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Durability and Generalizability of Time-Based Intervention Effects on Impulsive Choice in Rats

Carrie Bailey[a], **Jennifer R. Peterson**[b], **Aaron Schnegelsiepen**[a], **Sarah L. Stuebing**[a], and **Kimberly Kirkpatrick**[a]

[a]Department of Psychological Sciences, Kansas State University, Manhattan, KS 66506

[b]Department of Psychology, University of Alaska Fairbanks, Fairbanks, AK 99775

Abstract

Impulsive choice involves choosing a smaller-sooner (SS) reward over a larger-later (LL) reward. Due to the importance of timing processes in impulsive choice, time-based interventions have been developed to decrease impulsive choice. The present set of experiments assessed the durability and generalizability of time-based interventions. Experiment 1 assessed fixed interval (FI) or variable interval (VI) intervention efficacy over 9 months. The FI intervention decreased impulsive choice, and this effect persisted over time, but the VI intervention effects were only apparent when tested immediately after the intervention. Experiment 2 examined the generalizability of the FI and VI interventions on choice tasks manipulating the SS delay, LL delay, or LL magnitude. The FI intervention decreased sensitivity to delay, promoting LL choices in both delay tasks, but the VI intervention only altered choices when manipulating the SS delay. Experiment 3 further examined the FI intervention effects on tasks that manipulated the LL delay or magnitude immediately following the intervention. The intervention decreased sensitivity to both delay and magnitude. The experiments indicate that the FI intervention is effective at decreasing impulsive choice behavior for an extended period across changing delays and magnitudes, suggesting a relatively broad effect on choice behavior.

Keywords

impulsive choice; delay discounting; timing; intervention; rat

1. Introduction

Impulsive choice involves choosing a less valuable reward occurring sooner over a higher value reward occurring later (Mazur 2000; Odum 2011). Those who make more impulsive choices are typically described as having higher levels of impulsivity (Bickel et al. 2012; Bickel and Mueller 2009). Impulsive choice is a stable trait (Moeller et al. 2001) that has

Corresponding Author: Carrie Bailey, Department of Psychological Sciences, 492 Bluemont Hall, Kansas State University, Manhattan, KS 66506, USA, cturpen@ksu.edu.

been proposed as a trans-disease process (Bickel and Mueller 2009; Bickel et al. 2012) associated with substance abuse (Bickel, Odum, and Madden 1999; Fuemmeler, Kollins, and McClernon 2007; Perry and Carroll 2008; Perry, Nelson, and Carroll 2008; Stein et al. 2013), obesity (Rasmussen, Lawyer, and Reilly 2010; Weller et al. 2008), gambling (Dixon, Marley, and Jacobs 2003), and Attention Deficit-Hyperactivity Disorder (ADHD; Binder, Dixon, and Ghezzi 2000; Dixon et al. 1998; Dixon, Rehfeldt, and Randich 2003; Litrownik et al. 1977; Neef, Bicard, and Endo 2001).

Due to the trait nature and the trans-disease properties of impulsive choice, it is important to understand its relationship with various disorders and diseases (Bickel, Odum, and Madden 1999). Although some studies have reported no difference between controls and disease populations in delay discounting tasks (e.g., Holt, Green, and Myerson 2003; Kirby, Petry, and Bickel 1999), there is some indication that impulsive choice is not only correlated with substance abuse disorder but is also a precursor to the development of the disorder. Anker et al. (2009) showed that impulsive rats escalated cocaine usage when given the opportunity to self-administer, while rats low in impulsive choice self-administered at a constant rate. Perry and Carroll (2008) also found that rats high in impulsive choice obtained cocaine at a faster rate and increased cocaine self-administration compared to less impulsive rats. In regards to alcohol, Poulos, Le, and Parker (1995) measured impulsivity of rats using a delay to reward T-maze and classified them into high, average, and low impulsivity depending on water and alcohol choice behavior. Their results indicated that rats deemed as high in impulsivity self-administered alcohol more than both the average and low impulsive rats. The causal relationship between impulsive choice and diseases such as substance abuse suggests the need to develop interventions to moderate impulsive choice, which could reduce the likelihood of disease/disorder development.

To develop effective interventions to promote self-control, it is important to understand the processes that may lead to impulsive choices. The primary underlying process that has been proposed to lead to impulsive choice is delay discounting. Delay discounting results in rewards becoming less valuable as time increases, and reward value is most commonly proposed to decay hyperbolically (Baumann and Odum 2012; Mazur 2000; Takahashi 2005). More impulsive individuals discount rewards at a higher rate, thus showing a steeper decay function, compared to less impulsive individuals (Odum 2011). A potential underlying mechanism behind delay discounting is time perception (Litrownik et al. 1977; Takahashi 2005; Wittmann and Paulus 2008).

Individuals who are more impulsive tend to either overestimate delays or show decreased precision in their estimates, which may affect decision making in delay discounting tasks (Wilson et al. 2011; Wittmann and Paulus 2008; Marshall, Smith, and Kirkpatrick 2014; McClure, Podos, and Richardson 2014). A related construct is delay aversion, or avoidance of longer delays, which often occurs in impulsive rats and humans (Kirkpatrick, Marshall, and Smith 2015; Winstanley, Eagle, and Robbins 2006; Marshall, Smith, and Kirkpatrick 2014; Bitsakou et al. 2009; Sonuga-Barke et al. 1992). Avoiding delays decreases exposure to longer time periods which may then hamper the ability to learn those delays, resulting in temporal processing deficits (Galtress, Garcia, and Kirkpatrick 2012; Marshall, Smith, and

Kirkpatrick 2014). Moreover, if time is not perceived accurately or precisely, then rewards may be discounted at a higher rate (Baumann and Odum 2012).

Given the importance of timing processes in impulsive choice, time-based interventions have been developed to promote self-control. These interventions involve delivering time-based schedules of reinforcement outside of the choice task and then assessing the effects on impulsive choices. Eisenberger and Adornetto (1986) delivered a combined time- and effort-based intervention to typically developing children. Children were randomly assigned to high-effort/immediate-reward, low-effort/immediate-reward, high-effort/delayed-reward, or low-effort/delayed-reward groups. Children in the experimental groups completed a series of training tasks that matched the effort and reward delay corresponding to the assigned condition. Following training, all experimental groups and control groups were tested on the choice task. While the results showed that delay and effort did not generalize to both dimensions of the tasks, they did increase self-control within each task dimension; specifically, delay training resulted in more choices for the larger later in the delay task and effort training resulted in more choices for the larger reward requiring high effort in the effort task. This suggests that the interventions target specific processes in promoting self-control. However, delay and effort are likely tapping into different processes that may impair generalization across tasks. This study did not answer the question of whether delay training would transfer to a wider range of choice parameters within a more conventional impulsive choice task with delay and/or magnitude manipulations. Given the limited evidence on generalizability, further research is clearly needed to determine the extent to which interventions generalize across different dimensions, and to parse out the specific processes that may promote or deter generalization.

Time-based interventions have also been developed in rats. One approach has been to expose rats to long delays prior to testing impulsive choice, which resulted in increased LL choices (Stein et al. 2013; Stein et al. 2015). Moreover, exposure to fixed interval, variable interval, and differential reinforcement of low rate schedules, with durations in the range of the choice task, decreased impulsive choice and improved timing precision (Smith, Marshall, and Kirkpatrick 2015; Peterson and Kirkpatrick 2016). These results further suggest that targeting timing processes with time-based interventions may be a fruitful enterprise for promoting self-control. However, the previous studies did not assess whether the time-based interventions might generalize over time and across a wider range of choice parameters, which was the primary goal of the present studies.

To answer the question of durability of time-based interventions using a rodent model, Renda and Madden (2016) examined the effects of delay exposure in rats after a period of four months with a single delay intervention. In their study, the delay-exposure group completed training in which a lever press resulted in a reward after a delay of 17.5 s. Rats in the immediate-exposure group received the same reward but immediately following a lever press. The rats were tested after the intervention and then again 4 months later. They found evidence of increased LL choices in both the immediate and delayed tests, suggesting that the intervention effects were maintained for at least 4 months.

The present study had two goals for extending on the previous work. First, we examined the durability of both fixed and variable interval time-based interventions in moderating impulsive choice in rats. In our previous work, both interventions produced similar effects on impulsive choice when tested immediately following the intervention. Experiment 1 aimed to determine whether a fixed or variable delay exposure would be effective for long-term retention (over a period of 9 months) of intervention effects. The previous study by Renda and Madden (2016) indicates that we should expect to see durability of the intervention effects on choice in the fixed interval task, but the variable interval durability effects remain to be determined.

Second, we tested the generalizability of the intervention effects within the delay and magnitude dimensions to determine whether the time-based intervention produced specific effects on delay processing or if instead the effects would generalize to an impulsive choice under manipulations of reward magnitude. There is a gap in literature investigating the generalizability of time-based interventions in rats, which is critical for determining whether the interventions produce a broader impact on choice behavior within impulsive choice tasks. For example, Smith, Marshall, and Kirkpatrick (2015) only tested impulsive choice with manipulations of the SS delay and the other studies only tested intervention effects with manipulations of the LL delay (Peterson and Kirkpatrick 2016; Renda and Madden 2016; Stein et al. 2013; Stein et al. 2015). Experiment 2, therefore, assessed the generalization of a time-based intervention over three different sets of choice parameters in which SS delay, LL delay, and LL magnitude were manipulated. Finally, Experiment 3 assessed generalizability by testing the LL delay and magnitude tasks immediately following the intervention. The combined assessments of the durability and generalizability of the time-based interventions should provide a more complete picture of the relative efficacy of these interventions for moderating impulsive choice.

2. Materials and Methods (Experiments 1-3)

2.1. Animals

The housing conditions were the same throughout all three experiments. The rats were maintained in a 12:12 h light:dark cycle (lights on at 7 p.m.) and were pair housed. Red lights were used for illumination of the colony room and operant room during the dark cycle. The experimental sessions occurred during the dark cycle. The rats received 45-mg food pellets (BioServ, Flemington, NJ) in the operant chambers and supplemental chow was available in the home cage. Rats received a restricted diet to maintain their weights at approximately 85% of their free-feeding weight based on a growth curve obtained from the supplier. The rats had ad libitum water access in their home cages and operant chambers. All rats were obtained from Charles River (Stone Ridge, NY) and housed in the animal facility at Kansas State University (Manhattan, KS). Experiments 1, 2, and 3 were conducted with 24, 24, and 36 male Sprague Dawley rats, respectively. The rats in all studies were experimentally naïve. These rats were 31, 21, and 21 days of age on arrival for Experiments 1, 2, and 3, respectively.

2.2. Apparatus

All three experiments were conducted in twenty-four operant chambers (74 × 38 × 60 cm) obtained from Med Associates (Saint Albans, VT). The chambers were sound-attenuating and housed a ventilated operant box (25 × 30 × 30 cm). Each operant box had a front wall that functioned as a response panel for collecting behavioral data from the rat. The front wall, back wall, and floor were made of stainless steel. The two side walls and ceiling were composed of a transparent polycarbonate, and one of the side walls functioned as a door. Two pellet dispensers (ENV-203) located outside and atop the front wall delivered 45-mg food pellets (Bio-Serv, Flemington, NJ) to a food cup (ENV-200R7) centered on the lower portion of the front wall. The operant box had two retrac table levers (ENV-112CM) one on either side of the food cup, a house light (ENV-215) located at the top-center of the front wall, and two nose-poke response keys with cue lights (ENV-119M-1) located just above the retractable levers. On the back wall was an opening that contained a water bottle that provided ad libitum water access during operant sessions. Med PC IV software delivered and recorded events within the operant boxes at an accuracy of 2 ms.

2.3. Procedure

2.3.1. Initial training—All three experiments utilized the same initial training procedures, which consisted of magazine and lever press training. Magazine training involved delivery of a single 45-mg food pellet to the food cup on a random time 60-s schedule for a total of 30 pellets. After magazine training, the rats experienced a fixed ratio (FR) schedule followed by a random ratio (RR) schedule for lever training. For the FR 1 schedule of reinforcement, only one lever was inserted at a time and each lever press resulted in one food pellet until 20 food pellets were delivered (ten on each lever, pseudo-randomly alternating levers). This was followed by an RR 3 schedule of reinforcement, where 3 responses were required on average per food pellet until 20 pellets were delivered for responding on either of the levers. After RR 3 was completed, a RR 5 schedule was given in the same manner. For the RR schedules, both levers were inserted at the same time but were treated as independent of one another with each lever yielding 10 total food pellets. Initial training was delivered over three sessions (one session of magazine training and two of lever training).

2.3.2. Time-Based Interventions—Following the initial training, the rats received either an intervention or control procedure with rats randomly assigned to groups. Experiments 1 and 2 involved three groups ($n = 8$), Fixed interval (FI) intervention, Variable interval (VI) intervention, and No delay (ND) control. Smith, Marshall, and Kirkpatrick (2015) found that rats exposed to the FI and VI schedules displayed improved timing and decreased impulsive choice behavior. In Experiment 3, rats were randomly assigned to either FI intervention or ND control groups ($n = 18$). The interventions were delivered replicating the same procedure in all three experiments.

2.3.2.1. FI intervention: The FI intervention was a response-initiated FI schedule from Smith, Marshall, and Kirkpatrick (2015). The FI 10-s schedule was delivered on the lever designated for the SS outcome in the impulsive choice task and the FI 30-s schedule on the lever designated for the LL outcome. The schedules were delivered in blocks of sessions, with only one schedule available on one lever at a time. One of the levers (FI 10 or FI 30)

was inserted into the chamber at the start of a trial. Following an initial lever press, the trial initiated and then after the target delay, the first lever response resulted in food delivery. Food delivery involved 1 pellet for FI 10 s and 2 pellets for FI 30 s. There was an intertrial interval (ITI) of 60 s following food delivery. Sessions lasted until 100 total food pellets were delivered (either 100 FI 10 s or 50 FI 30 s trials). The FI 10-s sessions lasted for approximately 2 hr, and the FI 30-s sessions lasted for approximately 75 min. To equate the number of 10-s and 30-s trials, the 10-s phase lasted for 15 sessions and the 30-s phase lasted for 30 sessions, resulting in 45 total sessions. The order of delivery of the FI 10-s and 30-s schedules was counterbalanced across rats as were the SS and LL lever assignments.

2.3.2.2. VI Intervention: The VI intervention was identical to the FI intervention except for the distribution of intervals (Smith, Marshall, and Kirkpatrick 2015). The VI group was trained on VI 10- and 30-s schedules, with the VI 10-s schedule on the SS lever and the VI 30-s schedule on the LL lever. Delays on the VI schedule were uniformly distributed with means of 10 s (range = 0-20 s) and 30 s (range = 0-60 s).

2.3.2.3. ND control: The ND control group was adapted from Stein et al. (2013). The rats were exposed to FR 2 schedules of reinforcement on both levers. Rats received one of the levers and food was primed immediately after the first press so that the next response would deliver food. Thus, the minimum response requirement matched the FI and VI schedules. There was an ITI for the ND task of 70 or 90 s so that the rate of reinforcement matched the mean overall reinforcement rate on the FI and VI schedules (10 or 30 s plus the 60-s ITI). The ND 70 s was delivered on the SS lever for the choice task and resulted in 1 pellet, and the ND 90 s on the LL lever which resulted in 2 pellets. The ND task was delivered in blocks of sessions in the same fashion as the FI and VI interventions. Previous research has shown that use of the no delay condition is an effective control that does not result in any significant change in choice behavior (Stuebing et al. under revision).

2.3.3. Impulsive Choice Tasks—There were three different impulsive choice tasks that were delivered across the three experiments: SS delay, LL delay, and LL magnitude (see Table 1). The tasks are named according to which choice dimension was manipulated within the task. Each task was delivered for 30 sessions, with three 10-session phases that delivered different choice parameters within each phase.

Experiment 1 tested the durability of the FI and VI interventions. FI, VI, and ND groups received the SS delay task immediately following the intervention. After completion of this task the rats were maintained at 85% of their free-feeding weight and had ad libitum water access in the colony room for 9 months and then were retested on the SS delay task. Experiment 2 tested the generalizability of the FI and VI interventions. The rats initially received an SS delay task immediately following the interventions to mimic Experiment 1. This was followed by the LL delay and magnitude tasks that were delivered to all rats in a counterbalanced order to assess transfer of the interventions to these two tasks. Experiment 3 tested potential carryover effects observed in Experiment 2. Separate FI and ND groups received the LL delay and magnitude tasks immediately following the intervention.

For all three choice tasks, sessions consisted of 78 trials with 48 free-choice trials, 12 SS forced-choice trials, 12 LL forced-choice trials, and 3 each of SS peak and LL peak trials. Free choice trials were delivered by inserting both levers to collect an initial choice response. The unchosen lever was retracted and concurrently the cue light above the chosen lever illuminated, indicating the initiation of the delay to reward. The first lever press after the delay expired resulted in food delivery. The forced choice trials were delivered in the same fashion as free choice trials, but only one lever was inserted corresponding to either the SS or LL. The peak trials were the same as forced trials with only one lever available, but in this case the trial lasted for 90 s. The peak trials terminated with lever retraction and no food delivery. There was a 60-s ITI following all trials. Sessions lasted for approximately 2 hr.

2.3.3.1. SS Delay Task: The SS delay task was conducted to test preferences for the LL as a function of increasing SS delay, providing an index of sensitivity to the SS delay (see Table 1). This task was conducted in three phases with the LL choice remaining constant throughout. The LL choice was 2 pellets with a 30-s delay, and the SS choice resulted in 1 pellet. The first phase delivered a 5-s SS delay for 10 sessions, and then this was increased to 10 s and then to 20 s for the subsequent two phases of 10 sessions each.

2.3.3.2. LL Delay Task: The LL delay task was used to test how much the subjects preferred the LL choice as the LL delay became increasingly longer, providing an index of sensitivity to LL delay (see Table 1). The LL delay manipulation was conducted with 10 sessions of the LL lever having a 15-s delay, then 30-s delay for 10 sessions, and a 45-s delay for 10 sessions. Throughout this choice task, the LL choice resulted in 2 pellets, and the SS choice resulted in 1 pellet with a delay of 10s.

2.3.3.3. LL Magnitude Task: The two choice tasks mentioned above tested the timing component of impulsive choice while this task tested sensitivity to LL magnitude (see Table 1). The LL magnitude manipulation was conducted with the LL lever dispensing 2 food pellets, and then increased to 3 food pellets then 4 food pellets. Throughout this task, the LL choice was associated with a 30-s delay, and an SS choice was 1 pellet with a delay of 10 s.

2.4. Data Analysis

Impulsive choice behavior was analyzed in all three experiments using the same approach. The analysis was conducted over the last five sessions of each phase because choice behavior was stable across these sessions and thus provided a measure of steady state choice behavior. All choices during these sessions were entered into a repeated measures mixed effects generalized logistic regression (Pinheiro and Bates 2000) conducted using MATLAB (Release 2016A). The mixed effects regression models allow for parameter estimation of fixed effects (group-level variables) and random effects (individual differences; Schielzeth and Nakagawa 2013; Pinheiro and Bates 2000; Hoffman and Rovine 2007; Bolker et al. 2008). Mixed-effects models are the recommended analytical framework in psychology and neuroscience research (Boisgontier and Cheval 2016) because they allow for greater generalization to the population and result in reduced Type I error rates (Boisgontier and Cheval 2016; Moscatelli, Mezzetti, and Lacquanti 2012), as model estimates are calculated with respect to population means (Schielzeth and Nakagawa 2013). Because the models

capitalize on repeated measures regression, all choices can be entered into the model and are treated as correlated observations within individuals (Cnaan, Laird, and Slasor 1997). The inclusion of all choice observations greatly increases the precision of the models in comparison to the use of single-point mean observations in standard analyses.

All categorical variables were effects coded (all codes sum to 0) in all experiments. For the variable of group, the ND control was the reference group. In Experiment 1, test time (0 vs. 9 months) was treated as a categorical variable with the 0-month test as the reference. The continuous variables of SS/LL delay and LL magnitude were converted to a relative scale to facilitate comparisons across tasks and provide more meaningful estimates (Wileyto et al. 2004; Young 2017). For the SS delay task, SS delay was scaled with two different intercepts: (1) a zero intercept, which assessed predicted choices at a 0-s SS delay to determine any intervention effects on preferences for immediacy. For this intercept test, the SS delay (5, 10, or 20 s) was divided by the LL delay. (2) a magnitude preference intercept, which assessed predicted choices at a 30-s SS delay, at which point the SS and LL would have the same delay but for different magnitudes (see Young 2017). This assessed preference for the larger magnitude when the delays were the same. For this intercept test, we used the equation (LL Delay – SS Delay)/LL Delay (multiplied by −1 to transpose the slope estimates) so that the intercept test occurred when the LL and SS delays were equal. These two intercepts are of theoretical interest as they assess potentially different processes involved in preferences for immediacy and for larger magnitudes. For the LL delay and LL magnitude tasks, only a single intercept was tested as a zero LL delay or magnitude would not be a meaningful test. For the LL delay task, we assessed the predicted magnitude preference for the larger magnitude when the two delays were the same by scaling LL delay using the equation: (LL Delay – SS Delay)/max(LL Delay). For the LL magnitude task, we assessed the predicted delay preference for the shorter delay when the two magnitudes were the same by scaling LL magnitude using the equation: (LL Magnitude – SS magnitude)/max(LL magnitude).

The fixed effects were tested in a full factorial model for all variables that were manipulated in the study design, and in all models a random intercept was included. In Experiment 1, this included group (FI, VI, or ND), testing time (0 or 9 months), and SS delay; separate follow-up models were conducted on the initial (0 month) and delayed (9 month) post-test and for the zero and magnitude preference intercepts. In Experiment 2, separate models were conducted for each task. The models included the variables of group (FI, VI, or ND) and SS delay, LL delay, or LL magnitude, depending on the task. Two separate intercept models were conducted in the SS delay task as in Experiment 1. In Experiment 3, separate models were conducted for the LL delay and magnitude tasks. The models all included the variables of group (FI, VI, or ND), and LL delay or magnitude, depending on the task. Specific statistical tests are only reported for variables that met the significance criterion of $p < .05$. Significant group effects were assessed using the Coefficient Test function in MATLAB, comparing each intervention group to the ND control group and to each other.

3. Results and Discussion

3.1. Experiment 1

Figure 1 displays the proportion of LL choices as a function of SS delay for the two intervention (FI and VI) and control (ND) groups during the immediate (0 months; top panel) and nine-month (9 months; bottom panel) choice tasks. Both intervention groups displayed increased LL choices during the initial choice task, but only the FI group displayed increased LL choices during the delayed choice task. The overall regression analysis revealed a significant Group × Time × SS Delay interaction. To further understand the three-way interaction, separate analyses were conducted on the initial and delay post-test results.

3.1.1. Immediate Post-Test—The zero intercept regression model indicated a significant overall bias to make SS choices at the intercept, $t(16524) = -11.58$, $p < .001$, $b = -3.75$ [−4.38, −3.11], indicating that the rats showed an overall preference for immediacy. The FI ($b = -2.96$), $t(16524) = 2.49$, $p = .013$ and VI ($b = -3.34$), $t(16524) = 2.01$, $p = .044$, groups showed a decreased preference for immediacy compared to the ND group ($b = -4.94$). Choosing the immediate reward in this case is less optimal in terms of overall reward earning due to the use of a 60-s ITI, which results in an overall reward rate of 1 pellet in 60 s for the SS and 2 pellets in 90 s for the LL. Thus, the intervention moderated choices towards the more optimal delayed reward.

At the magnitude preference intercept, there was a significant preference to make LL choices, $t(16524) = 8.41$, $p < .001$, $b = 2.73$ [2.10, 3.37], indicating an overall preference for the larger reward of 2 pellets. The VI group ($b = 3.61$) displayed an increased preference for the larger magnitude, $t(16524) = 2.33$, $p = .020$, compared to the ND group ($b = 1.76$), but the FI group ($b = 2.82$) did not differ from the other two groups. At the intercept, the two delays would be the same, so the larger magnitude is the clearly better choice in terms of reward earning potential.

Tests of the slope of the choice function indicated a significant increase in LL choices with increasing SS delays, $t(16524) = 50.12$, $p < .001$, $b = 6.48$ [6.22, 6.73]. There was also a Group × SS Delay interaction. The FI group ($b = 5.78$) displayed a flatter slope than the ND ($b = 6.70$), $t(16524) = 2.73$, $p = .006$ and VI ($b = 6.95$), $t(16524) = 4.28$, $p < .001$, groups. Thus, the FI intervention reduced sensitivity to delay. The VI group did not differ from the ND group.

3.1.2. Nine-Month Post-Test—There was an overall bias to make SS choices at the zero intercept, $t(16619) = -9.93$, $p < .001$, $b = -5.62$ [−6.73, −4.51], and there was a significant preference to make LL choices at the magnitude preference intercept, $t(16619) = 6.93$, $p < .001$, $b = 3.92$ [2.81, 5.03], indicating an overall preference for the larger reward of 2 pellets. There were no significant group differences at either intercept, but the FI group generally made fewer SS choices at the zero intercept ($b_{FI} = -4.07$, $b_{VI} = -6.43$, $b_{ND} = -6.37$) and more LL choices at the magnitude preference intercept ($b_{FI} = 4.25$, $b_{VI} = 3.89$, $b_{ND} = 3.62$), in comparison to the VI and ND groups.

Tests of the slope of the choice function indicated a significant increase in LL choices with increasing SS delays, $t(16619) = 50.37$, $p < .001$, $b = 9.54$ [9.17, 9.91]. There was also a Group × SS Delay interaction. The FI group ($b = 8.32$) displayed a flatter slope than the ND ($b = 9.99$), $t(16619) = 3.55$, $p < .001$, and VI ($b = 10.32$), t(16619) = 4.58, $p < .001$, groups. Thus, the FI intervention continued to result in reduced sensitivity to delay.

3.1.3. Overall Summary—Overall, the FI and VI interventions produced stronger effects during the immediate post-test, with both groups showing reduced biases for immediacy and the VI group showing increased preference for the larger reward. These effects were not maintained in either group during the nine-month post-test. The FI intervention also reduced sensitivity to delay, resulting in flatter slopes that were predominantly due to elevated LL choices at the shorter delays. This effect of the intervention was maintained during the nine-month post-test. Thus, it appears that the FI intervention produced more robust and long-lasting effects on delay sensitivity compared to the VI intervention. Experiment 2 assessed whether the FI and VI intervention effects would transfer to other tasks in addition to the SS delay task.

3.2. Experiment 2

Figure 2 displays the proportion of LL choices as a function of SS delay (top panel), LL delay (middle panel), and LL magnitude (bottom panel).

3.2.1. SS Delay Task—As seen in Figure 2 (top panel), the logistic regression analyses indicated that there was an overall bias to choose the SS at the 0-s intercept, $t(15436) = -9.28$, $p < .001$, $b = -3.16$ [−3.83, −2.49], indicating that the rats showed an overall preference for immediacy. The FI group ($b = -2.46$) displayed fewer SS choices at the intercept, $t(15436) = 2.02$, $p = .043$, relative to ND group ($b = -4.14$), indicating a decreased preference for immediacy, but VI group ($b = -2.89$) did not differ significantly from the ND group. Tests of the magnitude preference intercept, at which point the two delays were equal (at 30 s), indicated an overall preference for the larger reward of 2 pellets, $t(15436) = 8.89$, $p < .001$, $b = 3.06$ [2.39, 3.74], but there were no group differences in magnitude preference.

There also was a significant increase in LL choices as a function of SS delay, $t(15436) = 48.88$, $p < .001$, $b = 6.23$ [5.98, 6.48]. Group FI ($b = 5.35$) displayed a flatter slope compared to Group ND ($b = 7.61$), $t(15436) = 7.59$, $p < .001$, and Group VI ($b = 5.72$) also displayed a flatter slope compared to Group ND, $t(15436) = 5.66$, $p < .001$. Thus, both intervention groups displayed reduced sensitivity to delay. Overall, the results of the SS delay task are consistent with the intervention promoting self-control by increasing LL choices at the shorter delay, and in the FI group reducing preference for immediacy.

3.2.2. LL Delay Task—The intervention groups were highly variable in their choice behavior, as evidenced by large standard error values, and chose the LL less often at the two shortest LL delays. The regression analysis indicated that there was an overall preference for the larger magnitude at the intercept, where the two delays would be the same (10 s), $t(15913) = 6.28$, $p < .001$, $b = 3.28$ [2.26, 4.30]. There were no group main effects at the intercept.

There also was an overall decrease in LL choices as a function of increasing LL delay, $t(15913) = -51.17$, $p < .001$, $b = -5.95$ [−6.18, −5.72], and there was a Group × LL Delay interaction. Specifically, the FI group displayed a significantly flatter slope ($b = -5.18$) compared to the ND group ($b = -6.36$), $t(15913) = 4.63$, $p < .001$ and the VI group ($b = -6.30$), $t(15913) = 3.83$, $p < .001$. Note that the visual depiction of the results in Figure 2 (middle panel) suggests a flatter slope in the VI group in comparison to the model results. This is due to a single rat in the VI group that had a very flat slope, which strongly affected the group mean curve in the figure. Because the mixed effects model accounts for such outliers as random effects, these individuals carry less weight in the fixed effects estimates in comparison with the individuals with functions that are more typical of the group. This explains why the VI group estimate for the slope is steeper than suggested in the figure.

Although there were no group main effects, the FI intervention resulted in flatter slopes indicating that the FI intervention reduced sensitivity to the LL delay. The VI intervention did not differ from the controls. Thus, the interventions did not successfully promote LL choices in the LL delay task, but the FI intervention did decrease sensitivity to delay. Overall, there were poor transfer of training effects of the intervention on the LL delay task.

3.2.3. LL Magnitude Task—Performance on the LL magnitude task was also highly variable, and the VI group had lower LL choices at the largest LL magnitude of 4 pellets. The regression revealed that there was an overall preference for the shorter SS delay at the intercept where the two magnitudes were the same (1 pellet), $t(13255) = -5.00$, $p < .001$, $b = -2.70$ [−3.76 −1.64]. LL choices increased as a function of increasing LL magnitude, $t(13255) = 40.51$, $p < .001$, $b = 7.40$ [7.04, 7.75]. There was no group main effect or interaction with LL magnitude. Thus, the intervention did not have any significant impact on choices in the LL magnitude task.

3.2.4. Overall Summary—Overall, the interventions did not transfer well to the two LL tasks. This may be a product of a specific transfer effect to only the SS delay task, but that seems unlikely for the LL delay task given that previous studies have reported successful intervention effects on tasks manipulating LL delay (Peterson and Kirkpatrick 2016; Renda and Madden 2016; Stein et al. 2013; Stein et al. 2015). It is, however, possible that the LL magnitude task may have shown a transfer failure if the interventions were selective for delay processing only, as shown previously by Eisenberger and Adornetto (1986) with regard to transfer between delay and effort. The SS delay task was tested first and thus provided a pure measure of transfer of the interventions. It is possible that the subsequent tasks suffered from carryover effects from the previous task(s) and this could explain the poor transfer of the interventions. This was examined for the FI intervention in Experiment 3.

3.3. Experiment 3

Figure 3 displays the proportion of LL choices as a function of LL delay (top panel) or LL magnitude (bottom panel). The figure shows that the FI group displayed an increase in LL choices at the longer LL delays and smaller LL magnitudes.

3.3.1. LL Delay Task—There was an overall preference for the larger magnitude at the intercept, $t(11230) = 7.85$, $p < .001$, $b = 2.39$ [1.80, 2.99], but there were no group differences in magnitude preference. Tests of the slope of the functions indicated that LL choices decreased with increasing LL delay, $t(11230) = -48.96$, $p < .001$, $b = -5.50$ [−5.72, −5.28]. There also was an Group × LL Delay interaction, $t(11230) = 8.34$, $p < .001$, $b = 0.94$ [0.72, 1.16]. Rats in the intervention group displayed flatter slopes ($b = -4.57$) compared to control rats ($b = -6.44$). This indicates that the FI intervention reduced sensitivity to delay.

3.3.2. LL Magnitude Task—There was a significant overall preference for the shorter delay (the SS) at the intercept, $t(9425) = -7.12$, $p < .001$, $b = -1.92$ [−2.45, −1.39]. There also was an overall effect of group, $t(9425) = 3.32$, $p < .001$, $b = 0.90$ [0.37, 1.43], indicating that the FI group ($b = -1.03$) showed a reduced preference for the shorter delay compared to the ND group ($b = -2.82$). This is consistent with the observation of reduced preference for immediacy in the FI group seen in the SS delay task in Experiments 1 and 2. However, in this case, choosing the SS at the intercept is the more optimal choice as the two magnitudes are the same and so the shorter delay (10 s vs. 30 s) is the better option. Thus, the intervention resulted in sub-optimal choices in the LL magnitude task at the intercept. The results suggest that the intervention may have induced a bias to wait for longer delays, which in most cases in the current tasks is the more advantageous outcome.

Tests of the slope of the choice function indicated that LL choices increased with increasing LL magnitude, indicating that the rats demonstrated magnitude sensitivity, $t(9425) = 38.03$, $p < .001$, $b = 6.71$ [6.37, 7.06]. There also was a Group × LL Magnitude interaction, $t(9425) = -6.85$, $p < .001$, $b = -1.21$ [−1.55, −0.86] in that the FI group ($b = 5.50$) showed reduced sensitivity to magnitude compared to the ND group ($b = 7.92$). This is consistent with the intervention effects on the SS and LL delay tasks in that the FI generally display flatter slopes due to increased LL choices. Thus, it appears that the intervention reduced sensitivity to magnitude.

3.3.3 Overall Summary—In both tasks, when tested initially the FI intervention reduced the slope of the choice function due to increased LL choices. The increase in LL choices was most apparent when the value of the SS was relatively higher. In the LL delay task, this was at the longer LL delays and in the LL magnitude task, this was at the smaller LL magnitudes. These results are consistent with the patterns observed in the SS delay task in Experiments 1 and 2, where the intervention resulted in flatter slopes due to increased LL choices at the shortest SS delays (when the SS value was relatively higher). The intercept test on the LL magnitude task indicated that the intervention resulted in an increased bias to choose longer delays, even though doing so was suboptimal. There were no effects of the intervention on preferences for the larger magnitude.

4. General Discussion

The three experiments assessed the durability and generalizability of time-based intervention effects on impulsive choice. Experiment 1 demonstrated both FI and VI interventions reduced the preference for immediate rewards, the VI increased the preference for larger magnitudes, and the FI reduced sensitivity to delay. Only the FI demonstrated durability of

effects up to at least 9 months, or approximately 19 human years (Sengupta 2013). During the delay test, the FI continued to show reduced sensitivity to delay, but the reduced preference for immediacy was no longer observed. This suggests that the FI intervention efficacy may have been reduced in strength over time, but the effects were still apparent.

Experiment 2 set out to investigate whether the FI or VI intervention could generalize to multiple choice tasks with different parameters. Both interventions decreased sensitivity to delay in the SS delay task, but only the FI reduced the preference for immediacy. In the LL delay task only the FI intervention was effective at decreasing sensitivity to delay, but this was not accompanied by any increase in LL choices. There were no intervention effects in the LL magnitude task. Experiment 3 sought to determine whether the poor transfer of the interventions in Experiment 2 may have been due to carryover effects by assessing the FI intervention efficacy on the LL delay and LL magnitude tasks immediately following the intervention. The FI intervention generalized to both choice tasks, decreasing sensitivity to delay and magnitude. This suggests that the failure of generalization in Experiment 2 was due to carryover effects.

The combined results of the three experiments indicate that the FI intervention generalized to all three choice tasks upon initial testing, consistently showing reduced sensitivity to delay and magnitude across the three experiments, and the FI intervention effects on sensitivity to delay were maintained over 9 months. The VI intervention effects were less robust, but there was also some indication of reduced sensitivity to delay by the VI in Experiment 2. The predominant process invoked to explain differences in the slope of the choice function (i.e., sensitivity to delay or magnitude) is delay discounting, which is integral to understanding impulsive choice (Mazur 2001; Odum 2011). Steeper slopes of the delay discounting curve are representative of a higher discounting rate (i.e., larger *k*-value). The shallower slopes of the intervention groups, and particularly the FI intervention, suggest that the intervention decreased the overall delay discounting rate, which resulted in flatter slopes in all tasks. Given that steep discounting rates are associated with a wide range of diseases and disorders (Bickel et al. 2012; Bickel and Mueller 2009), the present results suggest that the FI intervention may be a key target for development for future therapeutic applications.

In addition, the FI intervention also reduced the preference for immediacy in the SS delay task by increasing LL choices at the zero intercept in Experiments 1 and 2. This shift in preference resulted in more optimal behavior, as choosing the LL at all delays resulted in increased overall reward rates. Relatedly, the FI intervention increased the preference for the LL at the delay preference intercept in the LL magnitude task in Experiment 3. Here, however, the increase in LL choices was suboptimal as the SS (10 s for 1 pellet) was associated with a higher reward rate than the LL (30 s for 1 pellet). This suggests that the intervention may induce a bias to choose longer delays, regardless of whether that choice is more optimal or not. Future research should manipulate the SS and LL under conditions where the SS or LL may be more or less optimal to examine intervention effects on optimal decision making.

The present results are interesting given that recent research has suggested that time-based interventions may target timing processes. It has been previously suggested that delay aversion may be an important factor in impulsive choice (Kirkpatrick, Marshall, and Smith 2015; Winstanley, Eagle, and Robbins 2006; Marshall, Smith, and Kirkpatrick 2014; Bitsakou et al. 2009; Sonuga-Barke et al. 1992) and that the interventions may increase LL choices by forcing exposure to long delays. In addition, Marshall et al. (2014) found that poor timing precision predicted impulsive choice, while others have reported increased timing precision in rats following FI and VI interventions (Peterson and Kirkpatrick 2016; Smith, Marshall, and Kirkpatrick 2015). Interestingly, the previous papers all reported that timing precision predicted the overall preference for the LL rather the slope of the choice function. One advantage of the present report is that we utilized mixed effects regression models, which allow for better dissociation of effects on the intercept and slope of the choice functions compared to standard statistical techniques (e.g., ANOVAs). The use of these models revealed that the interventions (especially the FI) may target specific timing processes by increasing preference for longer delays while concomitantly targeting general choice processes by decreasing discounting rates. These findings advance our understanding of the potential mechanisms of the interventions that can be informative for future applications.

It is clear from the present results that the VI intervention efficacy in modifying choice behavior is weaker than the FI intervention. The VI effects on the SS delay task had disappeared after 9 months, and there were no signs of transfer of the VI to the LL delay or magnitude tasks in Experiment 2 (although this could have been due to the testing order effects). This suggests that training on individual delays is more effective in increasing self-control than training with a range of delays. Rats do appear to time variable intervals (Church and Lacourse 2001; Church, Lacourse, and Crystal 1998; Kirkpatrick and Church 2003, 2004), but variable interval timing may involve some different processes from fixed interval timing as rats appear to learn the distribution of intervals as well as the mean duration of the variable interval (Church and Lacourse 2001; Kirkpatrick and Church 2003). Given that the choice task involves fixed intervals, it seems that training on specific intervals may have a comparative advantage in transferring to the fixed intervals in the choice task. The present FI interventions used the SS (10 s) and LL (30 s) delays that were delivered on at least one lever in at least one of the phases of each choice task; future research should examine whether training with other specific delays that are not directly tested in the choice task would generalize as effectively as training with the actual choice delays as this could provide further insights into the nature of the intervention effects on choice.

Another factor that could have affected the results is within-task order effects. All task manipulations were conducted in an ascending order, which could have resulted in anchoring effects to the initial parameters (Smith, Peterson, and Kirkpatrick 2016). At a minimum, this could have impacted on the slope and intercept estimates from the regression models. It is additionally possible that the intervention effects may be expressed differently if delay or magnitude were tested in a descending order. For example, amphetamine and methylphenidate produce different effects depending on whether the delays are tested in an ascending or descending order (Maguire, Henson, and France 2014; Tanno et al. 2014). This a potentially important variable that should be examined in future research.

In summary, the experiments demonstrated the FI intervention is durable for at least 9 months and can generalize to multiple choice tasks, including a reward magnitude task. The intervention is effective at increasing preferences for longer delays and decreasing sensitivity to delay or magnitude, which presumably reflects reduced delay discounting. The time-based interventions appear to be improving delay discounting, while also reducing delay aversion, and improving timing precision. The experiments provide promising results for translational research using an FI intervention to address impulsive choice across a variety of diseases and disorders.

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Highlights

- Time-based interventions were used to reduce impulsive choice behavior
- The interventions were tested for their durability and generalizability
- The fixed-interval intervention lasted for at least 9 months and generalized across choice tasks
- The fixed-interval intervention appears to reduce delay discounting rates

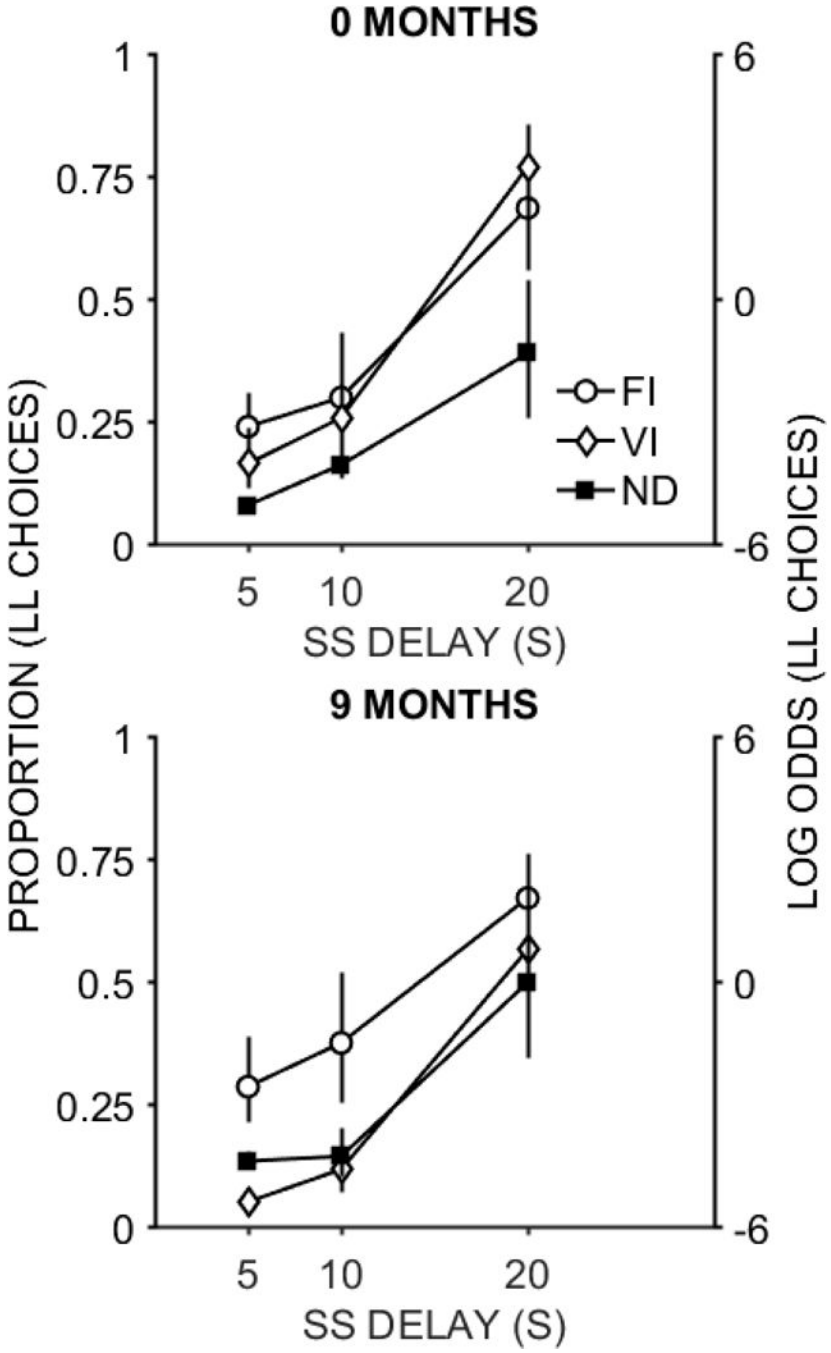

Fig. 1.

The proportion of larger-later (LL) choices as a function of smaller-sooner (SS) delay for initial (0 months; top panel) and delayed (9 months; bottom panel) choice task in the fixed interval (FI), variable interval (VI), and no-delay (ND) groups. The right ordinate axis provides the log odds of LL choices as a general reference for interpretation of the unstandardized regression coefficients (*b* values). The error bars are ± one standard error of the mean, determined from the mixed effects model.

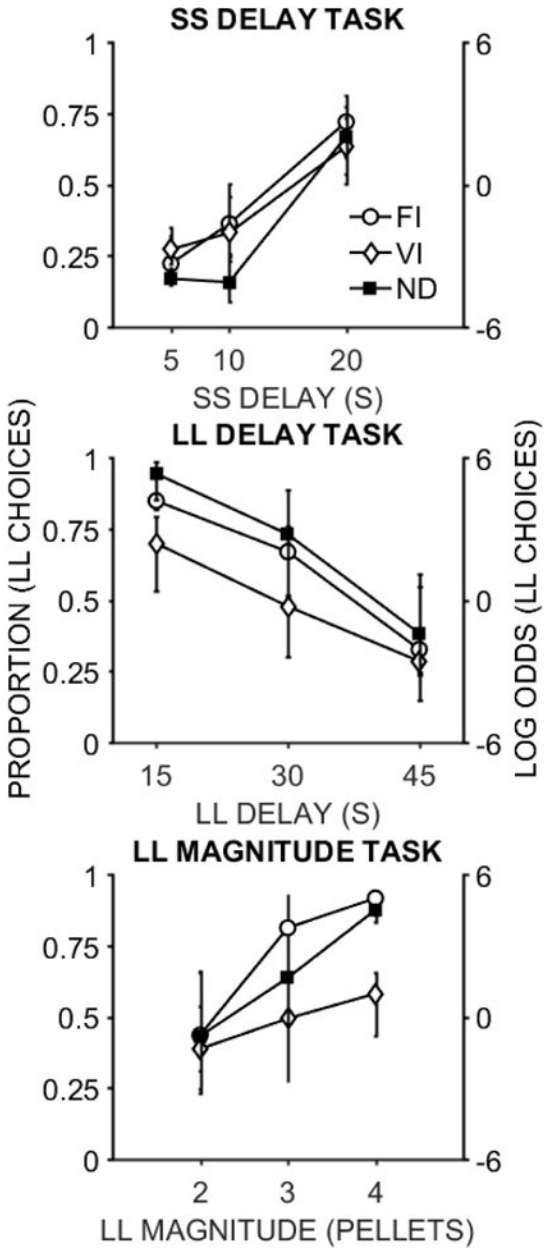

Fig. 2.

The proportion of larger-later (LL) choices as a function of smaller-sooner (SS) delay (top panel), LL delay (middle panel), and LL magnitude (bottom panel) in the fixed interval (FI), variable interval (VI), and no-delay (ND) groups. The right ordinate axis provides the log odds of LL choices as a general reference for interpretation of the unstandardized regression coefficients (*b* values). The error bars are ± one standard error of the mean, determined from the mixed effects model.

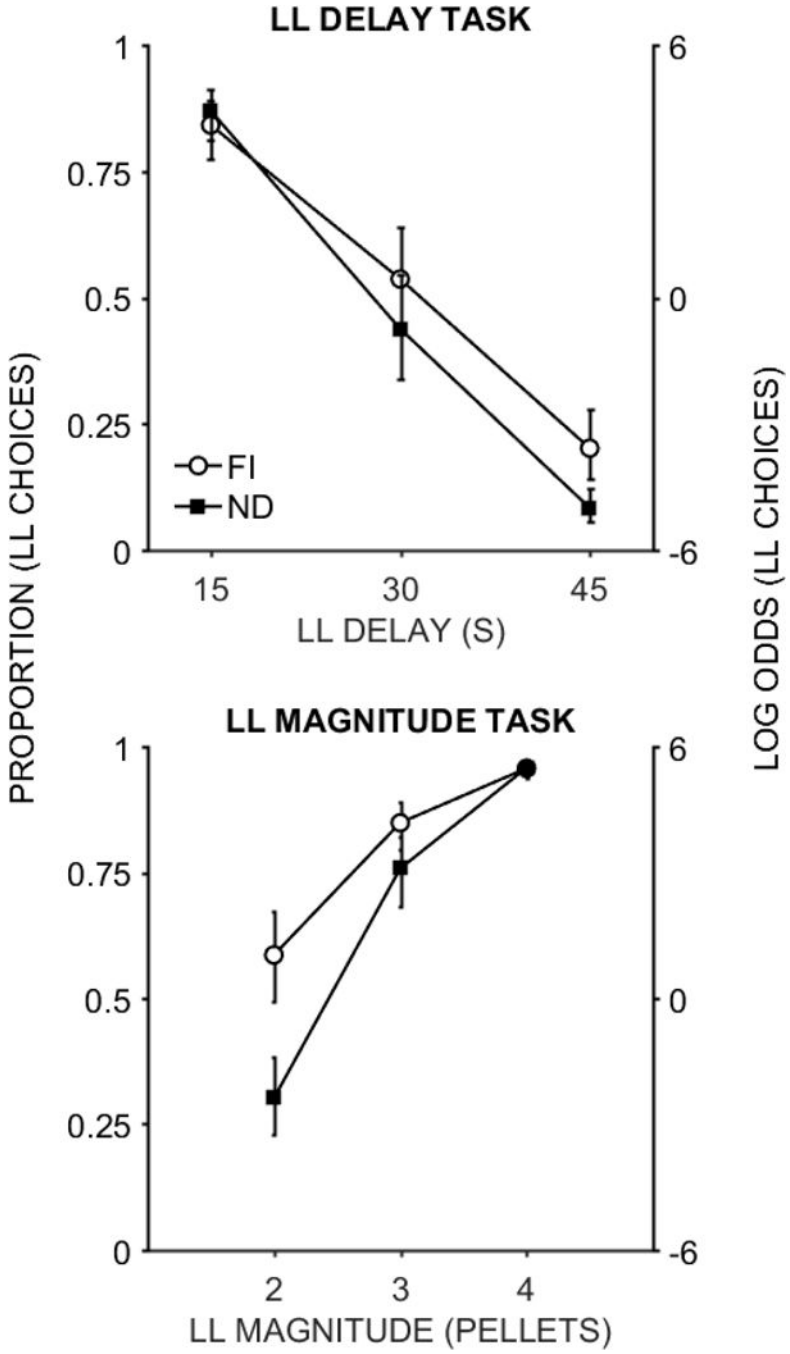

Fig. 3.

The proportion of larger-later (LL) choices as a function of LL delay (top panel) and LL magnitude (bottom panel) in the fixed interval (FI) and no-delay (ND) groups. The right ordinate axis provides the log odds of LL choices as a general reference for interpretation of the unstandardized regression coefficients (*b* values). The error bars are ± one standard error of the mean, determined from the mixed effects model.

Table 1

The task design for the SS Delay, LL Delay, and LL magnitude tasks administered in Experiments 1-3. The SS delay task manipulated the delay to reward on the SS lever, while holding the amounts of reward and the LL delay constant. The LL delay task manipulated the delay to reward on the LL lever, and the LL magnitude task manipulated the magnitude of reward on the LL lever.

Experiment	SS Delay	LL Delay	LL Magnitude
1	SS: 5→10→20 s, 1 p LL: 30 s, 2 p	—	—
2	SS: 5→10→20 s, 1 p LL: 30 s, 2 p	SS: 10 s, 1 p LL: 15→30→45 s, 2 p	SS: 10 s, 1 p LL: 30 s, 2→3→4 p
3	—	SS: 10 s, 1 p LL: 15→30→45 s, 2 p	SS: 10 s, 1 p LL: 30 s, 2→3→4 p

Exp = Experiment; SS = Smaller-Sooner; LL = Larger-Later; s = seconds; p = pellets