suggested that steep delay discounting is a trans-disease process and that therapeutic reductions in discounting may ameliorate discounting-related pathology.

One method by which steep delay discounting may be therapeutically addressed is suggested by the neural substrates involved in impulsive choice. McClure, Ericson, Laibson, Loewenstein, and Cohen (2004) found that the evolutionarily older limbic system is more active when individuals choose a smaller-sooner reward (SSR) over a larger-later reward (LLR). By contrast, the evolutionarily newer frontal cortex and parietal system are more active when the LLR is chosen (see also, Ballard & Knutson, 2009; McClure, Ericson, Laibson, Loewenstein, & Cohen, 2007). Bickel et al. (2007) proposed a framework to characterize the above correlations by parsing neural activity into two distinct systems—the impulsive system (limbic areas, including the nucleus accumbens) and the executive system (frontal cortex and parietal system). The impulsive

system disproportionately weights immediate over delayed rewards, whereas the executive system works to reduce this bias. This *Competing Neurobehavioral Decision Systems* (CNDS) theory posits that maladaptive behavior is the result of a weak executive system, a strong impulsive system, or some combination thereof.

Studies supporting the CNDS theory include those demonstrating that a) separate neural systems are activated when choosing SSRs versus LLRs (McClure et al., 2007; McClure et al., 2004; Tanaka et al., 2004), b) transcranial magnetic stimulation of brain structures responsible for executive-system behavior affects delay discounting (Essex, Clinton, Wonderley, & Zald, 2012; Figner et al., 2010; Sheffer et al., 2013), c) steep discounting and executive dysfunction are independently correlated with many of the same maladaptive behaviors (e.g., Gunstad et al., 2007; Kubler, Murphy, & Garavan, 2005; Petry & Casarella, 1999; Roca et al., 2008; Weller et al., 2008), d) taxing the executive system (i.e., increasing working memory load) increases delay discounting (Hinson, Jameson, & Whitney, 2003; but see Franco-Watkins, Pashler, & Rickard, 2003 for an alternative interpretation), e) poor working-memory ability is correlated with steep delay discounting in humans (Shamosh et al., 2008) and in rats (Renda, Stein, & Madden, 2014; but see Delli-Hagedorn, 2006), f) overlap analyses of neuroimaging studies that separately assessed working memory and delay discounting revealed large activity clusters in the left lateral prefrontal cortex that were unique to these two processes (Wesley & Bickel, 2013), and g) one study has demonstrated decreased delay discounting following working-memory training (WMT) in human stimulant-dependent individuals (Bickel, Yi, Landes, Hill, & Baxter, 2011). In the latter study, participants were randomly

assigned to either a WMT group or a sham-training group. Where the former group completed a commercially available training regimen designed to enhance working-memory performance, the latter completed the same program but were given the correct answers. Pre- to post-training reductions in the discounting of delayed rewards were observed only in the WMT group.

We sought to evaluate if WMT would decrease delay discounting in male Long Evans rats. Beyond evaluating the cross-species generality of the WMT effect on delay discounting, there were two reasons for conducting this study. First, Bickel et al. (2011) reported that WMT participants' post-training assessment of working memory was not different from their pre-training assessment. This may have been because the post-training working-memory assessment was sufficiently different than that of the WMT program, or perhaps because participants completed a maximum of only 15 sessions of WMT. To address the former, rats completed a working-memory assessment that was similar to the training task; the latter was addressed by exposing our rats to 140 sessions of WMT. Second, if WMT could be used to experimentally reduce delay discounting in rats, then this would provide an opportunity to evaluate the causal relation between differences in delay discounting and subsequent propensity for drug-taking (Stein et al., 2013).

In the present experiment, an adjusting-delay procedure was used to quantify pre-training rates of delay discounting. Rats with the most similar pre-training discounting rates were paired. One rat from each pair was randomly assigned to the WMT group; the other rat was assigned to the Sham-training group. WMT was a variation of the titrating-

delay match-to-position (TDMTP) task, a commonly used operant preparation to assess working memory in nonhumans (see, Kangas, Vaidya, & Branch, 2010; Porritt & Poling, 2008). We selected this task for two reasons. First, Bickel et al. (2011) hypothesized that the width of the temporal window across which an organism could recall events would be negatively correlated with rates of delay discounting (see also, Yi, Landes, & Bickel, 2009); by significantly increasing the span of time across which rats could recall sample-stimulus information, we expected significant decreases in delay discounting. Second, the medial prefrontal cortex is implicated in delayed match-to-position tasks (see, e.g., Sloan, Good, & Dunnett, 2006). According to the CNDS theory, improvements in this frontal area should produce a stronger executive system, thereby decreasing delay discounting. Following 140 sessions of WMT or Sham training, groups were compared on working-memory performance and delay discounting.

Method

Subjects

Subjects were 38 experimentally naïve male Long-Evans rats (Harlan, Indianapolis, IN), approximately 75 days old at intake. Rats were housed individually within polycarbonate cages in a temperature- and humidity-controlled animal colony room operating on a 12-hr light/dark cycle (light onset at 7:00 am). Free access to water was available in rats' home cages throughout the study. Rats were food restricted to maintain their weights at approximately 85% of their dealer-supplied free-feeding growth

curve. Approval for this study was granted by the Institutional Animal Care and Use Committee at Utah State University.

Apparatus

Nineteen identical operant chambers were used (Med-Associates, St. Albans, VT). Each chamber was equipped with a white-noise speaker and housed within a sound-attenuating cube. Experimental manipulanda were positioned on the front and rear walls of the chamber. A food receptacle was centered on the front wall (6 cm above the grid floor). A pellet dispenser positioned outside of the chamber delivered 45 mg food pellets (Bio-Serv, Frenchtown, NJ) to the food receptacle. To either side of the food receptacle were two low-profile retractable levers (10.5 cm above the grid floor). One identical lever was centered on the rear wall (10.5 cm above the grid floor). A 28-V DC cue light was positioned above each lever.

Procedures

Figure 2-1 illustrates the approximate timing and sequence of experimental conditions.

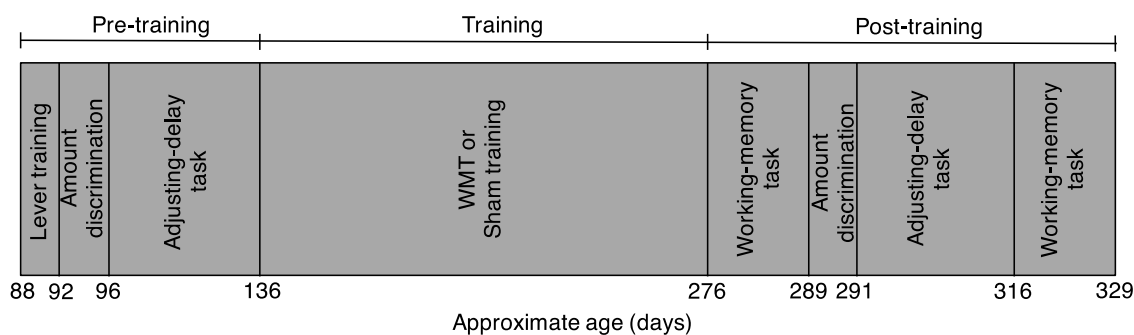


Figure 2-1. Order of experimental conditions and approximate age of rats. Age varied due to mastery-based criteria.

Pre-training tasks.

Lever training. An autoshaping procedure was used to establish lever pressing on the two levers located on the front wall. Levers were presented in a strictly alternating order and rats continued in the 100-trial sessions until they pressed the lever to earn food in $\geq 90\%$ of the trials. In subsequent sessions, the rear-wall lever was inserted at the beginning of each trial. A single press to this lever inserted one lever on the front wall (order alternating between trials) and a single press delivered two food pellets. Initial training ended when the rat completed $\geq 90\%$ of the arranged trials for two consecutive sessions.

Amount discrimination. To ensure that rats could discriminate between 1- and 3-pellets of food, an amount-discrimination task was conducted. Each 60-trial session was partitioned into 15 blocks of 4 trials each. The first two trials within a block were forced-choice trials. These trials began with the insertion of the rear-wall lever and the illumination of its associated cue light. When the lever was pressed it retracted, the cue light turned off, either the left or right lever on the front was inserted (order randomly determined), and the cue light above the lever was lit. For half of the rats, when the left lever was pressed the lever retracted, the cue light turned off, and 1 pellet was delivered to the food receptacle (for the remaining rats, 3 pellets were delivered; pressing the other lever led to the other reward amount). The remaining two trials in a block were free-choice trials in which both the left and right levers (and cue lights) were presented following a rear-wall response. A response to either lever retracted both levers, extinguished both cue lights, and delivered the reward assigned to the pressed lever.

Failure to respond on forced- or free-choice trials within 30-s was scored as an omission. Omitted forced-choice trials were repeated. A variable ITI ensured that new trials began every 90 s. Amount-discrimination sessions continued until the 3-pellet reward was selected on $\geq 90\%$ of the free-choice trials for two consecutive sessions.

Assessing delay discounting. An adjusting-delay task was used to quantify delay discounting (Mazur, 1987). Trial structure was the same as that used in the amount-discrimination task but when the lever associated with the larger reward was pressed a delay was imposed between the response and the 3-pellet reward. During the delay, the lever(s) retracted and the cue light above the LLR lever remained illuminated. The delay, initially set at 0 s, adjusted based on each rat's choices in the preceding trial block. Choosing the LLR on both free-choice trials incremented the delay by 1 s, whereas choosing the SSR on both free-choice trials decreased the delay by 1 s. The delay remained constant if both rewards were selected once in the two free-choice trials. The final delay value obtained in a session served as the starting delay for the subsequent session. A programming error occurred during the first 19-25 sessions in which both cue lights accompanied the delay to the LLR. An additional 20 sessions were conducted following the correction of the programming error. Adjusting delays typically stabilize in 30 sessions or less (see, e.g., Craig, Maxfield, Stein, Renda, & Madden, 2014; Mazur, 2012) and have good test-retest reliability when assessed in a fixed number of sessions (McClure, Podos, & Richardson, 2014). Each rat's mean adjusted delay (MAD) over the final nine sessions served as the measure of delay discounting.

Working-memory training and Sham training.

Group Assignment. Rats with the most similar MADs were paired. One rat from each pair was randomly assigned to the WMT group and the other to the Sham group.

Interim Training. All rats completed a training phase that shaped the sequence of responses required in the subsequent task. Sessions were composed of 80 trials, which began with presentation of either the left or the right lever (strictly alternating between trials) and the corresponding cue light. A lever press caused the rear-wall lever, and its cue light, to be presented. Pressing the rear-wall lever resulted in a 2-pellet reward and initiated a 20-s ITI, with white-noise accompaniment. To signal the upcoming trial, the white-noise speaker cycled on and off (every 0.25 s) during the final 3 s of the ITI. Failure to respond on any lever within 10 s was scored as an omission and that trial was repeated. Across several sessions, the response requirement programmed on the side levers was gradually increased from a fixed-ratio 1 (FR 1) to an FR 10.

Working-memory training (WMT). Rats assigned to the WMT group completed 140 WMT sessions in which they earned food by making correct choices in a modified TDMTP task (see, e.g., Kangas et al., 2010; Porritt & Poling, 2008). In this procedure, rats were required to remember a cue over a delay period (i.e., retention interval) in which the cue was absent. The retention interval gradually increased (decreased) as the rat's percent correct was above (below) the accuracy criteria described below. Data from the first 65 sessions of this procedure have been previously reported (see Renda et al., 2014).

Each trial began by inserting either the right or the left lever (i.e., the “sample lever”) and illumination of the corresponding cue light. The sample lever inserted was selected randomly with the constraint that each lever was presented an equal number of times per session and the same sample lever could not be presented in more than four trials consecutively. Upon completion of an FR 10 on the sample lever, the lever was retracted, its cue light darkened, the rear-wall lever was inserted into the chamber (and its cue light illuminated), and the retention interval timer was initiated. A fixed interval (FI) schedule programmed on the rear-wall lever served as the retention interval timer; a single response after the interval elapsed presented the left and right front-wall levers and their cue lights simultaneously (i.e., the “comparison levers”). The FI arrangement on the rear-wall lever was designed to a) reduce the likelihood of mediating behavior during the retention interval (e.g., sitting in front of the correct sample lever) and b) require an operant response during the retention interval, thereby making the task more similar to the NIMH definition of working memory (NIMH, 2010). That is, rats had to actively maintain task relevant information and resist interference during the rear-wall task (for a similar procedure, see Harper, Hunt, & Schenk, 2006). A response on the comparison lever that matched the position of the sample stimulus was scored as correct and resulted in two food pellets; a mismatch was scored as incorrect and did not result in food delivery. After correct or incorrect trials, a fixed 20-s ITI, with white-noise accompaniment, was initiated. To signal the upcoming trial, the white-noise speaker was cycled on and off every 0.25 s during the final 3 s of the ITI.

Limited-hold contingencies were in place such that a response was required within 25 s for the sample lever and 10 s for the rear-wall and comparison levers. Failure to respond before the limited-hold elapsed was scored as an omission. A correction procedure was in place such that omitted or incorrect trials were repeated until the correct comparison lever was selected. During each session, eight 0-s retention interval trials occurred pseudorandomly (with the constraint that only two could occur consecutively). Intermixing these 0-s retention interval trials has been shown to maintain higher accuracy and minimize response bias (see Jones & White, 1994; Sargisson & White, 2001). Sessions ended after 48 (non-correction) trials or 2 hrs, whichever occurred first.

After the first session, the duration of the first retention interval within a session was set equal to the last retention interval experienced in the preceding session. Subsequently, following every eighth trial, percent correct was calculated over the preceding 20 (non-correction) trials; for the first two calculations within a session, responses made in the prior session were used. Based on these percent correct calculations, the duration of the retention interval in the next trial was changed (or not) using the titration rules outlined in Table 2-1. In general, if local percent correct was very high, the retention interval increased in duration; the opposite was true when percent correct declined. After 65 sessions, the retention interval was reset to 0 s because the accuracy of some rats' performance was declining, due in part to side bias. To continue WMT while better detecting and ameliorating this problem, the retention interval decreased when percent correct began to decrease on any single lever (early

Table 2-1.

Criteria used to titrate the duration of the retention interval and amount by which the interval was titrated. Different criteria were used in the range of sessions shown in the first column.

Session	Increase if overall % correct is	Decrease if overall % correct is	Decrease if % correct on either lever is	Titration increment
1-65	$\geq 90\%$	$< 70\%$	$< 70\%$	0.25 s or 2%*
66-95	$\geq 90\%$	$< 80\%$	$< 80\%$.06 s
96-140	$\geq 90\%$	$< 80\%$	$< 80\%$	0.25 s or 2%*

Note: *whichever was larger.

detection of lever bias) and increased more slowly across sessions 66-95; the latter restriction was relaxed in sessions 96-140 (see Table 2-1).

Sham training. Sham-trained rats also completed 140 sessions, each composed of 48 trials. Events occurring within the trial were, with one exception, exactly as experienced by their MAD-matched WMT rat. For example, if on the first trial the WMT rat received a left sample stimulus and experienced 10-s retention interval, then the Sham rat to which it was matched started the session with a left sample stimulus and experienced a 10-s “retention” interval. However, at the end of the retention interval the Sham rat was presented with only one pseudorandomly selected comparison lever (no more than four consecutive presentations of the same comparison lever and an equal number of left and right lever presentations each session). For the Sham-trained rat, food was delivered after pressing the comparison lever with a probability set to the overall obtained reinforcement rate of its MAD-matched WMT rat. Trials in which the WMT rat failed to respond (i.e., omissions) were not completed by the Sham rat. Sham rats

completed the same response requirements on the front- and rear-wall levers and the same limited-hold contingencies were in place. Omitted trials were repeated.

Post-training tasks.

Assessing working memory. To evaluate the effects of WMT vs. Sham training on subsequent working-memory performance, all rats completed a TDMTP task. This task, outlined by Kangas et al. (2010), was used because it provides a sensitive, continuous metric of working-memory performance that is not subject to ceiling effects. With the following three exceptions, the trial structure was identical to the WMT task: a) the retention interval duration was increased by 1 s following two consecutive correct trials and decreased by 1 s following a single incorrect trial, b) the correction procedure was omitted, and c) no 0-s delay trials were arranged. To ensure that the Sham rats could accurately complete the task, the retention interval was initially set to 0 s and both rats in the WMT/Sham pair completed this match-to-position task until the Sham rat achieved \geq 85% correct for two consecutive sessions. Sessions ended after 48 completed trials or after 2 hrs, whichever came first. Based on pilot data collected in our lab, 10 working-memory assessment sessions were conducted under the TDMTP task.

Reassessing delay discounting. The amount-discrimination and adjusting-delay tasks (as described above) were repeated, with the latter lasting a fixed 25 sessions.

Reassessing working memory. To determine if the effects of WMT on working-memory performance persist, the working-memory assessment was repeated for 10 sessions using the procedures described above.

Data analysis

To quantify delay discounting, MADs were calculated over the final nine sessions of the pre- and post-training adjusting-delay tasks for all rats, with lower MADs reflecting steeper delay discounting. Because MADs were not normally distributed, they were natural log-transformed before statistical analyses were conducted. Matched-samples t-tests were used to assess between-group differences in pre- and post-training MADs. The slopes of lines of best fit were used to evaluate any differences in trend over the final nine sessions. To determine if pre-training MADs were predictive of changes in delay discounting following working-memory (or sham) training (i.e., a rate-dependent effect; see Bickel, Landes, Kurth-Nelson, & Redish, 2014), change in delay discounting scores (post-training MAD divided by pre-training MAD) was regressed onto mean-centered pre-training MADs. Separate regression analyses were conducted for WMT and Sham groups. T-tests were used to determine if the slope coefficients (b) significantly differed from zero. In the post-training working-memory assessments, the average retention interval within a session served as the measure of working-memory performance, with higher retention intervals indicative of better working memory. For data collected in these sessions, a mixed-model ANOVA with a within-subject factor (Session) and a between-subject factor (Group) was used to evaluate if retention intervals were higher in the WMT group and if they increased more rapidly across sessions when compared to the Sham group. Bonferroni corrected post-hoc comparisons were made by conducting separate one-way ANOVAs resulting in a criterion alpha value of .005. Another mixed-model ANOVA was conducted to determine if retention intervals

changed from the first post-training working-memory assessment to the reassessment, with Time as the within-subject factor and Group as the between-subject factor.

Results

Following random assignment of rats to the WMT or Sham-training group, there was no significant between-group difference in pre-training MADs in the initial test of delay discounting, $t(18) = .98$, $p = .34$ (see Table 2-2) and the linear trends in grouped MAD values over the last nine sessions were judged to be equivalent and stable (WMT slope = 0.028, Sham slope = 0.027). There were no significant between-group differences in free- or forced-choice omissions or latency to make a response over the final nine sessions of the delay-discounting assessment, $p > .25$ in all cases (see Table 2-3).

Table 2-2.

Pre- and post-training mean adjusted delays (SEM) for WMT and Sham-trained rats.

Group	MAD (s)	
	Pre-training	Post-training
WMT	20.63 (3.72)	17.95 (2.50)
Sham	19.34 (3.39)	15.65 (3.18)

Note: MADs and SEM were calculated over the final nine sessions of the adjusting-delay procedure. No significant between-group differences were observed. MAD, mean adjusted delay; WMT, working-memory trained rats; Sham, sham-trained rats.

Table 2-3.

Omissions and response latencies (s) on forced- and free-choice trials (SEM) during the pre- and post-training adjusting-delay task.

	Pre-training		Post-training	
	WMT	SHAM	WMT	SHAM
Forced-choice omissions	0.64 (0.47)	0.22 (0.11)	0.32 (0.21)	0.08 (0.03)
Free-choice omissions	0.35 (0.22)	0.11 (0.04)	0.22 (0.18)	0.08 (0.02)
Latency to respond: Forced-choice	1.91 s (0.14)	1.84 s (0.11)	1.77 s (0.15)	1.58 s (0.09)
Latency to respond: Free-choice	1.79 s (0.11)	1.79 s (0.10)	1.73 s (0.13)	1.64 s (0.10)

Note: Omissions and latencies to respond to forced- and free-choice trials were averaged over the final nine sessions of the adjusting-delay procedure. No significant between-group differences were observed. WMT, working-memory trained rats; Sham, sham-trained rats.

Figure 2-2 shows the titrating retention intervals of individual rats assigned to the WMT group. Data are from the final 75 sessions of WMT². After 140 sessions of training, there were no visually apparent increasing trends and the average retention interval from sessions 131-135 was not significantly different from the average retention interval from sessions 136-140, $t(18) = .37, p = .72$. Over the final five sessions of WMT, the mean latency to respond on the rear-wall lever for WMT rats was 1.83 s ($SD = 1.69$), suggesting that these rats did not linger in front of the to-be-remembered sample-stimulus lever during the retention interval. This is consistent with our observations of rats in a pilot study in which no overt mediating behaviors (e.g., pressing the rear-wall lever while

² Spline curves fit to these rats' retention intervals over the first 65 sessions are presented in Renda et al. (2014). No significant differences were observed between the retention interval achieved at session 65 and those reached by session 140, $t(18) = .45, p = .66$.

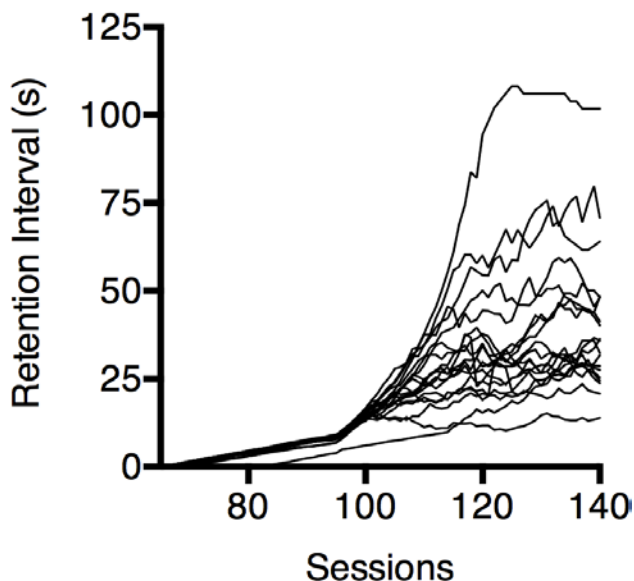


Figure 2-2. Retention intervals during working-memory training. Each line shows the average retention interval obtained in each session for individual rats across the final 75 sessions of working-memory training. Rats in the Sham-training group experienced the same “retention” intervals during these sessions.

orienting body position to the previously inserted sample lever; see Chudasama & Muir, 1997) were recorded.

Table 2-4 shows motivational measures collected during the final five sessions of WMT and Sham training. The only significant difference between groups was the latency to press the comparison lever, which was longer in the WMT group, $t(18) = 4.40, p < .001$; an expected outcome given that only WMT rats were required to choose between two comparison levers.

Figures 2-3A and 2-3B show individual rats’ retention intervals across the 10 sessions of the first post-training working-memory assessment for rats assigned to the WMT and Sham groups, respectively. Figure 2-3C represents the average retention intervals for the WMT group (black data path) and the Sham group (gray data path). There was a significant main effect of Session, $F(1, 18) = 81.68, p < .001$, and a

Table 2-4.

Omissions and latencies to respond to the sample and comparison stimuli (SEM) during WMT/Sham training and the initial and final working-memory assessments.

	Training		Initial Assessment		Final Assessment	
	WMT	SHAM	WMT	SHAM	WMT	SHAM
Sample omissions	1.25 (0.73)	0.16 (0.11)	8.51 (3.44)*	0.96 (0.86)	11.89 (4.84)	2.37 (1.05)
Comparison omissions	0.01 (0.00)	0.01 (0.00)	0.06 (0.05)	0.01 (0.01)	0.05 (0.04)	0.01 (0.01)
Latency to respond: sample	3.84 s (0.81)	3.24 s (0.56)	7.08 s (0.98)**	3.44 s (0.67)	6.65 s (0.81)*	4.19 s (0.74)
Latency to respond: comparison	1.85 s (0.10)***	1.37 s (0.06)	5.84 s (0.68)**	3.14 s (0.53)	5.85 s (0.62)*	3.69 s (0.54)

Note: Omissions and latencies to respond to the sample and comparison stimuli were averaged over the final five sessions of WMT/Sham training and the two post-training assessments of working memory. Significantly different than Sham-trained rats: * $p < .05$, ** $p < .01$, *** $p < .001$. WMT, working-memory trained rats; Sham, sham-trained rats.

significant interaction between Session and Group, $F(1, 18) = 27.75$, $p < .001$; thus, retention intervals increased more rapidly in the WMT group. Post-hoc comparisons revealed significant between-group differences in the average retention interval obtained at every session, p 's $< .001$. Table 2-4 depicts omission and latency data for the WMT and Sham rats in these post-training assessments of working memory. In the final five sessions of the initial working-memory assessment, WMT rats had significantly more sample omissions, $t(18) = 2.10$, $p = .05$, and significantly longer latencies to respond on the sample and comparison levers, $t(18) = 3.04$, $p < .01$ and $t(18) = 3.15$, $p < .01$, respectively. No significant difference was observed in comparison omissions over the final five sessions, $p > .30$.

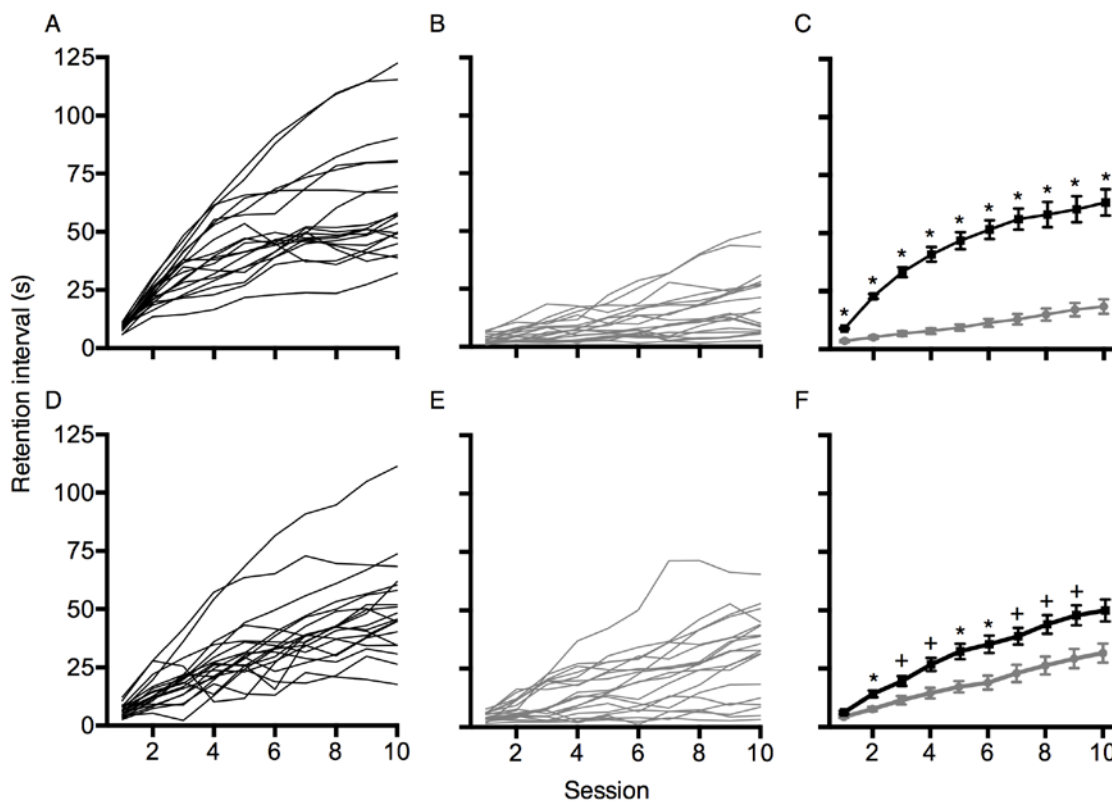


Figure 2-3. Average retention intervals from each session of post-training working-memory assessments. Panels A and B show retention intervals obtained during the initial working-memory assessment for individual WMT and Sham rats, respectively. Panel C shows between-subject averages and *SEM* for the WMT group (black data paths) and the Sham group (gray data paths). Panels D and E show the average retention intervals in the reassessment of working memory for individual WMT and Sham rats, respectively. Panel F shows the between-subject averages and *SEM* from this final assessment, separated by group. * $p < .001$; + $p < .005$

Table 2-2 shows post-training MADs for the WMT and the Sham-trained groups.

No significant between-group differences were observed, $t(18) = .72$, $p = .48$. Likewise, there were no significant between-group differences in free- or forced-choice omissions or latency to make a response over the final nine sessions, p 's $> .20$ (see Table 2-3).

There was no significant correlation between post-training MADs and the average retention interval obtained during the final session of WMT, $r = .22$, $p = .36$; likewise, there were no significant correlations between post-training MADs and the final retention

interval obtained during the initial assessment of working memory for the WMT or the Sham-trained groups, $r = .27, p = .27$ and $r = .36, p = .13$, respectively.

In a reanalysis of the data obtained by Bickel et al. (2011), Bickel et al. (2014) reported rate-dependent effects of WMT on delay discounting. That is, individuals with steeper pre-training discounting rates had the greatest reduction in discounting rates following WMT. In the present study, low pre-training MADs (i.e., steeper delay discounting) were not predictive of larger post-training changes in MADs for the WMT group, $b = -.26, t = -1.29, p > .20$, or the Sham group, $b = -.31, t = -1.81, p > .05$.

Figures 2-3D and 2-3E show individual rats' retention intervals over the final working-memory assessment (following the delay-discounting assessment) for the WMT and Sham groups, respectively. Figure 2-3F represents the average retention interval obtained each session for the WMT group (black data path) and the Sham-trained group (gray data path). There was a significant main effect of Session, $F(1, 18) = 86.75, p < .001$, and a significant Session by Group interaction, $F(1, 18) = 5.19, p = .01$. Post-hoc comparisons revealed significant between-group differences in the average retention interval from sessions 2-9, p 's $< .005$. With the Bonferroni corrected alpha value of .005, the differences at session 1 and session 10 only approached significance, $p = .009$ and $p = .006$, respectively. There were no significant correlations between post-training MADs and the reassessment of working memory for the WMT or the Sham-trained groups, $r = .37, p = .12$ and $r = .34, p = .15$, respectively. Table 2-4 shows omission and latency data for the WMT and Sham rats in the final assessment of working memory. Over the last five sessions, WMT rats had significantly longer latencies to respond to the sample and

comparison levers, $t(18) = 2.21, p < .05$ and $t(18) = 2.51, p < .05$, respectively. There were no significant differences in sample or comparison omissions over the final five sessions, p 's $> .05$.

A separate ANOVA conducted on the retention intervals obtained at session 10 of the first working-memory assessment and the reassessment revealed a significant Time by Group interaction, $F(1, 18) = 30.31, p < .001$, but no significant main effect of Time, $p = .99$. Thus, retention intervals tended to decrease slightly for the WMT rats and increase slightly for the Sham rats from the initial assessment of working memory to the reassessment.

Discussion

The current study examined effects of extended WMT on subsequent working-memory performance and delay discounting in male Long-Evans rats. Although WMT enhanced post-training working-memory performance relative to the Sham-trained rats, there was no significant between-group difference in post-training delay discounting. These findings are in contrast to Bickel et al.'s (2011) report that WMT decreased human stimulant abusers' rates of delay discounting by approximately 50%.

What underlies this null effect of WMT on delay discounting is, of course, impossible to say with certainty. Recognizing the speculative nature of what follows, we will discuss four possible accounts for this trans-species failure to replicate the Bickel et al. (2011) findings; perhaps these speculations will prove useful in designing future experiments. First, it is possible that the working-memory ability of the WMT rats did not

improve (relative to the Sham-trained rats) by the working-memory training that was provided. One piece of evidence against this is the post-training retention intervals across which our rats remembered the sample stimulus are, to the best of our knowledge, the highest reported in the titrating-delay match-to-position literature (e.g., Porrirt & Poling, 2008, using a similar procedure, reported a mean peak retention interval of 32.85 s, *SEM* = 4.56, whereas our WMT rats achieved a mean peak retention interval of 68.32 s, *SEM* = 5.71, in the post-training reassessment of working memory). More robust evidence that WMT positively impacted working-memory ability would have been obtained had WMT rats performed better than Sham rats in a novel working-memory task (for review of rodent working-memory preparations, see Dudchenko, 2004; Pontecorvo, Sahgal, & Steckler, 1996) and future studies might include such a post-training test phase. One caution is that effects of working-memory training often do not generalize to improved performance on novel tasks (Ball et al., 2002; Owen et al., 2010; Redick et al., 2013); indeed such was the case in the Bickel et al. study—WMT did not enhance post-training working-memory performance when the tasks used in testing were different from those used in training.

A second possible account of the trans-species failure to replicate the Bickel et al. (2011) finding has to do with differences in the working-memory tasks used in training. In our WMT phase, the duration over which rats remembered the sample stimulus was increased when accuracy was high, whereas in the Bickel et al. study, the number of stimuli to be remembered was increased (i.e., memory capacity). For example, in the Sequence Recall of Digits test employed by Bickel and colleagues, humans were initially

asked to recall a sequence of three digits. With each correct response, the to-be-remembered sequence increased by one digit, up to a maximum of 10 digits; no explicit retention interval was arranged. By contrast, our rats recalled a single stimulus (left/right sample lever presentation) over long retention intervals. Our task was selected because Bickel et al. hypothesized that widening the temporal window across which events could influence behavior was important in influencing discounting; increasing the working-memory retention interval to a duration approximating the delays to reinforcement in the delay-discounting task seemed the most direct translation of this hypothesis. Beyond this, our task was designed to approximate the NIMH definition of working memory – “the active maintenance and flexible updating of goal/task relevant information...in a form that has limited capacity and resists interference.” Rats were required to maintain information about the location of the sample stimulus while completing an interference task on the rear-wall lever during the retention interval. Further, the rats were required to update task relevant information by forgetting the prior sample stimulus with each new trial. Nonetheless, our task did not increase rats’ ability to recall multiple stimuli (i.e., memory capacity) and this may underlie our failure to observe an effect of WMT on subsequent delay discounting. Future nonhuman studies should employ a working-memory task that could potentially expand subjects’ working-memory capacity (e.g., an odor non-match to sample task; Dudchenko, Wood, & Eichenbaum, 2000).

A third account of the trans-species failure to replicate relates to the nature of the rewards arranged in the two studies. In the Bickel et al. (2011) study, participants completed three delay-discounting tasks in which verbal descriptions of rewards and

delays were provided. In two of these tasks the rewards and delays were hypothetical and asymptotic working-memory performance was significantly correlated (or nearly so) with post-training discounting rates ($\rho = -.61, p = .02$ and $\rho = -.52, p = .06$ when the LLR was \$1000 and \$100, respectively). In the third discounting task, real rewards and delays were arranged such that participants received the outcome they had chosen on a randomly selected trial. In the latter task, working memory performance was not correlated with post-training discounting rates, $\rho = -.37, p = .19$. This finding is consistent with the current study (i.e., when real rewards were arranged in both studies, improvements in working memory were not predictive of lower delay discounting). Why the effects of working-memory enhancement would be confined to the discounting of hypothetical events is not immediately obvious.

A final account of the trans-species failure to replicate is that the Bickel et al. (2011) finding is a Type 1 error. Participants that completed WMT in that study did not improve their working-memory ability in a post-training assessment of working memory and the extent to which participants' working-memory skills improved on the training tasks was not reported. Bickel et al. hypothesized the training tasks were sufficiently different from the post-training working-memory assessment, such that skills acquired in one task did not generalize to the other. Why these enhanced skills generalized to the delay-discounting task is unclear. A direct replication of this study is needed to address this concern.

In conclusion, the current study failed to provide evidence that WMT reduces delay discounting in male rats. This finding is inconsistent with the human literature and

may be due to procedural differences, a species difference, or a Type 1 error. Future studies should examine the effects of increasing rats' working-memory *capacity* on subsequent delay discounting. There is also a need to replicate the effects of WMT on human delay discounting with real and hypothetical rewards. Experimentally manipulating nonhuman delay discounting is important as it allows an exploration of the possible causal relation between individual differences in delay discounting and maladaptive behaviors (e.g., in nonhuman models of drug self-administration).

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CHAPTER 3
IMPULSIVE CHOICE AND PRE-EXPOSURE TO DELAYS: III.
FOUR-MONTH TEST-RETEST OUTCOMES IN
MALE WISTAR RATS¹

Abstract

Delay discounting describes the tendency for organisms to devalue outcomes because they are delayed. Robust, positive correlations exist between excessive delay discounting and many maladaptive behaviors (e.g., substance abuse, obesity). Several studies have demonstrated that delay discounting can be reduced and this may hold promise for improving treatment outcomes. One method of reducing delay discounting provides rats with extended training with delayed reinforcement (i.e., delay-exposure training) and this significantly reduces impulsive choices, relative to rats trained with an equal number of immediate-reinforcement sessions (i.e., immediate-exposure training). To evaluate the stability of this effect, 12 weanling male Wistar rats were randomly assigned to receive either delay-exposure or immediate-exposure training for 120 sessions. Impulsive choice was assessed using an increasing-delay procedure immediately following training and 120 days after completion of the initial assessment. Delay-exposed rats discounted delayed food rewards significantly less than immediate-

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exposed rats in the initial assessment and the reassessment conducted 120 days later. These results are encouraging as they suggest that the effects of delay-exposure training are robust to the passage of time and intervening experience.

Introduction

Impulsivity is a multifaceted construct that describes many forms of maladaptive behaviors (for review, see Evenden, 1999). One such form of impulsivity—impulsive choice—involves preference for smaller, sooner rewards (SSR) over larger, later rewards (LLR). Delay discounting describes the subjective devaluation of the LLR, and this process is thought to underlie impulsive choice (for reviews, see Madden and Johnson, 2010; Stein and Madden, 2013; Odum, 2011).

Strong, positive correlations have been observed between excessively discounting delayed rewards and many problematic behaviors such as substance abuse (e.g., Heil et al., 2006; Madden et al., 1997; Vuchinich & Simpson, 1998; for meta-analysis, see MacKillop et al., 2011), poor health behaviors (e.g., Bradford, 2010; Daugherty and Brase, 2010), and pathological gambling (e.g., Albein-Urios et al., 2012; Alessi and Petry, 2003; Petry, 2001). Because excessive delay discounting is a common process shared among many problematic behaviors, some consider it a trans-disease process (Bickel et al., 2012; Bickel and Mueller, 2009). If excessive delay discounting underlies poor decision-making, exploring techniques for reducing impulsive choice may yield therapeutic benefits for a wide range of behavioral maladies (Bickel et al., 2015; Gray and MacKillop, 2015; Koffarnus et al., 2013).

Impulsive choice can be experimentally reduced in humans (for review, see Gray and MacKillop, 2015; Koffarnus et al., 2013) and nonhumans (Mazur and Logue, 1978; Stein et al., 2013, 2015). In humans, reductions in impulsive choice have been observed using a number of strategies such as working-memory training (Bickel et al., 2011), contingency management of substance use (e.g., Landes et al., 2012; Yi et al., 2008), and episodic future thinking (e.g., Peters and Büchel, 2010; Lin and Epstein, 2014). In nonhumans, a training regimen involving early and extended exposure to delayed reinforcement resulted in significant decreases in impulsive choice (Stein et al., 2013, 2015). In the latter studies, one group of weanling Long Evans rats learned to press a lever for food delayed by 17.5 s; the rats subsequently completed 120 sessions of this Delay-Exposure (DE) training. A second group of rats completed the same sessions but food was delivered immediately after the lever press (Immediate-Exposure group; IE). At the post-training impulsive-choice assessment, DE rats made significantly fewer impulsive choices than IE rats (common language [CL] effect size² = .80 and .82, respectively in Stein et al., 2013, 2015). These differences remained significant at retests conducted approximately 66 and 48 days, respectively, after rats were given the opportunity to consume oral alcohol.

One goal of the current study was to systematically replicate the methods of Stein et al. (2013, Stein et al., 2015) to evaluate the duration of the DE effect at a longer

² CL effect size was calculated, as it is robust to normality violations (see McGraw and Wong, 1992); as applied to these data, CL effect size is the likelihood that a randomly sampled DE rat will make fewer impulsive choices than a randomly sampled IE rat (Lakens, 2013).

follow-up interval. As such, the follow-up interval was extended to 120 days and rats did not consume alcohol during the test-retest interval. A second goal of the current study to examine whether the DE effect generalizes to a different strain of rats. To that end, Wistar rats were used instead of Long Evans rats. Wistar rats are commonly used in studies assessing delay discounting as a predictor for cocaine self-administration (e.g., Anker et al., 2009; Perry et al., 2005; Perry et al., 2008; Regier, Claxton, Zlebnik, & Carroll, 2014; Broos et al., 2012). Evaluating the DE effect in Wistars was conducted as a precursor to a larger study of the effect of this training on cocaine self-administration.

Method

Subjects

Subjects were 12 naïve, male Wistar rats (Harlan, Indianapolis, IN) approximately 21 days old at intake. Rats were block-randomized to either the DE or IE groups ($n = 6$ per group). Rats were individually housed in an animal colony operating on a 12 hr light:dark cycle (light onset at 7:00 am). After 5 days of free access to food, rats were gradually food restricted to 85% of their dealer-supplied growth curve free-feeding weights. They were maintained at this weight for all behavioral assessments but were otherwise given free access to food during the test-retest interval. Throughout the experiment, rats had free access to water in their home cage. Experimental sessions were conducted daily at the same time. Supplemental food was provided 2 hrs post-session.

Apparatus

Six identical operant chambers (Med Associates, St. Albans, VT), housed within

ventilated sound-attenuating cubicles and equipped with white-noise speakers, were used. Two low-profile retractable levers were positioned on the front wall of each chamber (10.5 cm above the grid floor). A pellet dispenser delivered 45-mg food pellets (Bio-Serv, Frenchtown, NJ) to a receptacle that was centered between the two front-wall levers. An identical lever was centered on the opposing chamber wall (10.5 cm above the grid floor). Above each lever was a 28-V cue light.

Procedures

Figure 3-1 depicts the order of experimental conditions and approximate age of the rats.

Delay-Exposure and Immediate-Exposure Training. An autoshaping procedure was used to establish responding on the rear-wall lever (for a detailed description, see Stein et al., 2013). Autoshaping continued until rats pressed the rear-wall lever to earn $\geq 90\%$ of the reinforcers for 2 consecutive sessions. Next, rats received 120 sessions of DE or IE training. For both groups, the presentation of the rear-wall lever and the cue light marked the beginning of each trial. For DE rats, one lever press retracted the lever and initiated a 17.5-s delay during which the cue light remained illuminated.

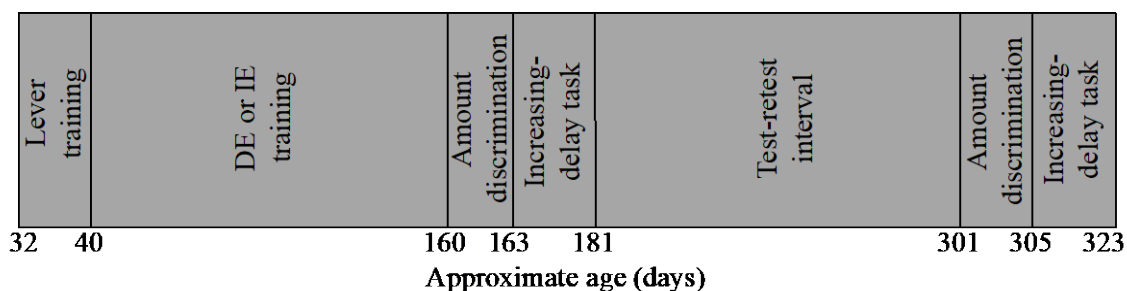


Figure 3-1. Order of experimental conditions and approximate age of the rats.

Following the delay, the cue light was extinguished and two food pellets were delivered. For IE rats, one lever press immediately extinguished the cue light and two food pellets were delivered. For the remainder of the trial, no experimental stimuli were presented; trials began every 60 s. Failure to respond within 20 s of lever insertion was scored as an omission and omitted trials were repeated. Sessions ended after 80 completed trials or after 2 hrs, whichever came first.

Impulsive-Choice Task. Immediately following DE or IE training, an increasing-delay procedure (Evenden and Ryan, 1996) was used to assess impulsive choice. Sessions were divided into three trial-blocks, each separated by a 7-min blackout. Each trial-block consisted of 6 forced- and 14 free-choice trials. In forced-choice trials, the rear-wall lever and cue light were presented at trial onset. One response retracted the lever, extinguished the light, and either the left or right front-wall lever and cue light were presented. One response to the front-wall lever retracted the lever, extinguished the light, and the reinforcer associated with that lever was delivered. A post-food blackout ensured that new trials began every 90 s. Free-choice trials were identical to forced-choice trials with the exception that both levers (and cue lights) were presented following a rear-wall lever press, and both levers were retracted following a choice. Failure to respond to any lever within 30 s was scored as an omission and forced-choice trials were repeated.

Amount-discrimination sessions were conducted initially; all free-choice trials in these sessions were between one and three food pellets sans delay. Following 2 consecutive days with $\geq 90\%$ choice of the larger reward, the delay to the larger reward was increased across trial-blocks in the following order: 0, 15, and 30 s. If the LLR was

selected, the cue light above the lever remained lit until the delay elapsed and three pellets were delivered. Following 7 sessions in the impulsive-choice procedure, a single amount-discrimination session was conducted to evaluate if choice was sensitive to reward amount and delay, or instead showed a habitual pattern of avoiding the larger reward after the first trial block. Subsequent to that probe session, testing continued for at least 6 more sessions and until the following stability criteria were met: 1) $\geq 80\%$ choice of the larger reward in the 0-s delay block for 5 consecutive sessions, 2) percent LLR choice in each of the final 5 sessions did not deviate by more than 20% from the 5-day mean, and 3) no monotonic increasing or decreasing trend was observed over the last 3 sessions. Testing was terminated upon meeting this stability criterion.

Impulsive choice was reassessed 120 days after the completion of the initial assessment. During the test-retest interval, all rats completed approximately 22 sessions in an operant task not relevant to the current experiment (all rats completed the same task, with no significant differences in reinforcer rate across groups). Subsequently, rats were returned to their free-feeding weights and remained in their home cages until the impulsive-choice reassessment.

Data Analysis. Separate, independent-samples *t*-tests were used to examine between-group differences in the following measures from training: 1) number of days to acquire rear-wall lever pressing and 2) trials completed, omissions, and response latencies during DE/IE training (averaged over the final 10 sessions).

Percent LLR choice was averaged across the final 5 days of the assessments. To quantify impulsive choice, area under the curve (AUC; see Myerson et al. 2011) was

calculated from the average percent LLR choice for each rat; higher AUC values indicate greater preference for the LLR. Pearson's r correlation coefficients were used to examine the relationship between post-training AUC scores and those obtained 120-days later at the retest. Separate, mixed-model ANOVAs were used to examine the main effects of the within-subject factor (Time), the between-subject factor (Group), and the interaction for the following measures: 1) AUC values, 2) number of days to meet the amount-discrimination criteria and the impulsive-choice stability criteria, 3) percent LLR choice during the amount-discrimination probe sessions, and 4) omissions and response latencies (averaged over the final 5 sessions). Post-hoc comparisons of significant findings were made by conducting separate, independent-samples t -tests. Bonferroni's correction was applied to the post-hoc comparisons resulting in a criterion alpha value of .025. All other tests were deemed statistically significant at $p < .05$.

Results

The behavior of one DE rat was excluded from analysis because an intractable side bias was evident in the impulsive-choice reassessment; this exclusion did not affect the significance of the tests prior to the follow-up. No between-group difference was observed in the number of days to establish rear-wall lever pressing, $p = .58$ (see Table 3-1). During the final 10 sessions of DE/IE training, there were no significant between-group differences in the number of trials completed, omissions, or response latencies, p 's $> .22$ (see Table 3-1).

Table 3-1.

Mean days to acquire rear-wall lever pressing and the mean number of trials completed, response latencies, and omissions in DE/IE training (\pm SEM).

	DE	IE
Days to acquire lever pressing	8.20 (1.28)	7.17 (1.22)
Trials completed	80.00 (0.00)	80.0 (0.00)
Response latencies	1.59 (0.44)	1.73 (1.14)
Omissions	1.50 (0.82)	0.38 (0.38)

Note: The number of trials completed, response latencies, and omissions were calculated over the final 10 sessions of DE/IE training. No significant between-group differences were observed. DE, Delay-exposure group; IE, Immediate-exposure group

In the impulsive-choice assessments, there were no main effects of Time or Group and no Time x Group interaction in the number of days to meet the amount-discrimination criteria, p 's > .18, or in the number of sessions required to meet the stability criteria, p 's > .30 (see Table 3-2). Figure 3-2 depicts mean percent LLR choice (\pm SEM) in the initial assessment (left panel) and the reassessment (right panel) of impulsive choice. The inset bar graphs show the mean (\pm SEM) and individual-subject AUC values. From test to retest, there was no main effect of Time and no Time x Group interaction, $p = .57$ and $p = .34$, respectively. However, a significant main effect of Group was observed, $F(1, 9) = 27.28$, $p < .001$. Post-hoc comparisons revealed significant between-group differences in AUC in the initial assessment, $t(9) = 7.49$, $p < .0001$; $CL = .99$, and the reassessment, $t(9) = 3.30$, $p < .01$; $CL = .92$. In addition, there was a strong, positive correlation between the initial and reassessment of AUC scores in the DE group, $r = .91$, $p < .05$, but not in the IE group, $r = .40$, $p = .44$. No significant main effects of Time or Group and no Time x Group interaction were observed in percent LLR choice

Table 3-2.

Mean days to meet the discrimination and stability criteria, mean percent LLR choice in the probe sessions, and the mean omissions and response latencies in the initial assessment and reassessment of impulsive choice (\pm SEM).

	Initial Assessment		Reassessment	
	DE	IE	DE	IE
Days to meet amount-discrimination criteria	3.00 (0.45)	2.50 (0.22)	4.20 (1.24)	3.00 (0.52)
Days to meet stability criteria	17.80 (3.80)	19.33 (3.30)	15.00 (0.45)	20.83 (5.52)
Percent LLR choice: Probe session	0.98 (0.01)	0.94 (0.04)	0.96 (0.02)	0.97 (0.02)
Omissions	0.44 (0.26)	0.40 (0.36)	0.60 (0.55)	0.10 (0.10)
Latency to respond: SSR Forced-choice	2.19 (0.55)	1.56 (0.10)	2.02 (0.33)	1.37 (0.09)
Latency to respond: LLR Forced-choice	1.62 (0.38)	2.05 (0.44)	1.70 (0.38)	1.83 (0.47)
Latency to respond: SSR Free-choice	2.12 (0.31)	1.61 (0.10)	3.82 (1.32)	1.49 (0.18)
Latency to respond: LLR Free-choice	2.11 (0.57)	1.29 (0.09)	1.97 (0.39)	1.19 (0.09)

Note: Omissions and response latencies were calculated over the final 5 sessions of the initial and reassessment of impulsive choice. No significant main effects of Time or Group or Time x Group interactions were observed. DE, Delay-exposure group; IE, Immediate-exposure group

for the amount- discrimination probe sessions, p 's > .34 (see Table 3-2). Finally, there were no main effects of Time or Group and no Time x Group interaction in the number of omissions, p 's > .29, or the latency to respond on forced- and free-choice SSR or LLR trials, p 's > .08 (see Table 3-2).

Discussion

The present research examined the longer-term effects of DE training in male Wistar rats. As in prior research conducted with Long Evans rats (Stein et al., 2013,

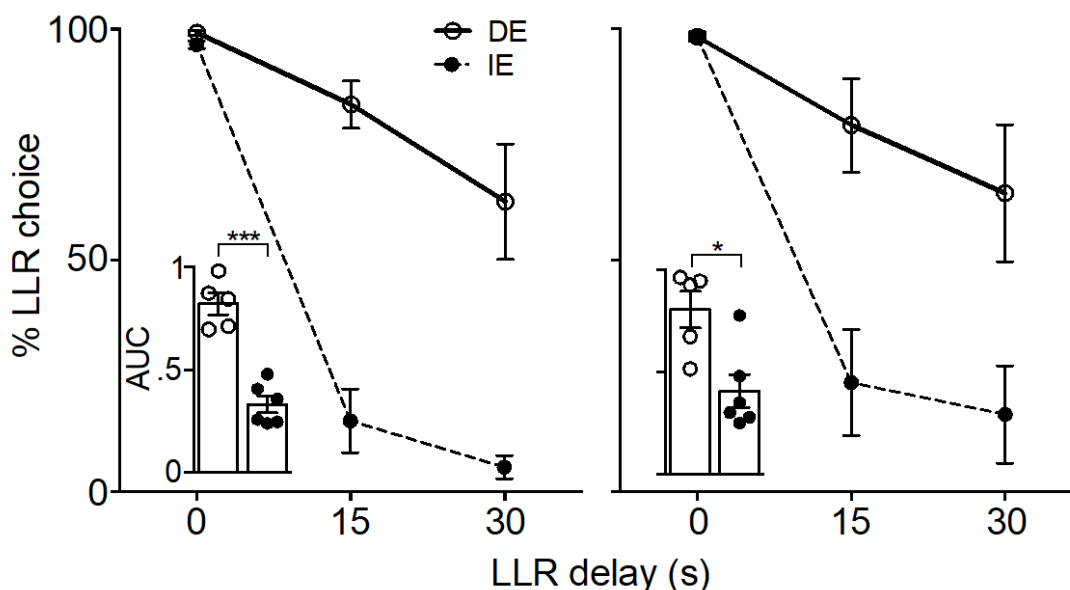


Figure 3-2. Mean percent LLR choice in the initial assessment (left panel) and reassessment (right panel) of impulsive choice. Solid and dashed data paths represent the DE and IE group, respectively. The inset graphs represent mean and individual-subject AUC values for the DE rats (open data points) and the IE rats (closed data points). Error bars depict \pm SEM. * $p < .01$; *** $p < .0001$

2015), Wistar rats randomly assigned to the DE group made significantly fewer impulsive choices than those assigned to the IE group. The Stein et al. (2013, 2015) findings were extended to show that DE-training effects may be observed 120 days after the initial impulsive-choice assessment (the longest prior test-retest interval was 66 days). It is noteworthy that 120 days of the Wistar rats' life corresponds to approximately 11 human years when one considers the relative lifespans of these species (Hubrecht and Kirkwood, 2010); thus, the effects of DE training last a significant portion of the rats' lifespan.

In the Stein et al. (2013, 2015) studies, rats were given the opportunity to consume alcohol during the test-retest interval. Rats in the present study consumed no alcohol; however, both groups completed an operant task for a portion of the test-retest

interval. Because reductions in impulsive choice were observed at follow-up in spite of this intervening task, the present study, when combined with those of Stein et al., suggests that the effect of DE training on impulsive choice is robust to a variety of intervening events. Future research might further explore how robust the DE-training effect is by examining if it generalizes to other impulsive-choice assessments (e.g., adjusting-delay task; Mazur, 1987) or to impulsive-choice tasks arranged in different chambers or with different rewards. If DE training proves robust in these generalization tests, studies should be undertaken to adapt the training for use with, for example, pre-school children. Embedding DE training into a game played in pre-school classrooms might reduce impulsive choice in the game, in the classroom, and perhaps beyond.

Finally, it is noteworthy that the effect of DE training was more pronounced in this study than in prior reports (Stein et al., 2013, 2015). The reason for the larger effect size can only be speculated upon. Because the procedures are unchanged from past studies, the rat-strain difference (Wistars vs. Long Evans) may be responsible, a possibility to be evaluated in future studies.

Conclusion

The present study provides encouraging results for researchers interested in producing large, long-lasting reductions in impulsive choice that are robust to intervening experiences. Such an effect may provide a useful baseline against which future studies are conducted (e.g., effects of reducing impulsive choice on subsequent acquisition of cocaine self-administration; Perry et al., 2005).

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CHAPTER 4
IMPULSIVE CHOICE AND PRE-EXPOSURE TO DELAYS: IV.
EFFECTS OF DELAY- AND IMMEDIACY-EXPOSURE
TRAINING RELATIVE TO MATURATIONAL
CHANGES IN IMPULSIVITY¹

Abstract

Impulsive choice describes preference for smaller, sooner rewards over larger, later rewards. Excessive delay discounting (i.e., rapid devaluation of delayed rewards) underlies some impulsive choices, and is observed in many maladaptive behaviors (e.g., substance abuse, gambling). Interventions designed to reduce delay discounting may provide therapeutic gains. One such intervention provides rats with extended training with delayed reinforcers. When compared to a group given extended training with immediate reinforcers, delay-exposed rats make significantly fewer impulsive choices. To what extent is this difference due to delay-exposure training shifting preference toward self-control or immediacy-exposure training (the putative control group) shifting preference toward impulsivity? The current study compared the effects of delay- and immediacy-exposure training to a no-training control group and evaluated within-subject changes in impulsive choice across 51 male Wistar rats. Delay-exposed rats made

¹ Chapter 4 of this dissertation was adapted from “Impulsive choice and pre-exposure to delays: IV. Effects of delay- and immediacy-exposure training relative to maturational changes in impulsivity,” by C. R. Renda, J. M. Rung, J. E. Hinnenkamp, S. L. Lenzini, and G. J. Madden, in press, *Journal of the Experimental Analysis of Behavior*. Permission-to-use letters are provided in Appendix D.

significantly fewer impulsive choices than immediacy-exposed and control rats. Between-group differences in impulsive choice were not observed in the latter two groups. While delay-exposed rats showed large, significant pre- to post-training reductions in impulsive choice, immediacy-exposed and control rats showed small reductions in impulsive choice. These results suggest that extended training with delayed reinforcers reduces impulsive choice, and that extended training with immediate reinforcers does not increase impulsive choice.

Introduction

The subjective value of a reinforcer decreases as a function of the delay to its receipt. This process is referred to as delay discounting, and it often underlies a specific type of impulsivity—impulsive choice (for review, see Evenden, 1999). Impulsive choice describes preference for a smaller-sooner reward (SSR) over a larger-later reward (LLR). That is, if an LLR is discounted steeply, such that its subjective value falls below the objective (i.e., present) value of an SSR, preference will, all else being equal, be directed toward the SSR (i.e., an impulsive choice).

A large literature has revealed a positive correlation between steeply discounting delayed rewards and maladaptive behaviors such as substance abuse (e.g., Heil, Johnson, Higgins, & Bickel, 2006; Madden, Petry, Badger, & Bickel, 1997; Vuchinich & Simpson, 1998; for meta-analysis, see MacKillop et al., 2011), pathological gambling (e.g., Albein-Urios, Martinez-Gonzalez, Lozano, Clark, & Verdejo-Garcia, 2012; Alessi & Petry, 2003; Petry, 2001; for review, see Reynolds, 2006), obesity (e.g., Davis, Patte, Curtis, &

Reid, 2010; Weller, Cook, Avsar, & Cox, 2008; for meta-analysis, see Amlung, Petker, Jackson, Balodis, & MacKillop, 2016), risky sexual behaviors (Chesson et al., 2006), and other health-decrementing behaviors (e.g., Bradford, 2010; Daugherty & Brase, 2010; Odum, Madden, Badger, & Bickel, 2000). How steeply an individual discounts delayed rewards is also correlated with the severity of substance use (e.g., Albein-Urios et al., 2012; MacKillop et al., 2010; Vuchinich & Simpson, 1998). The possibility that steep delay discounting plays a causal role in human addictive behavior comes from longitudinal studies showing that discounting rates predict initiation of substance use in humans (Audrain-McGovern et al., 2009; Khurana et al., 2013; Kim-Spoon, McCullough, Bickel, Farley, & Longo, 2014). Similarly, high levels of impulsive choice in rats precedes and predicts acquisition of cocaine self-administration (e.g., Perry, Larson, German, Madden, & Carroll, 2005; Perry, Nelson, & Carroll, 2008) and may be related to responding in other drug self-administration preparations (e.g., escalation, demand, maintenance; e.g., Anker, Perry, Gliddon, & Carroll, 2009; Koffarnus & Woods, 2013; Marusich & Bardo, 2009; for review, see, e.g., Stein & Madden, 2013). This (and other) evidence led Bickel, Koffarnus, Moody, and Wilson (2014) to suggest that excessive delay discounting may serve as a behavioral marker for addiction. As such, it may prove useful in identifying individuals at risk for developing an addiction, and interventions designed to decrease the extent to which delayed outcomes are discounted may prevent or ameliorate human addictive disorders (Bickel, MacKillop, Madden, Odum, & Yi, 2015; Gray & MacKillop, 2015).

Koffarnus, Jarmolowicz, Mueller, and Bickel (2013) reviewed four studies that used therapeutic interventions to reduce delay discounting in substance-dependent individuals. Moderate effect sizes (Cohen's $d = -0.41$ to -0.59) were observed through working-memory training (Bickel, Yi, Landes, Hill, & Baxter, 2011), contingency management for both smoking (Yi et al., 2008) and opioid-dependence (Landes, Christensen, & Bickel, 2012), and a money-management intervention for cocaine and/or alcohol use (Black & Rosen, 2011). In addition, reductions in delay discounting have been observed with other strategies such as episodic future thinking (e.g., Lin & Epstein, 2014; Peters & Büchel, 2010) and framing effects (e.g., DeHart & Odum, 2015; Magen, Dweck, & Gross, 2008).

In nonhumans, systematic training regimens have produced reductions in impulsive choice (e.g., Mazur & Logue, 1978; Renda & Madden, 2016; Smith, Marshall, & Kirkpatrick, 2015; Stein et al., 2013; Stein, Renda, Hinnenkamp, & Madden, 2015). In the Stein et al. (2013, 2015) and Renda and Madden (2016) studies, one group of weanling rats was trained for 90-120 sessions to press a lever that produced food following a 17.5-s delay (i.e., delay-exposure [DE] training). In each of these studies, a second group of rats was trained for the same duration to press the same lever, but with the same amount of food delivered immediately (i.e., immediacy-exposure [IE] training). After training, a within-session, increasing-delay procedure (e.g., Evenden & Ryan, 1996) was used to assess impulsive choice. Compared to rats in the IE group, DE rats made fewer impulsive choices in all three studies; the common language (*CL*) effect

sizes² were large: $CL = .80$ (Stein et al., 2013), $CL = .82$ (Stein et al., 2015), and $CL = .99$ (Renda & Madden, 2016). In addition, significant between-group differences in impulsive choice remained following test-retest intervals of approximately 48 (Stein et al., 2015; $CL = .76$), 66 (Stein et al., 2013; $CL = .73$), and 120 days (Renda & Madden, 2016; $CL = .92$).

Although DE training produces large and lasting between-group differences in impulsive choice, it is unclear whether this difference is attributable to decreases in impulsive choice in the DE group, increases in impulsive choice in the IE group, or some combination of the two. The IE group served as the control group in these prior studies, holding constant the rats' experience with levers, the chamber, number of opportunities to respond for a food reinforcer, etc., but with no exposure to delayed-reinforcement contingencies. If extended exposure to immediate reinforcement increases impulsive choice in IE rats, then prior reports have over-estimated the impulsivity-reducing effects of DE training. Additionally, prior research has shown that impulsive choice in rodents decreases with age (e.g., Doremus-Fitzwater, Barreto, & Spear, 2012; Pinkston & Lamb, 2011; Simon et al., 2010). Because DE training spans from early adolescence (~34 post-natal days) into adulthood (~160 post-natal days), any reductions in impulsive choice in the DE group may reflect maturation; IE training may inhibit this developmental progression thus accounting for the between-group differences observed in prior research.

² As applied to these data, CL effect size is the probability that a randomly selected DE rat will make less impulsive choices than a randomly selected IE rat (Lakens, 2013). CL effect size is robust to violations of normality (see McGraw & Wong, 1992).

The current study sought to address this limitation by assessing pre-training levels of impulsive choice and by the addition of a control group that did not receive training. First, rats completed a locomotor assessment³ using a circular corridor apparatus. Next, impulsive choice was assessed using a within-session, increasing-delay procedure (e.g., Evenden & Ryan, 1999). Rats were assigned to the DE ($n=17$), IE ($n=17$), or no-training control (CONT; $n=17$) groups in a way that minimized between-group differences in locomotor activity and pre-training levels of impulsive choice. Following the pre-training assessments, DE and IE rats received 120 sessions of their respective training. The CONT group completed the same pre- and post-training assessments but they were follow while rats in the DE/IE groups completed training. Finally, impulsive choice was reassessed immediately post training.

Method

Subjects

Subjects were 52 naïve male Wistar rats (Harlan Laboratories, Indianapolis, IN), approximately 21 days old at intake. One rat assigned to the IE group was excluded from analysis because of a persistent side bias. This study was conducted in cohorts of four to eight rats per cohort over the course of approximately 22 months. All rats were individually housed in a humidity and temperature controlled animal colony room that

³ The locomotor assessment served as a precursor for future studies in our lab examining the effects of DE/IE training on subsequent drug self-administration. Because locomotor activity in the circular corridor is predictive of drug self-administration (e.g., Piazza et al., 1989), matching based on this variable ensures that differences in drug responding are not due to differences in baseline locomotor activity. Prior research has found no difference in locomotor behavior (as measured with the circular corridor) between high- and low-impulsive rats (see Perry et al., 2005; Perry et al., 2008).

operated on a 12-hr light:dark cycle (lights on at 7:00 am). Following 7 days of ad-libitum food access, rats were gradually restricted to 85% of their growth curve free-feeding weights. Unless otherwise noted, all rats were maintained at their 85% weight for the duration of the study. Free access to water was available in the home cage.

Experimental sessions were conducted at the same time each day and supplemental food was delivered approximately 2 hrs post session. All work was conducted under a protocol approved by the Institutional Animal Care and Use Committee at Utah State University.

Apparatus

Nineteen operant chambers (Med Associates, St. Albans, VT), each housed within a sound-attenuating cubicle with a ventilation fan, were used. Two low-profile retractable levers were positioned on the front wall (6.5 cm above the grid floor) of the chamber. A food dispenser was positioned outside the chamber that delivered 45-mg pellets (Bio-Serv, Frenchtown, NJ) to a receptacle centered between the two front-wall levers (2.5 cm above the grid floor). An identical lever was centered on the rear-wall of the chamber (6.5 cm above the grid floor). A 28-V cue light was placed above each lever and a white-noise generator was positioned in the upper right corner of the rear wall (13 cm above the grid floor). During lever training, an 8-ounce plastic water bottle was mounted outside the chamber. The spout entered the chamber to the left of the rear-wall cue light (4 cm above the grid floor).

Locomotor activity was assessed with a circular corridor apparatus constructed of two PVC pipes (30.5 cm in height, 66.0 and 45.7 cm, for the diameter of the outside and inside walls, respectively; see, e.g., Perry et al., 2008; Piazza, Deminiere, Le Moal, &

Simon, 1989). Four infrared sensors were mounted within the walls of the corridors (5.1 cm above the grid floor), and were equidistant from each other such that their placement formed four quadrants (i.e., one sensor at 0°, 90°, 180°, and 270°). The top of the apparatus was covered with a removable sheet of clear Plexiglas. The room was equipped with a white-noise generator.

Procedures

Figure 4-1 depicts the order of experimental conditions and the median age of rats during each condition. Briefly, locomotor activity was assessed followed by lever-press training. Next, rats completed amount-discrimination training and a pre-training impulsive-choice assessment. Rats were then assigned to the DE, IE, or CONT group. While DE and IE rats completed their respective training, CONT rats remained fallow in their home cages but were otherwise treated identically as DE and IE rats; that is, CONT rats were maintained at their 85% free-feeding weight, handled, and fed in the

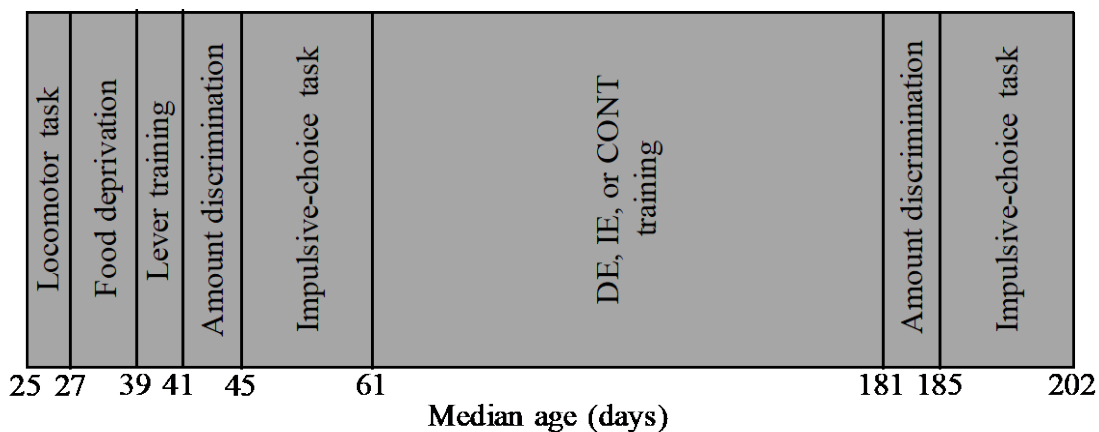


Figure 4-1. Order of experimental conditions and the median age of the rats during each condition.

same manner as the other groups. After 120 days, all rats completed amount-discrimination training followed by the post-training impulsive-choice assessment. The details of each phase are outlined below.

Locomotor assessment. Prior to food deprivation, locomotor activity was assessed using the procedures outlined by Perry et al. (2005). Rats were placed in the circular corridor apparatus for two 45-min sessions, and sessions were conducted across two consecutive days. Locomotor counts were defined as an interruption of two adjacent photobeams in succession; breaking the same photobeam twice consecutively was not scored as a locomotor count. A white-noise generator was on for the duration of testing.

Lever training. Lever training was conducted during overnight sessions; access to water was provided during these sessions. Each session consisted of four 20-trial blocks during which white noise was presented, and each block was separated by a 60-min blackout during which no stimuli were presented. Initially, rats were trained to press the two front-wall levers. Each trial began with the insertion of either the left or right front-wall lever (order pseudorandomly determined). If 55 s elapsed without a response, the cue light above the lever was illuminated for up to 5 s. If the lever was not pressed during the 60-s trial, the lever retracted, the cue light turned off, and one food pellet was delivered. Pressing the lever during the trial delivered one food pellet, retracted the lever, and a new trial was initiated. Training continued until rats pressed the inserted lever on \geq 90% of the trials in the final two trial blocks. The same procedure was used to train rear-wall lever pressing, the exception being that the consequence of pressing the rear wall was the retraction of that lever and the insertion of one of the front-wall levers. One food

pellet was delivered for pressing the front-wall lever. Training continued until rats pressed the rear- and front-wall levers on $\geq 90\%$ of the trials in the final two trial blocks. Throughout the experiment, sessions were conducted at approximately the same time daily (between 9:00 am and 5:00 pm), and individual rats progressed to the next phase after meeting the task-specific progression criteria (if present).

Pre-training amount discrimination. Amount-discrimination sessions were composed of three, 20-trial blocks, with each block separated by a 7-min blackout. Each block was composed of 6 forced-choice trials followed by 14 free-choice trials. All trials began by activating the light-cued rear-wall lever. When this lever was pressed, either one (forced-choice trials) or two (free-choice trials) front-wall levers were inserted into the chamber and the corresponding cue light(s) illuminated. Pressing either lever once retracted the lever(s), turned the cue light(s) off, and delivered the food amount programmed on the lever—either one or three pellets (lever assignment counterbalanced across rats). An adjusting inter-trial interval (ITI) ensured that a new trial started every 60 s. Failure to respond to a lever within 30 s retracted the lever(s), turned off the cue light(s), and was scored as an omission. Omitted forced-choice trials were repeated. White noise was presented throughout the session during this and all subsequent phases. Sessions ended when all 60 trials were completed or if 2 hrs elapsed. Amount-discrimination training sessions continued until rats selected the three-pellet alternative on $\geq 90\%$ of the trials across two consecutive sessions.

Pre-training impulsive-choice assessment. Impulsive choice was assessed using a within-session, increasing-delay procedure (e.g., Evenden & Ryan, 1996). Sessions

were structured identically to the amount-discrimination sessions, with the exception that the delay to the three-pellet alternative increased across the three successive trial blocks in the following order: 0, 15, 30 s. The one-pellet alternative was always delivered immediately.

Following 6 sessions, all rats completed a single amount-discrimination probe session (i.e., the delay to the three-pellet reward was 0 s throughout the session). This session was conducted to ensure that rats were not habitually responding to avoid the LLR during the second and third trial blocks. After this probe session, rats were returned to the increasing-delay procedure for at least 6 additional sessions and until the following stability criteria were met: 1) $\geq 80\%$ choice of the three-pellet alternative in the 0-s delay block for 5 consecutive sessions, 2) area under the curve⁴ (AUC; see Myerson, Green, & Warusawitharana, 2001) in each of the final 5 sessions did not deviate by more than 20% from the mean of these final 5 sessions, and 3) no monotonic increasing or decreasing trend in AUC over the final 5 sessions.

If, during the impulsive-choice assessment, preference for the three-pellet alternative in the 0-s delay block fell below 60% for two consecutive sessions, rats were placed into remedial amount-discrimination sessions (programmed as above and continued until achieving two consecutive days of $\geq 90\%$ choice of the three-pellet alternative). If this failed to re-establish sensitivity to reward amount, two or more sessions were conducted in which only the lever associated with the three-pellet

⁴ AUC is a summary measure of delay discounting, reflecting the area under the stable percent LLR choices made at the range of delays investigated. Thus, higher values of AUC reflect a greater preference for the LLR (i.e., greater self-control).

alternative was presented for 60 trials. Subsequently, remedial amount-discrimination sessions were conducted until the aforementioned criterion was met. Thereafter, impulsive-choice sessions continued until the stability criteria were met.

Group assignment. Because this study was conducted in cohorts, rats were assigned to DE, IE, or CONT groups in a way that minimized between-group differences in pre-training impulsive choice (AUC) and 2-day mean locomotor counts.

DE, IE, and no training. During DE and IE training sessions, each trial began with the insertion of the rear-wall lever and illumination of the cue light above that lever. For DE rats, a single press retracted the lever and initiated a 17.5-s delay, after which the cue light turned off and two food pellets were delivered. For IE rats, a single response retracted the lever, turned off the cue light, and delivered two food pellets immediately. Two pellets were delivered so the reward amount during exposure training would not match either reward available in the impulsive-choice assessments. For both groups, failure to press the rear-wall lever within 20 s was scored as an omission and omitted trials were repeated. An adjusting ITI ensured a new trial began every 60 s. Sessions ended when the rats completed 80 trials or if 2 hrs elapsed. DE and IE training continued for 120 sessions. Rats in the CONT group were handled, weighed, and treated identically to rats in the DE and IE groups, but were fallow for 120 days. Due to experimenter error, six CONT rats were fallow for an additional 9-32 days; there was no difference in post-training impulsive choice (AUC) for CONT rats that received additional fallow days and those that received 120 days ($p = .94$).

Post-training amount discrimination. After DE, IE, or no training, amount-discrimination training sessions were conducted. The procedures and criteria to progress to the next phase were as described above with the exception that the food amounts assigned to the left and right levers during the pre-training amount-discrimination phase were switched. These assignments were unchanged for the remainder of the experiment.

Post-training impulsive-choice assessment. After rats met the amount-discrimination criteria, impulsive choice was reassessed. Procedures, stability criteria, and remedial sessions (if necessary) were as described above.

Data Analysis

Before conducting statistical analyses, univariate and bivariate normality of variables was assessed as appropriate; univariate normality was tested using the Shapiro-Wilk test. When the data in question significantly differed from a normal distribution, nonparametric tests were used in lieu of their parametric counterpart.

Prior to examining differences in impulsive choice, group differences in lever and exposure training were examined. A Kruskal-Wallis test was used to examine between-group differences in the number of days to meet the lever-training acquisition criteria. Wilcoxon rank-sum tests were used to examine differences between the DE and IE groups on response latencies during the final 5 sessions of exposure training. All rats completed all 80 trials during these final sessions, so no analysis of trials completed was conducted. For all analyses here and below, p values $< .05$ were considered statistically significant.

Group differences in non-choice dependent measures from the impulsive-choice assessments were also evaluated. Kruskal-Wallis tests were conducted to examine between- and within-group differences on: 1) sessions to meet the amount-discrimination criterion, 2) sessions to stability of LLR choice, 3) omissions, and 4) latencies to press the SSR and LLR levers on forced- and free-choice trials (the latter two measures were averaged over the final 5 sessions). Minimal between-subject variability in pre-training impulsive choice precluded a valid assessment of the trait-like stability of this behavior over time.

The effects of training and maturation on impulsive choice were examined using a generalized linear mixed effects (GzLME) analysis (for similar approaches, see Young, in press; Young, 2017). Of particular interest were the within-group differences in choice from pre- to post-training for CONT rats (maturation effects), differences in choice between the IE and CONT groups at the post-training assessment (to determine if IE training increases impulsivity), and finally, differences in choice between the DE and CONT groups (to determine if DE training increases self-control relative to changes due to maturation). Differences between the DE and IE groups in degree of impulsive choice were assessed for the purpose of evaluating the replicability of previous reports (Renda & Madden, 2016; Stein et al., 2013; Stein et al., 2015). Individual choices at each delay (SSR or LLR, coded as 0 and 1, respectively) across the final 5 sessions of the pre- and post-training impulsive-choice assessments served as the dependent variable in the GzLME analysis. This yielded 210 choices per rat (14 free-choice trials per delay x 3

delays x 5 stable sessions), per assessment. The outcome was specified as binomial to accommodate the binary nature of choice, and a logit link function was used.

Ultimately, the GzLME is the equivalent of a repeated-measures logistic regression. The independent variables included in the model were Assessment (Pre-training/Post-training), Group (DE/IE/CONT), and Delay (0 s/15 s/30 s) all as categorical variables, with all of their interactions; a significant three-way interaction was anticipated due to the nature of the study design (i.e., DE rats should have bigger changes in the likelihood of choosing the LLR from pre- to post-training than IE or CONT rats, and self-control should decrease as the delay to the LLR increased, but to different extents across groups due to training and/or maturation). A random intercept of subject was included in the model. The results were nominally the same whether Delay was entered as a continuous or categorical predictor; thus, for ease of interpretation and facilitating comparisons, the categorical type was chosen. To evaluate the significance of the predictors in a manner similar to obtaining F -statistics in ANOVAs, Wald tests were computed using the Companion to Applied Regression (car) package (Fox & Weisberg, 2002). The necessity of random slope effects of Delay (i.e., the functional equivalent of allowing for individual differences in discounting rates, above and beyond that captured by group-level differences) was subsequently evaluated using a likelihood ratio test. No other random effects were evaluated.

All analyses were conducted in *R* (R Core Team, 2013). Normality testing was conducted using the nortest package (Gross & Ligges, 2015). GzLME models were fitted using the lme4 package (Bates, Mächler, Bolker, & Walker, 2015), and the lsmeans

package (Lenth, 2016) was used to generate contrasts from the GzLME (to examine maturational and/or training effects). All other analyses were conducted using base *R* functions, except where noted.

Results

By nature of the assignment of subjects to groups, all groups were equivalent on measures of locomotor activity (see Table 4-1) and pre-training AUC at the start of the experiment ($ps \geq .28$). Likewise, there were no between-group differences in the number of days to acquire lever pressing, Kruskal Wallis $\chi^2 (2, N = 51) = .31, p = .86$ (see Table 4-1).

During DE and IE training, rats in both groups completed all trials. Figure 4-2 shows individual-subject latencies to respond and omissions during DE and IE training (top and bottom panel, respectively); bars correspond to medians and error bars to *IQR*. Over the final 5 sessions, DE rats had significantly longer response latencies, $W = 226, p = .004$, and made significantly more omissions, $W = 230, p < .001$, than IE rats.

Table 4-1.

Median (Q1-Q3) two-day locomotor counts and the number of days to meet lever-training acquisition criteria.

	DE	IE	CONT
Locomotor counts	19.7 (16.6-24.0)	19.1 (16.8-21.7)	19.8 (15.3-23.4)
Days to acquisition criteria	2 (2-2)	2 (2-2)	2 (2-2)

Note: DE, IE, and CONT indicate delay-exposure, immediacy-exposure, and no-training control groups, respectively. No significant between-group differences were observed.

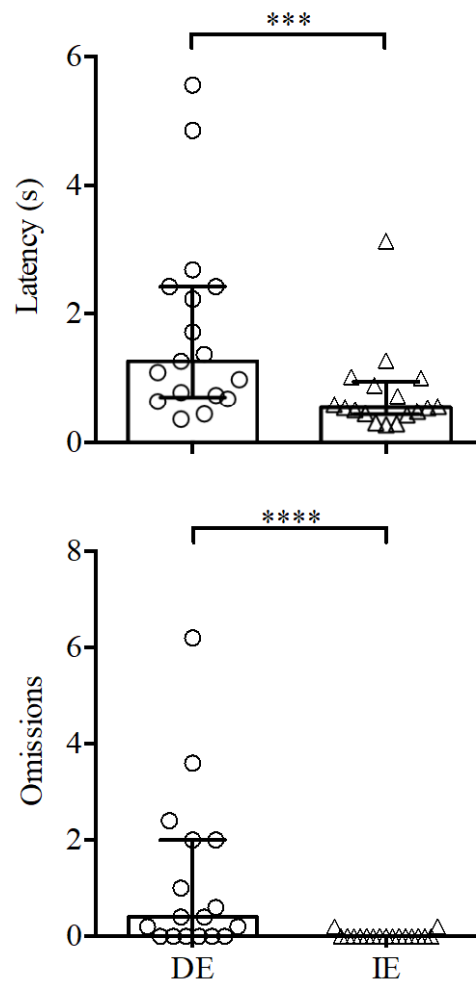


Figure 4-2. Median and individual-subject latencies to lever-press (top panel) and response omissions (bottom panel) in delay- (DE) and immediacy-exposure (IE) training. Error bars depict $\pm IQR$. *** $p < .005$, **** $p < .001$.

Table 4-2 shows pre- and post-training data from amount-discrimination and impulsive-choice phases. The median number of sessions to meet the stability criteria are shown, along with omissions and response latencies. No between-group differences in omissions or latencies were statistically significant in the pre- or post-training assessments, although differences in the latencies to respond on smaller-sooner forced-choice trials in the post-training assessment approached significance, $\chi^2(2, N = 51) =$

Table 2.

Median days to meet the amount-discrimination and impulsive-choice stability criteria, and the median omissions and response latencies in the pre- and post-training impulsive-choice assessment (Q1-Q3).

	Pre-training			Post-training		
	DE	IE	CONT	DE	IE	CONT
Days to discrimination criteria	4 (3-8)	4 (3-8)	4 (3-5)	4 (3-5)	3 (2-4)*	4 (3-5)
Days to stability criteria	18 (15-27)	15 (14-23)	16 (15-18)	16 (14-20)	17 (14-21)	18 (15-24)
Omissions	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.5)	0.0 (0.0-0.0)
Response latency: Forced-choice SSR	1.6 (1.4-1.7)	1.6 (1.5-2.0)	1.8 (1.6-1.9)	1.8 (1.4-2.1)	1.5 (1.3-1.8)	1.4 (1.2-1.6)**
Response latency: Forced-choice LLR	1.5 (1.4-2.1)	2 (1.5-2.4)	1.6 (1.3-2)	1.4 (1.1-1.7)	1.5 (1.1-2.2)	1.2 (1-1.5)*
Response latency: Free-choice SSR	1.7 (1.5-2.0)	1.7 (1.3-2.4)	1.9 (1.6-2.1)	1.6 (1.4-2.2)	1.5 (1.3-1.9)	1.4 (1.2-1.5)**
Response latency: Free-choice LLR	1.5 (1.3-1.6)	1.4 (1.3-1.8)	1.5 (1.3-1.6)	1.5 (1.3-2.2)	1.3 (1.1-1.5)	1.2 (1.1-1.7)

Note: DE, IE, and CONT indicate delay-exposure, immediacy-exposure, and no-training control groups, respectively. Omissions and response latencies were calculated from the last 5 sessions of the impulsive-choice assessments. There were no significant between-groups differences, though there were several within-group changes from pre- to post-training. Significant changes in bold, * $p \leq .05$, ** $p < .01$.

4.97, $p = .08$. From pre- to post-training, the only significant within-group non-choice difference was a reduction in the days to meet the amount-discrimination criteria in the IE group, $W = 88.5$, $p = .05$. Some response latencies either significantly, or nearly significantly declined from pre- to post-training in the CONT (forced SSR, $W = 66$, $p = .006$; forced LLR, $W = 75$, $p = .02$; free SSR, $W = 49$, $p = .001$) and IE groups (forced SSR, $W = 95$, $p = .09$; free LLR, $W = 90$, $p = .06$).

The left two columns of Figure 4-3 show individual-subject percent LLR choice across delays in the pre- and post-training impulsive-choice assessments for DE, IE, and CONT groups (top, middle, and bottom panels, respectively). The right column of Figure 4-3 shows individual-subject and median ($\pm IQR$) change in percent LLR choice from pre- to post-training across delays. In the GzLME analysis, the interaction between Assessment, Group, and Delay was significant, $\chi^2(4) = 57.55$, $p < .0001$, as were the majority of the other predictors in the model (see Table 4-3). This model was improved by allowing the effect of delay to vary across subjects, $\chi^2(5) = 461.57$, $p < .0001$.

Figure 4-4 shows the model-predicted percent LLR choice by delay ($\pm 1 SEM$) for all groups in the pre- and post-training impulsive-choice assessment (left and right panels, respectively). In the absence of a universally-agreed upon metric of fit for nonlinear models, the representativeness of the model predictions and the adequacy of the modeling procedure itself is reflected in comparing the group-level estimates in Figure 4-4 to the individual-subject values in Figure 4-3. At the pre-training assessment, all rats

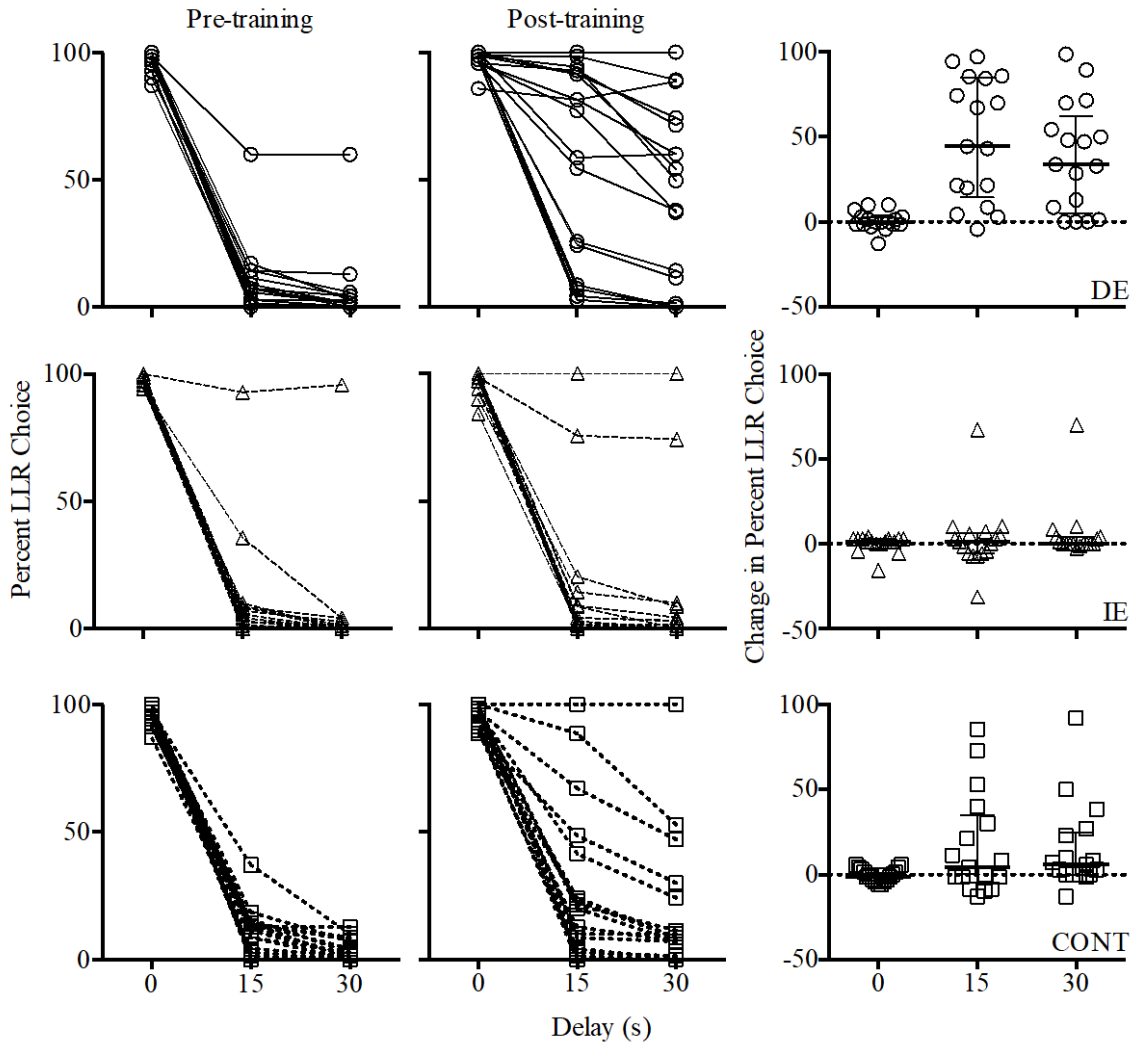


Figure 4-3. Individual-subject mean percent larger-later reward (LLR) choice from stable sessions, plotted as a function of delay to the LLR. Left and middle columns correspond to pre- and post-training assessments, respectively. The right column shows individual-subject and median change in percent LLR choice across delays. Top, middle, and bottom panels correspond to the delay-exposure (DE), immediacy-exposure (IE), and no-training control (CONT) groups, respectively. Error bars depict $\pm IQR$.

Table 4-3.

Significance of predictors in the generalized linear mixed effects analysis, as determined by Wald tests.

Predictor	Chi-Square	df	<i>p</i>
Group	3.90	2	.14
Assessment	753.95	1	< .0001
Delay	454.73	2	< .0001
Group*Assessment	180.39	2	< .0001
Group*Delay	4.20	4	.38
Assessment*Delay	197.19	2	< .0001
Group*Assessment*Delay	57.55	4	< .0001

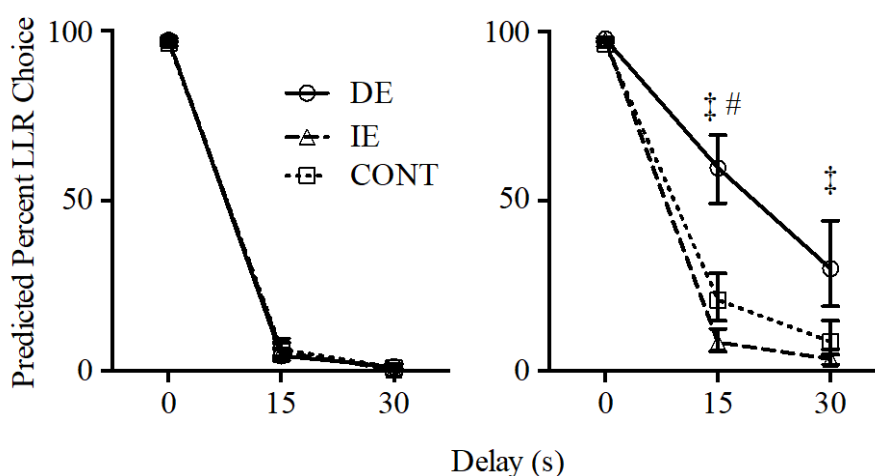


Figure 4-4. Predicted percent larger-later reward (LLR) choice plotted as a function of delay to the LLR, calculated from the fixed effects estimates from the generalized linear mixed effects model (predicted probabilities multiplied by 100). Left and right panels correspond to pre- and post-training assessments for delay-exposure (DE), immediacy-exposure (IE), and no-training control (CONT) groups. Error bars represent ± 1 SEM. Note that due to the nature of the model (i.e., logistic) error bars are not always symmetrical. ‡ and # represent DE/IE and DE/CONT differences, respectively (p 's $\leq .005$).

showed very low percent LLR choice at both the 15- and 30-s delays, and there were no significant differences between groups at any of the delays ($ps > .15$); thus, AUC was an adequate dependent measure for evaluating equivalence in choice at baseline.

Overall, DE training reduced impulsive choice relative to both IE and CONT rats. Replicating previous studies, DE rats showed significantly greater percent LLR choice than IE rats at both the 15-s (59.76% vs. 8.43%; $z = 4.57, p < .0001$) and 30-s delays (30.11% vs. 3.48%; $z = 2.81, p = .005$). The DE rats also showed greater self-control than the CONT rats, although the effects were slightly smaller. This was evidenced by significantly greater percent LLR choice at the 15-s delay (59.76% vs. 20.92%; $z = 2.86, p = .004$), but a difference that only approached significance at the 30-s delay (30.11% vs. 8.61%; $z = 1.75, p = .08$). At the 15-s delay, IE training produced a near-significant difference in percent LLR choice relative to CONT rats (8.43% vs. 20.92%, respectively; $z = 1.73, p = .08$); however, choice at the 30-s delay was unaffected by IE training (3.48% vs. 8.61%; $z = 1.08, p = .28$).

Lastly, there was evidence of a maturation-related reduction in impulsive-choice in the CONT group. From pre- to post-training, percent LLR choice significantly increased at both the 15-s (from 6.36% to 20.92%; $z = 10.90, p < .0001$) and 30-s delays (from 0.10% to 8.61%; $z = 11.56, p < .0001$).

Discussion

The present findings replicate the effect of DE training on impulsive choice (Renda & Madden, 2016; Stein et al., 2013; Stein et al., 2015). That is, DE-trained rats

made significantly more self-controlled choices than IE-trained rats. The present study, for the first time, evaluated the effect of DE training against a no-training CONT group. On average, DE training nearly tripled the prevalence of self-controlled choices; although at the 30-s delay to the LLR, this difference only approached statistical significance. This study is also the first to evaluate within-subject changes in impulsive choice from pre- to post- DE/IE training, revealing a large increase in self-controlled choices among DE rats (median increases of 44% and 33% at the 15- and 30-s delays, respectively), which surpassed the small developmental changes among CONT rats (median increases of 4% and 6% at the same delays). The significant difference in the magnitude of these changes was confirmed by the significant three-way interaction between Assessment, Group, and Delay; because all rats' choices were at the floor and undifferentiated during baseline, group differences at post-training illustrate the differential changes in impulsive choice. That the CONT group showed a small, but significant increase in self-control from pre- to post-training is consistent with past cross-sectional studies demonstrating a maturation effect in rats (Doremus-Fitwater et al., 2012; Simon et al., 2010), mice (Pinkston & Lamb, 2011), and humans (Green, Myerson, & Ostaszewski, 1999).

If DE training reduces impulsive choice relative to a no-training CONT group, one might expect IE training to have the opposite effect. The present findings provide little support for this hypothesis. Among IE rats, there was a modest increase in median self-controlled choices from pre-to post-training assessments at the 15-s delay (+1%) but not at the 30-s delay (no change). While this suggests that IE training did not increase impulsive choice above baseline levels, this conclusion is tempered by the preponderance

of impulsive choice at baseline. More illuminating is the post-training comparison of impulsive choice between IE and CONT groups. The group difference was not significant at either the 15- or 30-s delays to the LLR; however, the difference approached significance at the 15-s delay. Thus, no strong evidence supports the hypothesis that IE training reduces developmental increases in self-control. This conclusion should be evaluated further in future studies.

Two procedural changes from past studies of DE training are notable. First, in the present study, DE training commenced in early adulthood ($M = 67$ post-natal days) instead of adolescence ($M = 34$ post-natal days). That the effect size of the difference between DE and IE groups' post-training AUC scores, $CL = .81$, is comparable to prior reports ($CL = .80$ to $.99$; Renda & Madden, 2016; Stein et al., 2013; Stein et al., 2015) suggests that age at training initiation is not a critical variable influencing the effectiveness of DE training (see also Peterson & Kirkpatrick, 2016). Future studies may wish to examine the DE-training effect in older adult rats, as this may have translational utility should a form of DE training be developed for use in humans. Second, in prior studies, DE rats had no programmed experience with immediate reinforcement until the post-training impulsive-choice assessment. In the present study, the pre-training impulsive-choice assessment necessitated early experience with immediate reinforcement during amount-discrimination training and impulsive-choice sessions, particularly in the first trial block (0-s delay to all reinforcers). The present finding that DE training significantly reduced impulsive choice in rats that were not naïve to programmed immediate reinforcement suggests that sequestering rats from immediate reinforcement is

unnecessary. To the extent that these findings may be translated to humans, this finding suggests that a form of DE training could reduce impulsive choice in humans, who will have considerable prior experience with immediate gratification.

Because DE training produces large reductions in impulsive choice that last for at least 4 months (see Renda & Madden, 2016), three potentially fruitful directions for future research will be briefly discussed. First, all prior studies have provided rats with extensive DE training; is this lengthy training necessary, or would less DE training suffice? Second, is DE training robust to disruptors other than the passage of time? For example, while the effects of DE training generalize from the training lever (located on the rear wall of the chamber) to the choice levers (located on the opposite wall), we do not know if the effects of DE training would be disrupted if impulsive choice were assessed in a new chamber, with qualitatively different reinforcers, or if the delay-bridging stimulus presented between the response and the reinforcer were changed or omitted. Third, although DE training has proven effective in two outbred rat strains—Long Evans (Stein et al., 2013; Stein et al., 2015) and Wistars (current experiment; Renda & Madden, 2016), its effects have not been evaluated in female rats or in inbred strains known to make impulsive choices (e.g., Lewis rats; see, e.g., Anderson & Woolverton, 2005; Madden, Smith, Brewer, Pinkston, & Johnson, 2008). Answering these questions with rats may influence the direction taken if/when DE training is modified with the aim of influencing human decision-making, particularly among high-impulsive individuals at risk of developing a substance-use disorder.

Given that steep delay discounting is predictive of drug taking in human longitudinal studies (e.g., Audrain-McGovern et al., 2009) and high levels of impulsive choice are predictive of subsequent cocaine self-administration in rats (e.g., Perry et al., 2005), an important area for future DE-training research will be to further examine the effects of this training on subsequent drug self-administration. Stein et al. (2013) found that DE rats consumed more oral alcohol than did IE rats, but this effect was not replicated by Stein et al. (2015). Given the robust correlation between impulsive choice in rats and subsequent acquisition of cocaine self-administration (e.g., Perry et al., 2005; Perry et al., 2008; for review, see Stein & Madden, 2013) future research should evaluate the effects of DE training on cocaine self-administration. Future research might also evaluate the effects of DE training on behaviors that reflect clinical features of addiction in humans; for example, choosing to take an immediate drug reward when delays are imposed on access to non-drug rewards (Huskinson, Woolverton, Green, Myerson, & Freeman, 2015; Lamb, Maguire, Ginsburg, Pinkston, & France, 2016; Maguire, Gerak, & France, 2013).

In conclusion, the present findings replicate prior research on the impulsivity-reducing effect of DE training (Renda & Madden, 2016; Stein et al., 2013; Stein et al., 2015) and extend that finding to a no-training CONT group. While there is much research still to be conducted on the effects of a more refined or more effective version of DE training, that a form of systematic training can produce large and lasting reductions in impulsive choice is a hopeful finding given the robust relation between delay discounting and addictions (Bickel et al., 2014).

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CHAPTER 5
IMPULSIVE CHOICE AND PRE-EXPOSURE TO DELAYS: V.
PARAMETRIC MANIPULATION OF DELAY-
EXPOSURE TRAINING DURATION

Abstract

Preference for smaller, sooner over larger, later reinforcers characterizes one type of impulsivity—impulsive choice. Impulsive choice is related to a number of maladaptive behaviors, and interventions designed to reduce impulsive choice may ameliorate those behaviors. In rats, a training regimen involving prolonged exposure to delayed reinforcement (i.e., delay-exposure training) produces large and long-lasting reductions in impulsive choice. In prior studies, impulsive choice was assessed following at least 90 delay-exposure training sessions. Whether such an extensive training history is necessary has not been evaluated. The purpose of the present experiment was to parametrically manipulate training duration to determine if reductions in impulsive choice can be obtained in fewer sessions. One hundred sixty rats completed 0, 30, or 60 sessions of delay- or immediacy-exposure (i.e., control) training. Results showed that, relative to the 30-session condition, 60 sessions of delay-exposure training reduced impulsive choice, and the effect size for the 60-session condition is comparable to prior studies employing 90-120 training sessions. Importantly, the delay-exposure training effect observed following 60 sessions remained after a 120-day test-retest interval.

Introduction

Impulsivity is a multifaceted construct implicated in a number of problematic behaviors including risk taking, novelty seeking, inattention, impulsive action, and impulsive choice (for review, see Evenden, 1999). Operationally defined, impulsive choice is the preference for smaller-sooner rewards (SSRs) in lieu of larger-later rewards (LLRs). Delay discounting, one process that may underlie impulsive choice, characterizes the subjective devaluation of delayed reinforcers (e.g., Green, Myerson, Shah, Estle, & Holt, 2007; Madden, Bickel, & Jacobs, 1999; Mazur, 1987; Rachlin, Raineri, & Cross, 1991).

In humans, delay discounting has been associated with a number of pathological conditions. For instance, excessive delay discounting (i.e., rapid devaluation of delayed reinforcers) is observed in almost all types of substance use (for meta-analyses, see Amlung, Vedelago, Acker, Balodis, & MacKillop, 2017; MacKillop et al., 2011), with more pronounced effects in clinically addicted populations (MacKillop et al., 2011). In nonhumans, similar relationships are observed, though these findings are not without exceptions (for review, see Stein & Madden, 2013). For example, nonhuman impulsive choice predicts the acquisition (Perry, Larson, German, Madden, & Carroll, 2005; Perry, Nelson, & Carroll, 2008; Zlebnik & Carroll, 2015) and escalation (Anker, Perry, Gliddon, & Carroll, 2009) of cocaine self-administration, demand for cocaine (Koffarnus & Woods, 2013) and nicotine (Diergaarde et al., 2008), and maintenance of methamphetamine responding (Marusich & Bardo, 2009). Excessive delay discounting in

humans is also correlated with compulsive gambling (e.g., Alessi & Petry, 2003; Petry, 2001), obesity (e.g., Bickel et al., 2014; Jarmolowicz et al., 2014), internet addiction (Saville, Gisbert, Kopp, & Telesco, 2010), poor health behaviors (see, e.g., Bradford, 2010; Daugherty & Brase, 2010), and risky behaviors (e.g., Chesson et al., 2006; Odum, Madden, Badger, & Bickel, 2000). Given this accumulating evidence, excessive delay discounting may be a transdisease process (Bickel, Jarmolowicz, Mueller, Koffarnus, & Gatchalian, 2012; Bickel & Mueller, 2009). If true, then therapeutically reducing delay discounting may be an effective intervention for a number behavioral maladies.

A variety of behavioral approaches have been successful at changing delay discounting in humans (for reviews, see Gray & MacKillop, 2015; Koffarnus, Jarmolowicz, Mueller, & Bickel, 2013) and in nonhumans (e.g., Mazur & Logue, 1978; Smith, Marshall, & Kirkpatrick, 2015; Stein et al., 2013; Stein, Renda, Hinnenkamp, & Madden, 2015). One approach that generates large reductions in nonhuman impulsive choice involves prolonged exposure to delayed reinforcement (Renda & Madden, 2016; Stein et al., 2013; Stein et al., 2015). In these studies, weanling rats were first trained to lever press using a delayed- (delay-exposure [DE] group) or an immediate-reinforcement (immediacy-exposure [IE] group) autoshaping procedure. Next, both groups completed 90-120 training sessions in which lever pressing resulted in delayed or immediate food reinforcers (DE and IE training, respectively). Immediately following training, impulsive choice was evaluated using a within-session increasing-delay procedure (Eveden & Ryan, 1996). In each of these studies, DE rats made significantly fewer impulsive choices than IE rats. Renda, Rung, Hinnenkamp, Lenzini, and Madden (in press) showed that this

between-group difference is the result of DE training shifting preference toward the more self-controlled alternatives (and not IE training shifting preference toward the more impulsive alternatives).

Prior research has demonstrated that the DE training effect is robust to the passage of time and potentially disruptive intervening events (Renda & Madden, 2016; Stein et al., 2013; Stein et al., 2015). In Renda & Madden (2016), impulsive choice was reassessed 120 days after the initial assessment was completed. Impulsive-choice scores from the initial assessment and reassessment were significantly correlated in the DE group, and DE rats made significantly more self-controlled choices than IE rats at both time points. It is notable that, during a portion of the test-retest interval, rats were exposed to an operant task (Renda & Madden, 2016) or had the opportunity to self-administer oral alcohol (Stein et al., 2013; Stein et al., 2015).

DE training uses a multifaceted approach to reduce impulsive choice, and identifying the effective components of this training regimen is warranted. For example, DE rats learn to lever press with delayed reinforcement. Learning the contingent relation between a response and a delayed reinforcer may be a critical component of DE training. Killeen (2011) argued that the memory for a response that produces a reinforcer decays as the response-reinforcer delay is lengthened. He suggested that high levels of nonhuman impulsive choice (i.e., greater preference for the SSR) may reflect a failure to assign credit to the response that produced the LLR. As a result of learning to lever press with delayed reinforcement, DE rats may better learn the response-delayed reinforcer contingency resulting in greater preference for the LLR relative to IE rats. A second

component that may contribute to the effectiveness of DE training is that rats are exposed to DE/IE training for an extended period of time. Although previous research has varied the number of training sessions from 90 (Stein et al., 2015) to 120 (Renda & Madden, 2016; Renda et al., in press; Stein et al., 2015), the total number of trials was held constant. In these prior studies, rats completed approximately 9,600 training trials. Evaluating if such a prolonged training history is necessary or if the DE training effect increases as a function of training duration is warranted. If the same effect can be achieved in fewer sessions, this would reduce the overall cost in terms of time and money associated with this research line.

The purpose of the present study was to parametrically manipulate the duration of DE/IE training. A between-groups design was used to assess impulsive choice following 0, 30, or 60 sessions of DE or IE training. In all groups, lever pressing was established using a delayed- (DE groups) or an immediate-reinforcement (IE groups) autoshaping procedure. Next, DE/IE training duration was manipulated between-groups (0, 30, 60 sessions). The 0-session condition served to evaluate the effects of delayed- vs. immediate-reinforcement autoshaping on impulsive choice (i.e., whether learning the contingent relation between a response and a delayed reinforcer is sufficient to reduce impulsive choice relative to rats learning this relation with immediate reinforcement). Next, impulsive choice was assessed using a within-session increasing-delay procedure (Evenden & Ryan, 1996). To evaluate if any differences in training effectiveness were due to increased training duration, and not maturational reductions in impulsive choice (Doremus-Fitzwater, Barreto, & Spear, 2012; Pinkston & Lamb, 2011; Renda et al., in

press; Simon et al., 2010), an additional cohort of rats, matched to the age at which rats in the 60-session condition began the impulsive-choice assessment, completed the 0-session condition. Finally, if fewer training sessions produces comparable results to prior research (Renda et al., in press; Renda & Madden, 2016; Stein et al., 2013; Stein et al. 2015), a logical question is whether those changes in impulsive choice are durable. Thus, impulsive choice was reassessed following a 120-day test-retest interval for training conditions that produced comparable effect sizes to that of prior research.

Method

Subjects

One-hundred sixty experimentally naïve male Wistar rats (Harlan Laboratories, Indianapolis, IN) served as subjects. One-hundred twenty rats were approximately 21 days old at intake; the remaining 40 rats were approximately 87 days old at intake. This study was conducted over 22 months in cohorts of 15 to 40 rats per cohort. Subjects were individually housed in a temperature- and humidity-controlled animal colony room. Following 7 days of ad-libitum food access, rats were food deprived based on their dealer-supplied 85% free-feeding weights. Supplemental feeding was delivered approximately 2 hrs after experimental sessions to maintain desired weight. Free access to water was available in their home cage throughout the experiment. Animal care and procedures were in accordance with the Institution of Animal Care and Use Committee at Utah State University.

Apparatus

Thirty-six Med-Associates operant chambers were used. Each chamber was housed within a sound-attenuating cubicle outfitted with a ventilation fan. Experimental manipulanda were positioned on the front and rear chamber walls. Two retractable levers were positioned on the front wall of the chamber (6.5 cm above the grid floor). A food receptacle was centered between the two front-wall levers (2.5 cm above the grid floor). A pellet dispenser, positioned outside the chamber, delivered 45-mg pellets (Bio-Serv, Frenchtown, NJ) to the food receptacle. A third lever was centered on the rear wall of the chamber (6.5 cm above the grid floor). Above each lever was a 28-V cue light. A white-noise generator was positioned in the upper right-hand corner of the rear wall (13 cm above the grid floor).

Procedures

Conditions were completed in the following order: 0, 30, and 60 sessions of DE or IE training, followed by assessments of impulsive choice; rats were randomly assigned to receive DE or IE training with the constraint that DE and IE group sizes be equal at 20 rats. An additional cohort of 40 rats completed the 0-session condition; these rats were matched to the age at which the 60-session group began the impulsive-choice assessment (referred to as the “0-session Old condition”).

All groups completed lever training followed by 0, 30, or 60 sessions of DE or IE training. After autoshaping (0-session Young and Old conditions) or DE/IE training (30- and 60-session conditions), amount-discrimination training was conducted followed by

an impulsive-choice assessment. Rats in the 60-session condition completed a reassessment of impulsive choice 120 days after the initial assessment was completed. Rats in the 0-session Old condition completed a lever reversal immediately after the initial impulsive-choice assessment.

Lever training. An autoshaping procedure was used to establish lever pressing (c.f. Renda & Madden, 2016; Stein et al. 2013; Stein et al., 2015). Each 2-hr session consisted of 20 trials. The presentation of the rear-wall lever and corresponding cue light marked the beginning of a trial. For IE rats, a single lever press retracted the lever, extinguished the cue light, and delivered two food pellets immediately. For DE rats, a single lever press retracted the lever; however, two food pellets were delivered after a 17.5-s delay, and the cue light was extinguished following the delay period. Failure to respond within 15 s was scored as an omission, and omitted trials were not repeated (as in Stein et al., 2013; Stein et al., 2015). In this phase, and in all subsequent phases, white noise was presented for the duration of the experimental session. To encourage the same rate of response acquisition across groups, a cycle to trial (C:T) ratio of 11 to 1 was used (see Gibbon, Baldock, Locurto, Gold, & Terrace, 1977). The intertrial interval served as the cycle time; the maximum duration that the cue light could be illuminated served as the trial time. The cycle and trial time for IE rats was 165 s and 15 s, respectively. Because food was delivered after a 17.5-s delay in the DE group, the trial time was longer. To hold the C:T ratio constant across groups, the cycle and trial times for the DE group was 357.5 s and 32.5 s, respectively. Lever training continued until the rats responded on at least 18 of the 20 trials for 2 consecutive sessions.

Delay- and immediacy-exposure training. After meeting the lever training acquisition criteria, rats in the 30- and 60-session conditions completed DE or IE training. The presentation of the rear-wall lever and the cue light marked the beginning of the trial. For DE rats, a lever press immediately retracted the lever and initiated a 17.5-s delay. At the end of the delay, the cue light was extinguished, and two food pellets were delivered. For IE rats, a lever press retracted the lever, extinguished the cue light, and two food pellets were immediately delivered. For both groups, failure to respond to the lever within 15 s was scored as an omission, and omitted trials were repeated. New trials began every 60 s. Sessions ended after 80 completed trials or if 2 hrs elapsed.

Amount-discrimination training. Immediately following autoshaping (0-session Young and Old conditions) or DE/IE training (30- and 60-session conditions), amount-discrimination training sessions were conducted to ensure that rats could discriminate different reinforcer amounts. These sessions were composed of three 20-trial blocks separated by a 7-min intercomponent blackout. In each trial block, there were 6 forced-choice trials followed by 14 free-choice trials. Each trial began with the presentation of the rear-wall lever and cue light. A lever press retracted the lever, extinguished the cue light, and either one (force-choice trials) or both (free-choice trials) front-wall lever(s) and cue light(s) were presented. A lever press to a front-wall lever retracted the lever(s), extinguished the cue light(s), and the corresponding food reinforcer (either one or three pellets) was delivered. The assignment of reinforcer amount to the front-wall levers was counterbalanced across subjects. New trials began every 60 s. If a lever press did not occur within 30 s, the lever(s) was retracted and the cue light was extinguished. Omitted

forced-choice trials were repeated. Sessions ended after 60 trials were completed or after 2 hrs elapsed. Amount-discrimination training continued until percent larger-reward choice during the free-choice trials was $\geq 90\%$ for 2 consecutive sessions.

Impulsive-choice assessment. A within-session increasing-delay procedure was used to examine impulsive choice (see Evenden & Ryan, 1999). The task structure was the same as in amount-discrimination training with the exception that the delay to the larger reward increased across successive trial blocks (0, 15, and 30 s). Remedial amount-discrimination sessions were conducted if percent LLR choice in the 0-s delay dropped below 60% for 2 consecutive sessions (see Renda et al., in press, for the remedial-session protocol). The impulsive-choice assessment continued for at least 14 sessions and until the following stability criteria were met: 1) $\geq 80\%$ choice of the three-pellet alternative in the 0-s delay block for 3 consecutive sessions, 2) area under the curve (AUC; see Myerson, Green, & Warusawitharana, 2001) in each of the final 3 sessions did not deviate by more than 20% from the mean of the final 3 sessions, and 3) no increasing or decreasing trend in AUC over the final 3 sessions.

Impulsive-choice reassessment. For rats in the 60-session condition, impulsive choice was reassessed 120 days after the initial assessment was completed. During the test-retest interval, these rats remained in their home cages and had ad-libitum food access; food restriction resumed prior to the reassessment. The impulsive-choice reassessment included amount-discrimination training and was as described above, with the exception that the levers to which the SSR and LLR were assigned were reversed. If a lever bias was suspected, an additional lever reversal(s) was conducted.

Rats in the 0-session Old condition completed a lever reversal immediately following the initial assessment. The lever reversal was conducted because an uncharacteristically large proportion of these rats showed exclusive preference for the LLR across delays.

Data Analysis

Because rats in the 0- (Young), 30-, and 60-session conditions completed the autoshaping procedure at approximately the same age, the number of days to acquire lever pressing were collapsed across these conditions for the DE and IE groups, and compared to the 0-session Old DE and IE groups. Due to normality violations and the presence of outliers, data were rank-transformed, and group differences in responding were examined with a two-way ANOVA. Post-hoc analyses were conducted using Tukey's multiple comparisons test. For this and subsequent analyses, p -values $\leq .05$ were considered statistically significant. Spearman's ρ was used to assess the relation between the number of days to meet the autoshaping criterion and impulsive choice (AUC) for each group across conditions.

Latency to respond and omissions (both averaged over the final 3 sessions of training) were examined during DE/IE training. Due to normality violations and outliers, data were rank-transformed, and separate two-way ANOVAs were conducted. Minimal variability was observed for the number of trials completed in DE/IE training across all groups (i.e., nearly all rats completed all 80 trials), and this measure was not included for analysis.

For the impulsive-choice assessment, a Generalized Linear Mixed Effects

(GzLME) model was used to examine the effects of DE/IE training duration on impulsive choice (see Renda et al., in press). AUC (see Myerson, Green, & Warusawitharana, 2001) served as the dependent variable. Independent variables were Group (DE/IE), Condition (0-[Young]/30-/60-session), and the interaction. Planned post-hoc comparisons were the group differences in AUC for the 0-(Young), 30-, and 60-session DE conditions. Two separate GzLME models were used to compare the 0-session Young and 0-session Old DE and IE groups and the 0-session Old and 60-session DE and IE groups.

Rats in the 60-session condition completed an impulsive-choice reassessment 120 days after the initial assessment was completed. Wilcoxon matched-pairs signed rank test was used to examine within-subject changes in AUC at this follow-up, and Spearman's *rho* was used to assess correlations between initial and reassessment AUC values.

To facilitate comparisons across studies, common language (*CL*) effect sizes were calculated for the DE/IE groups at each condition. *CL* effect sizes were selected because they are robust to normality violations (see McGraw & Wong, 1992). AUC served as the dependent measure. *CL* effect size estimates range from .50 to 1.00 and describe the probability that a randomly selected DE rat will have a higher AUC value than a randomly selected IE rat (Lakens, 2013).

Results

Two rats were excluded from the experiment for failing to acquire lever pressing. Ten rats were excluded for failing to meet the amount-discrimination stability criterion in the initial impulsive-choice assessment. The significance of the analyses prior

to the exclusions were the same if these rats were included in the analyses.

Table 5-1 depicts the median days in autoshaping for the Young and Old rats, separated by DE and IE training groups (data collapsed across training-duration conditions in Young rats). No significant Group by Age interaction was observed, $p = .74$. However, there were significant main effects of Group (DE rats required more sessions than IE rats), $F(1, 147) = 37.19, p < .0001$, and Age (Young rats required more sessions than Old rats), $F(1, 147) = 10.58, p < .005$. Post-hoc comparisons showed that Younger DE rats took significantly longer to acquire lever pressing than all other groups, $p's \leq .05$. Older DE rats took longer to acquire lever pressing than older IE rats, $p < .01$. The relationship between days to acquisition was significantly correlated with AUC in the 0-session Young DE group, $rho = -.51, p < .05$, but not in any other group, $p's > .26$.

Table 5-2 shows the median trials completed, response latencies, and omissions, averaged over the last 3 sessions of DE/IE training. Across all groups, nearly all rats completed all 80 trials. No significant main effect of Training Duration or Group x

Table 5-1.

Median (Q1-Q3) days to meet the lever press acquisition criteria in autoshaping.

	Young		Old	
	DE	IE	DE	IE
Days to acquisition criteria	8 (5-14)**†	6 (3-6)	6 (4-8)*	4 (2-5)

Note: DE and IE represent delay- and immediacy-exposure training, respectively. The Young group included all rats from the 0-, 30-, and 60-session conditions as all rats in these conditions completed the autoshaping procedure at approximately the same age. Bolded text indicates within-condition DE/IE group differences. * $p < .01$; ** $p < .0001$; † different than all other groups, $p's \leq .05$.

Table 5-2.

Median (Q1-Q3) number of trials completed, response latencies, and omissions during DE/IE training.

	30 session		60 session	
	DE	IE	DE	IE
Trials completed	80 (80-80)	80 (80-80)	80 (80-80)	80 (80-80)
Latency	1.8 (1.1-3.3)**	0.6 (0.4-1.1)	1.4 (0.6-1.8)*	0.6 (0.4-1.2)
Omissions	3.0 (0.3-6.8)*†	0.0 (0.0-4.1)	0.3 (0.0-1.6)	0.0 (0.0-0.3)

Note: DE and IE represent delay- and immediacy-exposure training, respectively. Response latencies and omissions were calculated over the final 3 sessions of training. Bolded text indicates within-condition DE/IE group differences. * $p \leq .05$; ** $p < .001$; † different than all other groups, p 's $< .05$.

Training Duration interaction was observed for latency to respond, p 's $> .20$. However, there was a significant main effect of Group, $F(1, 73) = 23.58, p < .0001$. DE rats showed significantly longer latencies to respond during training than IE rats, p 's $\leq .05$. For omissions, the Group x Training Duration interaction was not significant, $p > .15$. There were significant main effects of Training Duration, $F(1, 73) = 7.36, p < .01$, and Group, $F(1, 73) = 9.83, p < .005$. Post-hoc comparisons revealed that the 30-session DE group made significantly more omissions than all other groups, p 's $< .05$.

In the 0-session Old condition, nine DE rats and five IE rats had AUC values $> .95$ (i.e., near-exclusive selection of the LLR across all delays). To rule out lever bias as an alternative explanation, a lever reversal was conducted immediately following the initial assessment for all rats in the 0-session Old condition. If the difference in AUC from the initial assessment to the lever reversal was $\pm .20$, an additional lever reversal(s) was conducted. Indicative of such a lever bias, two DE rats and four IE rats (all showing near-exclusive preference for the LLR across delays in the initial assessment) were

unable to meet the amount-discrimination criteria in the lever reversal after at least 20 amount-discrimination training sessions (for both groups, the median percent LLR choice at the 0-s delay was 0). Two IE rats met the amount-discrimination criteria in the lever reversal, but subsequently exhibited a lever bias such that they showed near-exclusive choice of one lever at the 15- and 30-s delays regardless of whether the SSR or LLR was assigned to that lever. In addition, one DE rat never acquired lever pressing, and one IE rat never met the initial amount-discrimination criteria. Data for these ten rats were excluded from subsequent analyses. For the remaining 30 rats ($n=17$ DE, $n=13$ IE), stable AUC values were averaged across the final two reversals in which AUC differed by $< .20$.

Figure 5-1 shows the individual-subject and median (*IQR*) AUC values for DE/IE groups across all conditions (data to the left of the dashed line are from the present experiment; data to the right are from previously published studies). In the GzLME analysis, the best model included main effects of Group, $\chi^2(2) = 8.40, p = .015$, and Training Duration, $\chi^2(1) = 10.37, p = .001$. However, there was no significant Group x Training Duration interaction, $\chi^2 = 1.19, p = .55$.

To investigate the main effects, pairwise comparisons were adjusted for multiple comparisons using the False Discovery Rate method (Benjamini & Hochberg, 1995). Compared to other methods, the False Discovery Rate method more liberally controls for Type I error, which reduces the likelihood of a Type II error. Uncorrected p -values were examined for the comparison of the 0- and 60-session DE groups for exploratory

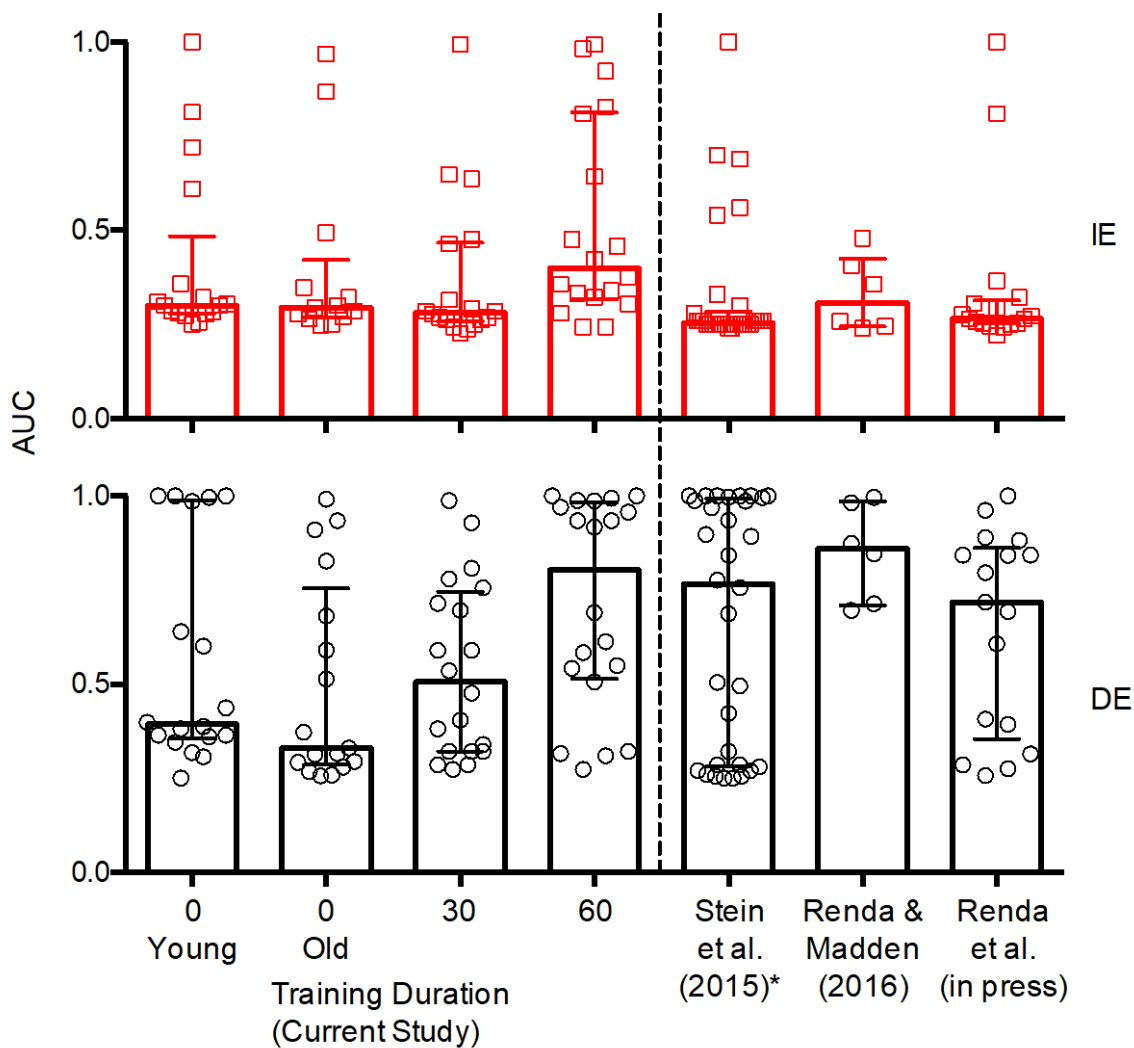


Figure 5-1. Area under the curve (AUC) for immediacy- (IE) and delay-exposed (DE) groups (top and bottom panels, respectively). Values to the left of the dashed line represent the data obtained from the current experiment; values to the right of the dashed line represent data from previously published studies. * indicates Long-Evans were used; all other studies employed Wistar rats.

purposes (both corrected and uncorrected p -values are reported).

Figure 5-2 shows the predicted AUC values obtained from the model. The main effect of Group revealed that DE rats had significantly higher AUC values than IE rats (for DE and IE groups, predicted AUC values were, respectively, .76 [$SE = .04$] and .52

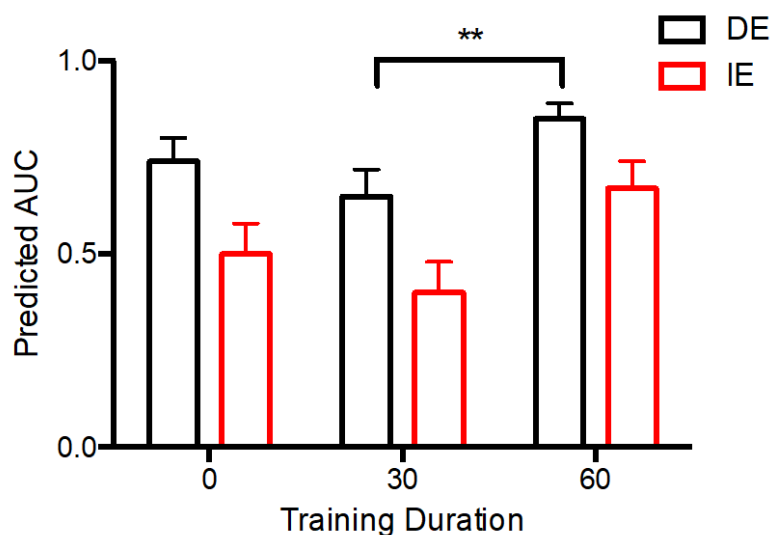


Figure 5-2. Predicted area under the curve (AUC) values (+SEM) for the delay- (DE) and immediacy-exposure (IE) groups across training duration. $**p \leq .01$.

[$SE = .06$], $z = 3.22$, $p = .001$). The main effect of Training Duration was confined to greater AUC values in the 60- relative to the 30-session condition, $z = 2.87$, $p = .01$.

Comparisons between the 0- and 30-session, and 0- and 60-session training durations were non-significant, z 's ≤ 1.77 , corrected p 's $\geq .12$, uncorrected p 's $\geq .077$.

The 0-session Old condition was included to evaluate if differences across training durations were simply maturational reductions in impulsive choice. Two separate analyses were conducted. The first included the 0-session Young and Old conditions. If maturation did account for the anticipated increase in self-control as a function of DE training duration, we would either expect a main effect of Age or a significant Age x Group interaction. Neither the main effect of Age, $\chi^2(1) = 0.91$, $p = .34$, nor the interaction, $\chi^2(1) = 0.75$, $p = .39$, was significant. There was a near-significant main effect of Group among these minimally trained 0-session rats, $\chi^2(1) = 3.78$, $p = .052$. DE rats had higher AUC values than IE rats (predicted AUC values for DE and IE rats were,

respectively, .66 [$SE = .06$] and .48, [$SE = .07$], $z = 1.88$, $p = .06$).

The second analysis included choices made by DE and IE rats in the 0-session Old and 60-session conditions. If maturation was responsible for the anticipated increase in self-control as a function of DE training duration, we would not expect a main effect of Condition (i.e., older rats would demonstrate less impulsive choice regardless of extended training), nor would we expect a Condition x Group interaction (i.e., the effect of DE vs. IE training would not depend on training duration). The interaction was non-significant, $\chi^2(1) = 1.86$, $p = .39$. Figure 5-3 shows the predicted AUC values obtained from the model including the non-significant interaction. Contrary to the maturation hypothesis, there was a significant main effect of Condition, $\chi^2(1) = 8.87$, $p = .003$. The 60-session rats had higher AUC values than the 0-session Old rats, $z = -2.85$, $p = .004$. There was also a significant main effect of Group, $\chi^2(1) = 6.51$, $p = .01$. DE rats had higher

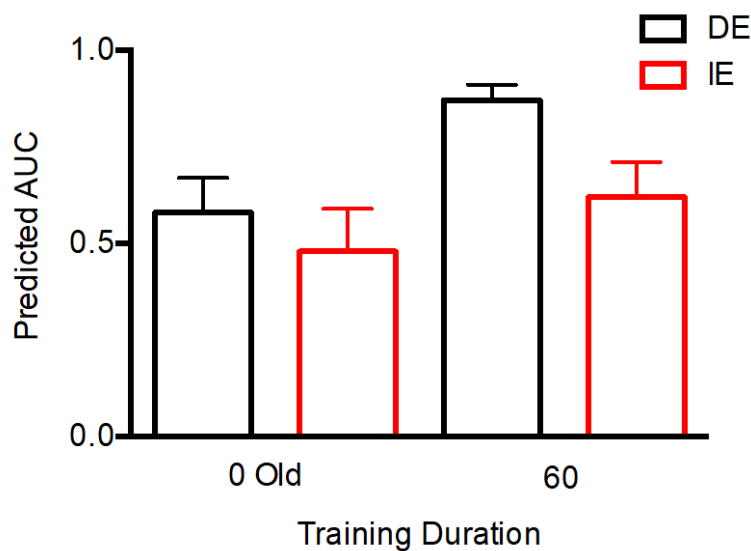


Figure 5-3. Predicted area under the curve (AUC) values (+SEM) for the delay- (DE) and immediacy-exposure (IE) groups in the 0-session Old and 60-session conditions.

AUC values than IE rats, $z = 2.43$, $p = .015$.

Impulsive choice was reassessed following a 120-day test-retest interval in the 60-session condition. In the reassessment, one DE rat and two IE rats were excluded from the analysis for failing to meet the amount-discrimination criteria or for demonstrating an intractable lever bias¹. Figure 5-4 depicts the initial (T1) and reassessment (T2) AUC values for the DE and IE groups. From the initial assessment to the reassessment, there was a significant decrease in AUC values in the IE group, $W = 85$, $p < .05$, although the rank order of these rats remained relatively consistent. This was evidenced by a strong

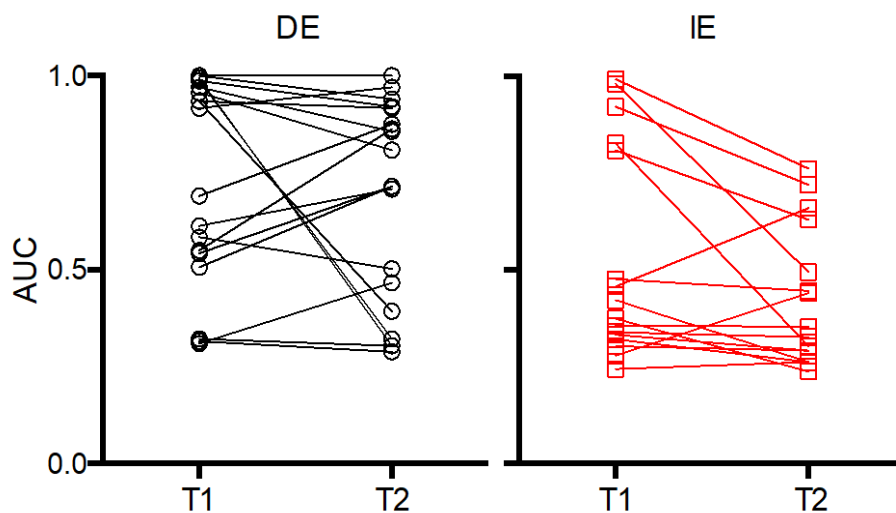


Figure 5-4. Individual-subject area under the curve (AUC) values for the delay- (DE) and immediacy-exposure (IE) groups (left and right panels, respectively). T1 and T2 represent the initial impulsive-choice assessment and the 120-day reassessment, respectively.

¹ In the impulsive-choice reassessment, a second lever reversal was conducted if percent LLR across delays was $\geq 90\%$ with the exception of rats that replicated their preference from the initial impulsive-choice assessment.

correlation between initial and reassessment AUC values, $\rho = .68, p < .005$. AUC values for rats in the DE group did not differ significantly from the initial assessment to the reassessment, $W = -21, p = .69$, and there was a near-significant correlation between these values, $\rho = .44, p = .058$. Thus, reductions in impulsive choice following 60-sessions of DE training remained after the 120-day test/retest interval.

CL effect sizes for DE/IE differences in AUC are provided in Table 5-3. For the 0-session Young and Old conditions, the effect sizes were small ($CL = .64$ and $.60$, respectively). In comparison, the addition of DE training in the 30- and 60-session conditions resulted in larger effect sizes; however, the *CL* effect sizes were equivalent ($CL = .71$), which is most likely attributable to the IE rats in the 60-session condition. These rats showed elevated levels of AUC compared to other IE groups in the current and previously published experiments (see Figure 5-1; Renda & Madden, 2016; Renda et al., in press; Stein et al., 2015). Because IE rats in the previously published experiments were older than those in the 60-session condition, this between-condition difference is unlikely due to maturation differences across the 0-, 30-, and 60-session conditions. Given the significant reduction in the 60-session IE group's AUC values from the initial impulsive-choice assessment to the reassessment (see Figure 5-4), this effect may reflect lever bias toward the LLR lever at the initial assessment. Finally, the *CL* effect size for the 60-session condition at the impulsive-choice reassessment was comparable ($CL = .80$) to previously published experiments.

Table 5-3.

Common language (CL) effect sizes for the DE/IE groups across conditions and for all published DE/IE studies.

	Days in training	CL effect size: Initial assessment	Test-retest interval	CL effect size: Reassessment
Current experiment	0 Young	.64	-	-
	0 Old	.60	-	-
	30	.71	-	-
	60	.71	120	.80
Stein et al. (2015)*	90†	.82	48	.76
Stein et al. (2013)*#	120	.80	66	.73
Renda & Madden (2016)	120	.99	120	.92
Renda et al. (in press)	120	.81	-	-

Note: * denotes Long Evans rats were used; all other studies used Wistar rats; # indicates that only 0- and 15-s delays were used in the impulsive-choice assessment; all other studies used 0-, 15-, and 30-s delays. † indicates that 90 training sessions were conducted, but the number of trials per session were approximately equal to the 120 conditions. DE and IE represent, respectively, delay- and immediacy-exposure training.

Discussion

The results of the current experiment replicate prior studies showing that DE-trained rats make significantly more self-controlled choices than IE-trained rats (Renda & Madden, 2016; Renda et al., in press; Stein et al., 2013; Stein et al., 2015). In the current study, DE/IE training duration was parametrically manipulated (0-, 30-, and 60-sessions). The results showed that increasing DE training duration from 30- to 60-sessions increased self-controlled choices, and the significant effect of 60 sessions of training was maintained at a follow-up test conducted 120 days later.

Although the 60-session DE rats made significantly more self-controlled choices than the 30-session DE rats, two unanticipated findings from the GzLME analysis were observed. First, the difference in AUC values between the 0- (Young) and 60-session DE

conditions was only marginally significant with an uncorrected p -value. The five 0-session Young DE rats that showed near-exclusive preference for the LLR across delays are likely responsible for this effect. The data for these rats may reflect sampling error or lever bias. In the lever reversal for the 0-session Old condition, six rats that showed near-exclusive LLR preference across delays could not pass amount discrimination when the lever assignments were reversed immediately after the stability criteria were met in the initial assessment. The absence of a lever reversal for the 0-session Young condition is a limitation of the current study.

A second unexpected finding was the lack of a Group x Training Duration interaction (i.e., we expected AUC to increase as a function of DE training duration; for the IE conditions, we expected AUC to remain relatively constant). However, the interaction was not significant, which is likely due to individual-subject variability particularly within the 0-session DE group and the 60-session IE group. As a whole, the 60-session IE group was more self-controlled than other IE groups in the current experiment and in previously published studies (see Figure 5-1). At the impulsive-choice reassessment, the 60-session IE rats demonstrated a significant reduction in AUC values, suggesting regression to the mean, lever bias, or both. Lever reversals are rare in the rodent impulsive-choice literature, but they may be needed to evaluate the replicability of initial preferences.

The 0-session Old condition was included in the current study to assess maturation as an alternative explanation for the expected increase in AUC as a function of DE training duration. As previously mentioned, the lever reversal conducted for this

group resulted in the exclusion of data for eight rats. Prior to the exclusion, there was a strong visual difference between DE and IE rats, which, in comparison to the 0-session Young condition, would suggest a possible interaction of age and delayed- vs. immediate-reinforcement autoshaping. Following the exclusion, there was no significant Condition x Group interaction.

Two comparisons were made with the 0-session Old condition. The first compared AUC values in the 0-session Young and 0-session Old conditions. No main effect of Condition (i.e., Age) was observed, which was not expected given that impulsive choice tends to decrease with age (Doremus-Fitzwater et al., 2012; Pinkston & Lamb, 2011; Simon et al., 2010). The second comparison was between the 0-session Old and 60-session conditions. A significant Condition x Group interaction and a significant main effect of Condition would provide evidence against maturation as an alternative explanation for the increase in self-control as a function of DE training. Although the interaction was not significant, there was a significant main effect of Condition (the 60 session DE/IE rats had greater AUC values than the 0-session Old DE/IE rats). The lack of an interaction is due, at least in part, to the 60-session IE rats. As previously mentioned, these rats had elevated AUC scores in comparison to all other IE groups and showed a significant reduction in AUC values at the 120-day reassessment. Although the interaction was non-significant, the estimates obtained from the model (see Figure 5-3), and the main effect of Condition, provide evidence that the effect of increasing DE training duration on impulsive choice is not due to maturation alone. Additional support comes from Renda et al. (in press) in which the effects of DE and IE training relative to

maturational reductions in impulsive choice were examined. In this study, a no-training control group completed a pre-test impulsive-choice assessment and a reassessment following 120 days. During the test-retest interval, these rats were fallow. At the reassessment, the no-training control group showed modest, but significant, reductions in impulsive choice (i.e., an effect of maturation on impulsive choice); however, 120 sessions of DE training resulted in significantly greater self-control relative to this no-training control group (i.e., the effects of 120 DE training sessions extended beyond the effects of simple maturation). The data for the no-training control group and the 0-session Old condition are comparable. Taken together, these data suggest that maturation alone cannot explain the effect of increasing DE training duration on impulsive choice.

A small, but near-significant effect of delayed- vs. immediate-autoshaping on impulsive choice was observed. Additionally, the number of days to master the delayed-reinforcement autoshaping criterion in the 0-session Young DE condition was significantly negatively correlated with impulsive choice (i.e., rats with greater self-control mastered the delayed-reinforcement autoshaping criterion in fewer days); this was not the case for any other group. Because of additional DE training sessions, we may expect this relationship to disappear in the 30- and 60-sessions conditions (i.e., additional training sessions helped rats that struggled initially in the delayed-reinforcement autoshaping procedure to discriminate the response-delayed reinforcer contingency). The lack of correlation between the number of days to meet the autoshaping criterion and AUC in the 0-session Old DE condition may suggest an effect of age or a Type 1 error in the 0-session Young DE group. Regardless, these findings provide some initial support

that learning the response-delayed reinforcer contingency may be related to nonhuman self-control (Killeen, 2011). However, the delayed-reinforcement autoshaping procedure was not sufficient to produce the large DE/IE differences observed in prior research. Continued exploration of the mechanism underlying DE training is an important avenue for future research as this may result in a more efficient and/or more effective training regimen.

Our initial question—does training duration influence the effectiveness of DE training—is difficult to answer given the individual-subject variability observed across the training conditions. Future research should add a 120-session DE/IE training condition with Wistar rats, which may result in more interpretable results from the GzLME analysis; such research is underway now. Regardless, the 60-session DE group was significantly more self-controlled than the 30-session DE group, and visually, it would appear that increasing DE training duration resulted in increased self-control. Importantly, 60 sessions of DE training produced reductions in impulsive choice that remained after a 120-day test-retest interval, and the obtained effect is comparable to studies employing 90-120 sessions. The *CL* effect sizes obtained for the current study provide support for these conclusions.

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CHAPTER 6

GENERAL DISCUSSION

Summary and Conclusions

Because excessive delay discounting (rapid devaluation of delayed reinforcers) is often observed in several maladaptive behaviors (e.g., substance abuse, pathological gambling, health-decrementing behaviors, etc.), efforts to reduce discounting may prove effective in future prevention and intervention research (see Bickel et al., 2015; Gray & MacKillop, 2015). The purpose of this dissertation was to explore two methods for changing nonhuman impulsive choice—working-memory training (WMT) and delay-exposure (DE) training. Having experimentally reduced impulsive choice in the latter training regimen, future research can use this procedure to directly evaluate the effects of this behavior change on other behaviors of interest (e.g., drug self-administration, nonhuman addiction models).

In Chapter 2, we failed to reduce nonhuman impulsive choice using a WMT procedure. The findings are in opposition to those reported for human stimulant-dependent individuals in Bickel et al. (2011). First, whereas Bickel et al. saw no effect of WMT on subsequent working-memory performance, we observed a lasting between-group difference. Second, whereas Bickel et al. found a significant reduction in delay discounting in the WMT group, we found no significant between-group difference.

The conflicting results could reflect a species difference or a number of procedural differences (e.g., Bickel et al. increased the number of to-be-remembered

stimuli, whereas we increased the retention interval). After the experiment presented in Chapter 2 was published, Rass et al. (2015) reevaluated the effects of WMT on delay discounting in opioid-dependent individuals. In their study, two groups of methadone-maintenance patients completed 25 sessions of WMT or Active-Control training. The WMT procedure was similar to that used by Bickel et al. (2011) in which the number of to-be-remembered stimuli increased as accuracy increased; the Active-Control group completed the same tasks, however, the number of to-be-remembered stimuli remained fixed at 2. Pre- and post-training assessments were conducted to evaluate the effects of WMT on working memory and delay discounting. The working-memory assessments included tasks that were both similar and dissimilar to the training program. Two delay-discounting tasks were used. One task involved all real contingencies such that every choice resulted in the consequence delivered after the specified delay (similar to the present Chapter 2) and the other was a hypothetical task (similar to Bickel et al., 2011). Rass et al. reported that WMT improved performance on the working-memory tasks that were similar to those arranged in WMT, but not on dissimilar tests of working memory. In contrast to Bickel et al., delay discounting in the hypothetical and real outcomes tasks were undifferentiated across WMT and Active-Control groups.

The findings from Rass et al. (2015) support the position that the effects of WMT do not generalize to working-memory assessments that are sufficiently different than the training program (for review, see Shipstead et al., 2012). However, Rass and colleagues did not observe an effect of WMT on delay-discounting performance. Procedural differences such as the participant sample (stimulant- vs. opioid-dependent participants),

control-group procedures (active vs. nonactive), assessment type (all real vs. hypothetical rewards), etc., could account for conflicting results. Direct and systematic replications are warranted to understand WMT as a method to reduce human and nonhuman impulsive choice.

Although WMT did not affect nonhuman impulsive choice, other strategies have been successful in reducing impulsive choice (e.g., Eisenberger, Masterson, & Lowman, 1982; Logue, Rodriguez, Pena-Correal, & Mauro, 1984; Mazur & Logue, 1978; Smith, Marshall, & Kirkpatrick, 2015; Stein et al., 2013; Stein et al., 2015). Chapters 3-5 sought to better understand DE/IE training, which generates large between-group differences in nonhuman impulsive choice.

The purpose of Chapter 3 was to replicate prior research with a different rat strain and to extend the test-retest interval from approximately 66 days (as in Stein et al., 2013) to 120 days. We found that 120 days of DE/IE training produced a significant between-group difference in impulsive choice in Wistar rats. Both groups completed an operant task for approximately 20 days of the test-retest interval. When impulsive choice was reevaluated 120 days after the initial impulsive-choice assessment was completed, the DE/IE training effect remained significant. Thus, DE/IE training produces long-lasting changes in impulsive choice that are robust to intervening experiences (see also Stein et al., 2013; Stein et al., 2015). This finding provides initial evidence that DE/IE training produces trait-like changes in impulsive choice. Future research should explore whether the DE/IE training effect would be obtained with a different impulsive-choice task (i.e., alternate form test-retest reliability; e.g., the adjusting-delay task; Mazur, 1987), and

whether this training would generalize if testing occurred in a different setting or with a different commodity.

Chapter 4 evaluated the effects of DE and IE training on impulsive choice relative to naturally-occurring reductions in impulsive choice. The results provide the first nonhuman longitudinal evidence for developmental reductions in impulsive choice (for cross-sectional evidence of this effect in rodents, see Doremus-Fitzwater et al., 2012; Pinkston & Lamb, 2011; Simon et al., 2010). Importantly, DE-trained rats showed large reductions in impulsive choice from pre- to post-training that extended beyond the effects of maturation. By contrast, IE training did not increase impulsive choice relative to no-training control rats. The results suggest that the DE/IE group differences observed in Chapter 4 and in prior research can be attributed to DE training shifting preference toward the more self-controlled alternatives.

Finally, Chapter 5 demonstrated that 60 DE training sessions resulted in greater self-control relative to 30 DE training sessions, and that 60 DE training sessions produced comparable results to the studies that have employed 90-120 sessions. Importantly, the large between-group difference in impulsive choice immediately following 60 sessions of DE/IE training remained after a 120-day test-retest interval.

The results from Chapters 3-5 provide a better understanding of the DE-training effect. DE training produces large, long-lasting reductions in nonhuman impulsive choice that can be obtained in 60 sessions. These findings add to the accumulating human (for reviews, see Gray & MacKillop, 2015; Koffarnus, Jarmolowicz, Mueller, & Bickel, 2013) and nonhuman (e.g., Mazur & Logue, 1978; Smith et al., 2015; Stein et al., 2013;

Stein et al., 2015) research suggesting that impulsive choice can be reduced. If excessive delay discounting is a transdisease process, then reducing impulsive choice may be an effective intervention for a wide range of behavioral addictions. Future basic and translational research examining how reducing impulsive choice influences maladaptive behaviors (e.g., substance use) is warranted.

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2810 Old Main Hill
Logan, UT 84321

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Date: 3-5-2018

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2810 Old Main Hill
Logan, UT 84321

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Date: 3-9-18

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Signed:

Date: 03/13/18

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EDUCATIONAL HISTORY

- | | |
|-------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| In progress | Ph.D., Psychology
Department of Psychology, Utah State University
Dissertation Title: Changing nonhuman impulsive choice
Major Professor: Gregory Madden, Ph.D. |
| 2011 | M.S., Psychology
Department of Psychology, Jacksonville State University
Thesis Title: Estimating parameters for the bipolar effect with a concomitant CFT/VI schedule of reinforcement
Major Professor: William Palya, Ph.D. |
| 2009 | B.S. (<i>cum laude</i> & honors in psychology), Psychology
Department of Psychology, Jacksonville State University |

PROFESSIONAL CERTIFICATIONS

- | | |
|-------------|----------------------------------|
| In progress | Board Certified Behavior Analyst |
|-------------|----------------------------------|

AWARDS

- | | |
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| 2013 | Society for the Advancement of Behavior Analysis Master's Thesis Grant Recipient |
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2007 First Place, College of Arts and Sciences Student Symposium,
Jacksonville State University, Jacksonville, AL.

PROFESSIONAL EXPERIENCE

2017-present Lead Registered Behavior Technician - Chrysalis, Logan, UT.
Duties include implementation of early intervention services,
administration of initial behavioral assessments, design and
implementation of descriptive and functional analyses, development
and evaluation of individualized programs for children with Autism
Spectrum Disorders. Supervisor: Jesse Yarger, BCBA, LBA.

2009-2011 Behavior therapist - Gadsden, AL.
Services provided to a child with Autism Spectrum Disorder. Services
included using behavior analytic principles to promote desired
behaviors at home and in a classroom setting, implementing discrete
trial training, and managing data collection. Supervisor: Todd
McKerchar, Ph.D., BCBA-D.

TEACHING EXPERIENCE

INDEPENDENT INSTRUCTOR

2018 Course: PSY 3400 (online), Advanced Analysis of Behavior (1
semester)
Department of Psychology, Utah State University

2015-2017 Course: USU 1010, University Connections (3 semesters)
Department of Psychology, Utah State University

2015-2016 Course: PSY 1400/1410 (Interactive Video Broadcast Course),
Analysis of Behavior: Basic Principles and Behavior Analysis
Laboratory (2 semesters)
Department of Psychology, Utah State University

2013- 2016 Course: PSY 1400/1410, Analysis of Behavior: Basic Principles and
Behavior Analysis Laboratory (4 semesters)
Department of Psychology, Utah State University

2015 Course: PSY 3500, Scientific Thinking and Methods in Psychology (1
semester)
Department of Psychology, Utah State University

2009-2011 Course: PSY 221, Behavior Analysis Laboratory (2 semesters)
Department of Psychology, Jacksonville State University

TEACHING ASSISTANTSHIPS

2017 Course: PSY 1010 (online), General Psychology (1 semester)
Department of Psychology, Utah State University

2017 Course: PSY 3010, Psychological Statistics (1 semester)
Department of Psychology, Utah State University

2011-2014 Course: PSY 1400/1410, Analysis of Behavior: Basic Principles and
Behavior Analysis Laboratory (3 semesters)
Department of Psychology, Utah State University

2009-2011 Course: PSY 310, Research Methods (3 semesters)
Department of Psychology, Jacksonville State University

2010 Course: PSY 450, History and Systems of Psychology (1 semester)
Department of Psychology, Jacksonville State University

2010 Course: PSY 436, Drugs, Society, & Human Behavior (1 semester)
Department of Psychology, Jacksonville State University

2006 Course: PSY 300, Statistics for Life Sciences (1 semester)
Department of Psychology, Jacksonville State University

REFEREED PUBLICATIONS

Renda, C. R., Rung, J. M., Hinnenkamp, J. E., Lenzini, S. L., & Madden, G. J. (in press).
Impulsive choice and pre-exposure to delays: IV. Effects of delay- and
immediacy-exposure training relative to maturational changes in impulsivity.
Journal of the Experimental Analysis of Behavior.

Renda, C. R. & Madden, G. J. (2016). Impulsive choice and pre-exposure to delays: III.
Four-month test-retest outcomes in male Wistar rats. *Behavioral Processes*, 126,
108-112.

Stein, J. S., **Renda, C. R.**, Barker, S. M., Liston, K. J., Shahan, T. A., & Madden, G. J.
(2015). Impulsive choice predicts anxiety-like behavior, but not alcohol or
sucrose consumption, in male Long-Evans rats. *Alcoholism: Clinical and
Experimental Research*, 39, 932-940.

- Renda, C. R.**, Stein, J. S., & Madden, G. J. (2015). Working-memory training: Effects on delay discounting in male Long-Evans rats. *Journal of the Experimental Analysis of Behavior*, *103*, 50-61.
- Stein, J. S., **Renda, C. R.**, Hinnenkamp, J. E., & Madden, G. J. (2015). Impulsive choice, alcohol consumption, and pre-exposure to delayed reward: II. Potential mechanisms. *Journal of the Experimental Analysis of Behavior*, *103*, 33-49.
- Craig, A. R., Maxfield, A. D., Stein, J. S., **Renda, C. R.**, & Madden, G. J. (2014). Do the adjusting-delay and increasing-delay tasks measure the same construct-delay discounting? *Behavioural Pharmacology*, *25*, 306—315.
- Renda, C. R.**, Stein, J. S., & Madden, G. J. (2014). Impulsive choice predicts poor working memory in male rats. *PLoS One*, *9*(4), e93263. doi: 10.1371/journal.pone.0093263
- Stein, J. S., Johnson, P. S., **Renda, C. R.**, Smits, R. R., Liston, K. J., Shahan, T. A., & Madden, G. J. (2013). Early and prolonged exposure to reward delay: Effects on impulsive choice and alcohol self-administration in male rats. *Experimental and Clinical Psychopharmacology*. Advance online publication. doi: 10.1037/a0031245.
- McKerchar, T. L., & **Renda, C. R.** (2012). Delay and probability discounting in humans: An overview. *The Psychological Record*, *62*, 817–834.

PAPERS PRESENTED AT PROFESSIONAL MEETINGS

- Renda, C. R.**, & Madden, G. J. (May 2017). Experimentally manipulating impulsive choice in rats. Paper presented at the annual meeting of the Association for Behavior Analysis International, Denver, CO.
- Madden, G. J., **Renda, C. R.**, & Rung, J. (February 2017). Delay Exposure Training. Paper presented at the annual meeting of the Winter Conference on Animal Learning and Behavior. Park City, UT.
- Renda, C. R.**, Draper, J., Hess, B., & Madden, G. J. (May 2016). Manipulating delay discounting in rats: Durability, generalization, current and future directions. Paper presented at the annual meeting of the Association for Behavior Analysis International, Chicago, IL.
- Renda, C. R.**, Stein, J. S., & Madden, G. J. (May 2014). The effects of working memory training in male Long-Evans rats. Paper presented at the annual meeting of the Association for Behavior Analysis International, Chicago, IL.

- Stein, J. S., **Renda, C. R.**, Liston, K. J., Barker, S., Madden, G. J. (May 2014). Impulsive choice and prolonged-exposure to reward delay in rodent models of drug self-administration. Paper presented at the annual meeting of the Association for Behavior Analysis International, Chicago, IL.
- Stein, J. S., **Renda, C. R.**, Johnson, P. S., Liston, K. J., Barker, S., Madden, G. J. (May 2013). *Impulsive choice and alcohol consumption in male Long-Evans rats: Naturally Occurring and Experimentally Induced Relations*. Paper presented at the annual meeting of the Association for Behavior Analysis International, Minneapolis, MN.
- Burt, C. R.**, & Palya, W. L. (May 2011). *Bipolar responding in fixed-temporal intervals*. Paper presented at the annual meeting of the Association for Behavior Analysis International, Denver, CO.
- Bitgood, S., & **Burt, C. R.** (July 2009). *Critical appraisal of a Native American Exhibition*. Paper presented at the annual meeting of the Visitor Studies Association, St. Louis, MO.
- Burt, C. R.**, & Bitgood, S. (February 2007). *The impact of multi-sensory stimulation on visitor behavior in museums: A review*. Paper presented at the College of Art and Sciences Student Symposium, Jacksonville State University, Jacksonville, AL.

POSTERS PRESENTED AT PROFESSIONAL MEETINGS

- Renda, C. R.**, Stein, J. S., Liston, K. J., Madden, G. J. (May 2013). *The effects of working memory training on delay discounting in rats*. Poster presented at the annual meeting of the Society for Quantitative Analysis of Behavior, Minneapolis, MN.
- Stein, J. S., Smits, R. R., Johnson, P. S., **Renda, C. R.**, & Madden, G. J. (May 2012). *Effects of prolonged exposure to delayed reinforcement on impulsive choice and alcohol consumption in rats*. Poster presented at the annual meeting of the Association for Behavior Analysis International, Seattle, WA.
- Burt, C. R.**, Nall, R. W., Palya, W. L. (May 2011). *Evaluating the bipolar effect with a concomitant CFT/VI schedule*. Poster presented at the annual meeting of the Society for Quantitative Analysis of Behavior, Denver, CO.
- Burt, C. R.**, Townley, S., & Palya, W. L. (November 2010). *Evaluating the entraining/organizing effect of a clock with a concomitant VI/CFT schedule*. Poster presented at the annual meeting of the Southeastern Association for Behavior Analysis, Asheville, NC.

Manora, T., **Burt, C. R.**, Palya, W. L., & Walter, D. (May 2010). *Laboratory studies in operant behavior: Half a century later*. Poster presented at the annual meeting of the Society for Quantitative Analysis of Behavior, San Antonio, TX.

Bitgood, S. & **Burt, C. R.** (July 2009). "*Museum Fatigue*": *It's more than you think!* Poster presented at the annual meeting of the Visitor Studies Association, St. Louis, MO.

Bitgood, S., **Burt, C. R.**, & Dukes, S. (October 2008). *Comparing two calculations of value: Ratio versus additive models*. Poster presented at the annual meeting of the Southeastern Association for Behavior Analysis, Atlanta, GA.

RESEARCH MENTORSHIP

2015-2016 Stephanie Lenzini*, undergraduate student, Department of Psychology, Utah State University.
Project Title: Within- and between-subject comparisons of delay- and immediacy-exposure training.

2014-2015 Jacy Draper*, undergraduate student, Department of Psychology, Utah State University.
Project Title: Assessing alternate-form test-retest reliability of the delay-exposure training effect.

2014-2015 Brian Hess*, undergraduate student, Department of Psychology, Utah State University.
Project Title: Assessing alternate-form test-retest reliability of the delay-exposure training effect.

*Co-mentored with Dr. Greg Madden

PROFESSIONAL SERVICE

2015 Guest Reviewer, *Addiction*

2011 Guest Reviewer, *The Psychological Record*

SERVICE TO THE COMMUNITY

2016 Supervised Michael Hernandez, a high school student at InTech Collegiate High School, North Logan, UT, in conducting a science fair project examining stimulus control in a rat.

MEMBERSHIPS IN PROFESSIONAL ASSOCIATIONS

2010-present	Association for Behavior Analysis International
2010-2016	Society for the Quantitative Analysis of Behavior
2008-2011	Southeastern Association for Behavior Analysis
2008	Visitor Studies Association