Impulsive Choice and Pre-Exposure to Delays: IV. Effects of Delay- and Immediacy-Exposure Training Relative to Maturational Changes in Impulsivity.

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 sizes[1] 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

[1] 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).

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.

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 assessment[2] 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 fallow 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

[2] 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).

a humidity and temperature controlled animal colony room that 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 oz 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 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 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 ≥ 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 ≥ 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 ≥ 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) ≥ 80% choice of the three-pellet alternative in the 0-s delay block for 5 consecutive sessions, 2) area under the curve[3] (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

[3] 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).

consecutive days of ≥ 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 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 Kruskall-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. Kruskall-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 1) and pre-training AUC at the start of the experiment (*p*s ≥ .28). Likewise, there were no between-group differences in the number of days to acquire lever pressing, Kruskal Wallis χ^2 (2, $N = 51$) = .31, $p = .86$ (see Table 1).

During DE and IE training, rats in both groups completed all trials. Figure 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 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, χ^2 (2, $N = 51$) = 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 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 3 shows individual-subject and median (± *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 3). This model was improved by allowing the effect of delay to vary across subjects, $\chi^2(5) = 461.57$, $p < .0001$.

Figure 4 shows the model-predicted percent LLR choice by delay (± 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 to the individual-subject values in Figure 3. At the pre-training assessment, all rats 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 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 females 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).

References

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Table 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.

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; $*p \leq .05$, $**p < .01$.

Table 3.

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

Predictor	Chi-Square	df	*p*
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

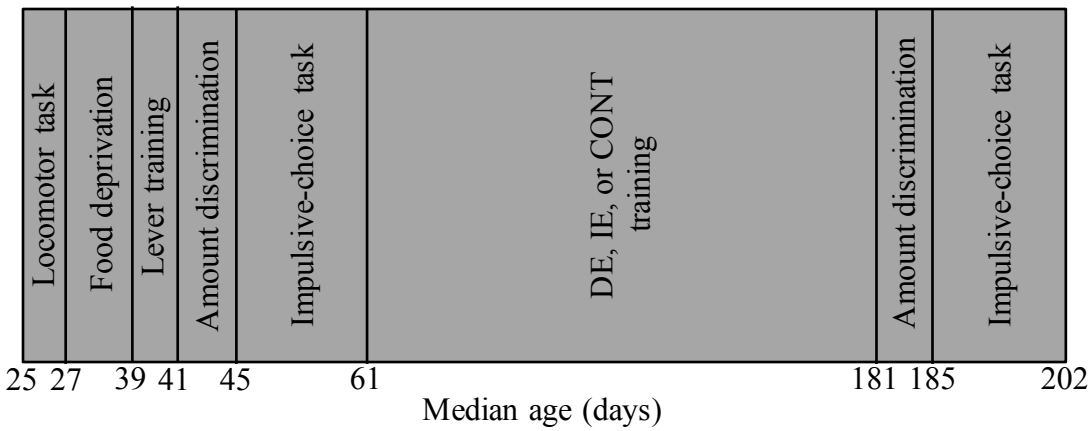

Figure 1. Order of experimental conditions and the median age of the rats during each condition.

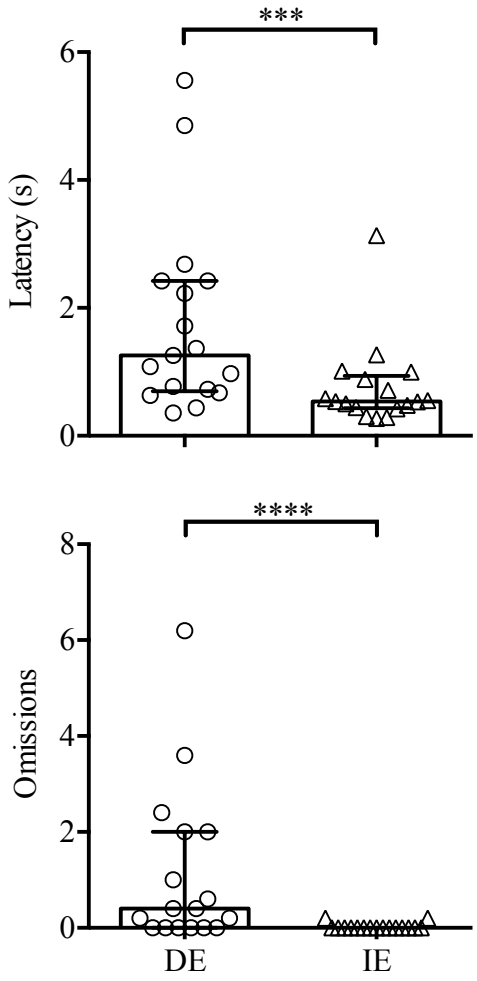

Figure 2. Median and individual-subject latencies to lever-press (top panel) and response omissions (bottom panel) in delay- (DE) and immediacy-exposure (IE) training. Error bars depict ± *IQR*. *** $p < .005$, **** $p < .001$.

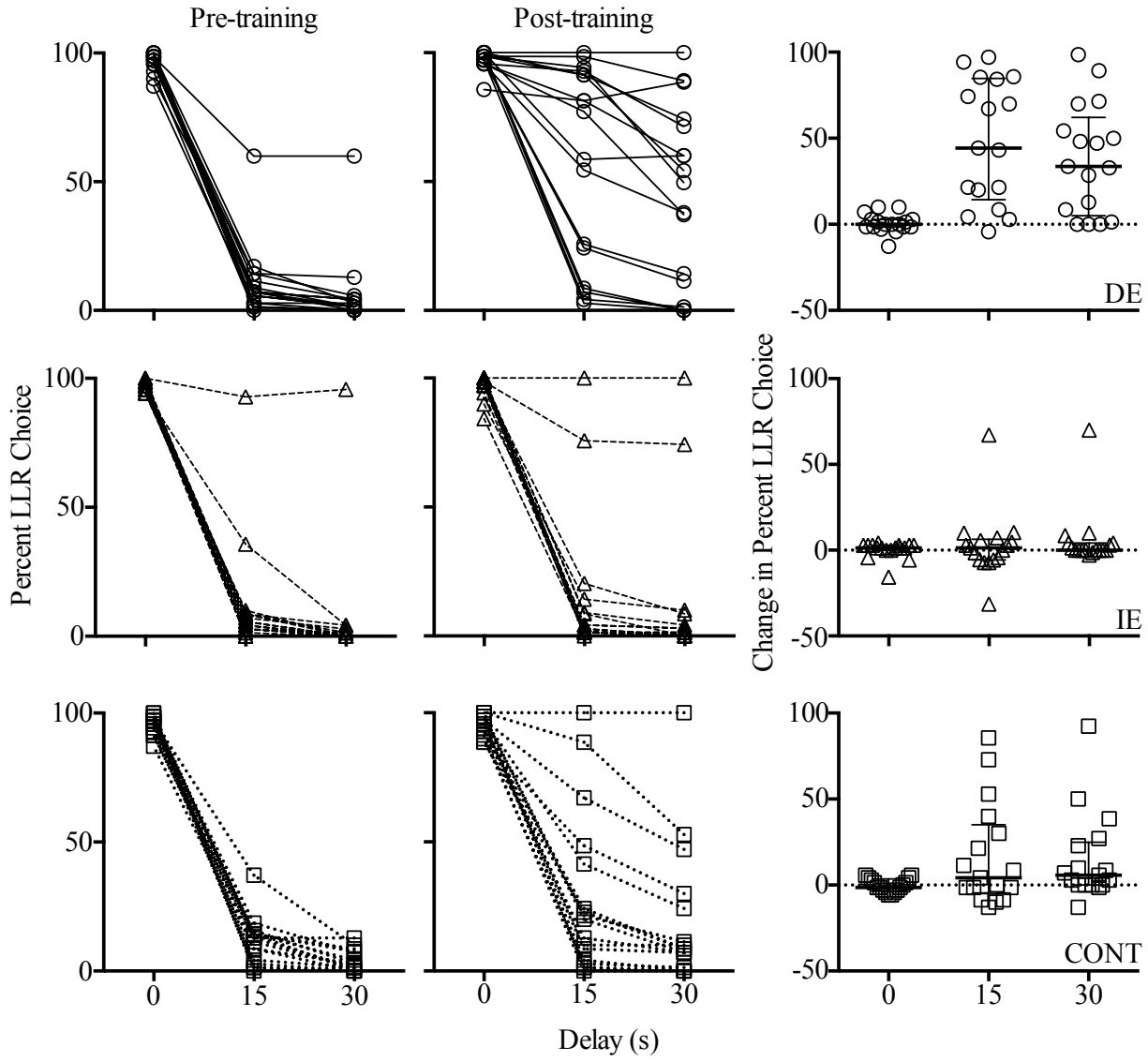

Figure 3. Individual-subject mean percent larger-later reward (LLR) choice from stable sessions, plotted as a function of delay to the LLR. Left and middle columns correspond to pre- and post-training assessments, respectively. The right column shows individual-subject and median change in percent LLR 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 ± *IQR*.

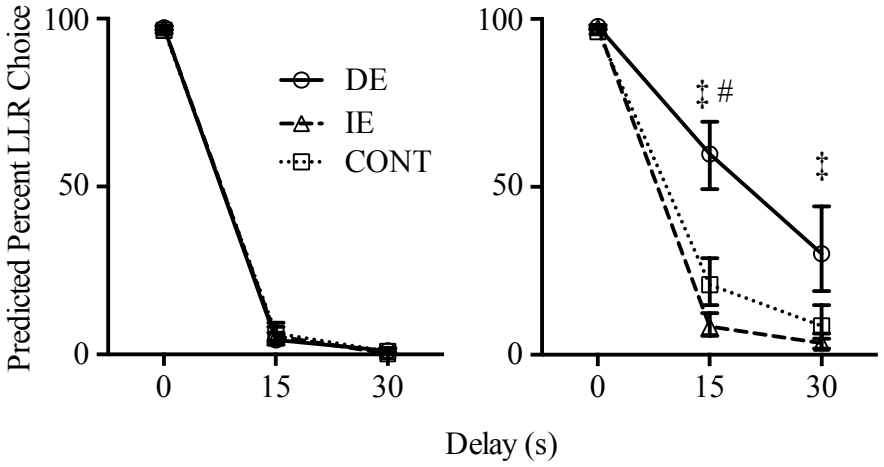

Figure 4. Predicted percent larger-later reward (LLR) choice plotted as a function of delay to the LLR, calculated from the fixed effects estimates from the generalized linear mixed effects model (predicted probabilities multiplied by 100). Left and right panels correspond to pre- and post-training assessments 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 ≤ .005).