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Delay Discounting for Sucrose in Alcohol-Preferring (P) and Non-Preferring (NP) Rats using a Sipper-Tube Within-Sessions Task

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Abstract

Background—Delay discounting (DD) is a measure of impulsivity that quantifies preference for a small reward delivered immediately over a large reward delivered after a delay. It has been hypothesized that impulsivity is an endophenotype associated with increased risk for development of alcohol use disorders (AUDs); however, a causal role of impulsivity is difficult to determine with human studies. We tested this hypothesis by assessing the degree of DD present in alcohol-naïve rats selectively bred for either high or low alcohol preference.

Methods—A novel adaptation of a within-sessions DD procedure was used to compare impulsivity differences between male alcohol-preferring (P) and non-preferring (NP) rat lines ($n = 6$ per line) using a 5% sucrose reward. Animals chose between two options: 2-sec sipper tube access delivered immediately (small reward) or 8-sec access after a variable delay (large reward). Each 50-min session consisted of 5 blocks of 10 60-sec trials. Within each session, the delay to the large reward increased in each block of trials. Delays were gradually increased over 3 sets to attain a final delay set of 3, 8, 15, 18, and 25 sec.

Results—Prior to starting delays, there were no significant differences between lines in sucrose consumption or percent choice for the large reward, and both lines exhibited a clear preference for the large reward. After delays were initiated, choice for the large reward decreased as the delay to its presentation increased. Although discounting of the large, delayed reward was observed for both lines, the degree of discounting, or “impulsivity,” was greater for P rats compared with NP rats.

Conclusions—P rats are more impulsive for sucrose rewards before exposure to alcohol compared with NP rats. Thus, individuals genetically predisposed toward developing AUDs may be more likely to engage in impulsive decision-making prior to alcohol exposure.

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Keywords

Alcohol-use disorder; Delay discounting; Impulsivity; Endophenotype; Sucrose

Introduction

Impulsivity is a principal behavioral characteristic of addiction, capable of identifying etiological predisposition, tracking disease severity, and gauging treatment efficacy (Bickel et al., 2014a; Bickel et al., 2014b; Murphy et al., 2002; Perry and Carroll, 2008). Delayed-reward discounting (DD) is a behavioral economic measure of impulsivity that quantifies an individual's propensity to choose a small reward delivered immediately instead of a large reward delivered after a delay (Johnson and Bickel, 2002; Oberlin and Grahame, 2009; Wilhelm and Mitchell, 2008). DD has been hypothesized to be an addiction endophenotype (Andrzejewski et al., 2011; MacKillop, 2013); however, it is currently unclear whether DD is a predisposing endophenotype, a result of protracted drug use, or a covariant of associated etiological processes (de Wit, 2009; Kalivas and Brady, 2012). It remains a formidable task to fully disentangle this "chicken or egg" question of impulsivity's role in addiction, as there are clear ethical limitations of systematically and randomly exposing individuals to alcohol. Although naturalistic longitudinal studies may help discern whether impulsivity predicts alcohol consumption or vice versa (Ferne et al., 2013), the use of animal models allows for greater license to control these variables. Herein, we employ an animal model of addiction predisposition to address whether the impulsivity endophenotype precedes drug exposure.

Previous animal studies have shown that impulsivity predicts several hallmark addiction-like behaviors, such as compulsive cocaine taking (Belin et al., 2008) and escalation of cocaine taking during extended-access procedures (Anker et al., 2009). Alcohol preference may also predict an addiction-like phenotype, as alcohol-preferring rodents display higher trait impulsivity compared to alcohol-non-preferring rodents. For example, using an adjusting amounts procedure (Richards et al., 1997), Oberlin and Grahame (2009) found that mice bred for high alcohol preference (HAP) showed significantly lower indifference points for a saccharin reward compared to mice bred for low alcohol preference (LAP). The indifference point was measured as the magnitude of an immediately delivered small saccharin reward that resulted in a preference equivalent to a large, delayed reward. Thus, a lower indifference point indicated that HAP mice discounted the value of the large, delayed reward more, or displayed higher DD, than LAP mice. Using a similar approach, Wilhelm and Mitchell (2008) reported that high-alcohol-drinking (HAD) rats exhibited significantly higher DD of a sucrose reward compared to low-alcohol-drinking rats (LAD). However, Wilhelm and colleagues (2007) have also previously reported that mice selectively bred to drink high amounts of alcohol did not display higher DD for a sucrose reward compared to their low-alcohol-drinking counterparts. These mixed results indicate that not all heritable predispositions towards high alcohol drinking are associated with elevated DD impulsivity. To clarify whether impulsivity is indeed a general characteristic of animals with high alcohol preference, we measured DD in a separate rodent AUD model.

We assessed the role of impulsivity as an addiction endophenotype using rat lines selectively bred for high and low alcohol preference (Murphy et al., 2002). These lines are not bred for, or initially characterized by, measures of impulsivity, but for voluntary ethanol consumption. The alcohol-preferring (P) rat line consumes >6.5 g ethanol/kg/day and meets behavioral criteria characteristic of AUDs, and is contrasted by the non-alcohol-preferring (NP) rat line which consumes <0.5 g ethanol/kg/day and fails to demonstrate behavioral characteristics of AUDs (Murphy et al., 2002). We asked whether the genotype that produces an AUD-like phenotype in P rats also confers trait impulsivity.

Endophenotypic differences in impulsivity between drug-naïve P and NP rats were assessed in the present study using a novel sucrose sipper-tube, within-sessions DD procedure. In this task, animals choose between immediate access to a small reward and delayed access to a large reward. Impulsivity is operationally defined as lower percent-choice for the large, delayed reward. We predicted that our results would extend previous reports that found higher trait impulsivity in high-alcohol-drinking rodents (Oberlin and Grahame, 2009; Wilhelm and Mitchell, 2008), and we hypothesized that P rats would exhibit lower percent choice for the large, delayed reward relative to the NP rats, thus demonstrating greater trait impulsivity.

Materials and Methods

Subjects

Subjects were experimentally naïve male P ($n = 6$) and NP ($n = 6$) rats bred at Indiana University. Upon their arrival, animals were approximately 10 weeks old and weighed between 277 g and 360 g ($M = 320$ g, $SEM = 6.3$ g). Subjects were singly housed in individually ventilated polycarbonate cages and had access to water *ad libitum*, except as noted below. Animals were weighed and handled at least 5 times per week and were maintained on a 12:12 hr light/dark cycle with lights on at 0800 h. All procedures were approved by the Institutional Animal Care and Use Committee at The College of New Jersey.

Apparatus

Operant testing took place in 4 stainless-steel chambers ($29.2 \times 24.1 \times 20.3$ cm) with acrylic doors, ceilings and rear walls (Med Associates, St. Albans, VT, USA). The left wall of each operant chamber was equipped with 2 retractable levers, 1 retractable sipper bottle module positioned between the levers, and 1 stimulus light above each lever. A white houselight was located on the right wall. The levers controlled the presentation of the sipper bottle into the chamber. Stainless-steel ball-bearing sipper spouts (5.7 cm) were inserted in rubber stoppers attached to 50-mL plastic centrifuge tubes. A plastic spacer (1.3 cm) was positioned on the spout, which ensured that each spout entered 0.4 cm into the chamber. Experimental events were recorded with a personal computer using Med-PC software (Med Associates) located in the same room. Chambers were enclosed in sound-attenuating plywood cabinets with individual exhaust fans to provide ventilation.

Lever Press Training

All training and experimentation took place between 1230 and 1630h. Following a 10-day period of habituation to the home cage, the animals were trained to lever press for 10% sucrose (10S, 10 g sucrose/100 ml water) in 2 phases over 6 sessions (3 sessions/phase). Sessions were 60 min and began with the illumination of the houselight and the extension of both levers into the operant chamber. During both phases, completion of a fixed-ratio-1 (FR-1) requirement on either lever resulted in immediate entry of the sipper bottle into the operant chamber for 15 sec. The 2 phases were identical except that during the first phase, a random time 60-sec (RT-60'') schedule also was in effect, providing access to the sipper bottle every 60 sec on average, regardless of the animals' lever-press responding (Andrzejewski et al., 2011). During the second phase, the RT-60'' schedule was eliminated.

Delay Discounting (DD) Task

After lever press training, subjects were trained on a DD procedure adapted from the method described by Evenden and Ryan (1996). In this procedure, animals responded for sipper tube access to 5% sucrose solution (5S, 5 g sucrose/100 ml water). Reward size was defined as the duration of access to the sipper tube. During initial training, small and large rewards were 3- and 12-sec access respectively; however, before final testing, reward sizes were reduced by 30% (2 and 8 sec access) to prevent possible satiation within a session.

Two types of trials occurred within each session of the DD procedure: "choice" and "forced." Choice trials required animals to choose between a small reward presented immediately and a large reward presented after a delay that varied within the 50-min session. Figure 1 depicts the sequence of events of each 60-sec choice trial. All trials began with the extension of both levers into the operant chamber and the illumination of the houselight. Animals then had a maximum of 5 sec in which to respond; if they did not respond, the houselight was extinguished, the levers were retracted for the remainder of the 60-sec trial, and the trial counted as an omission.

Forced trials were arranged to expose the animal to the consequences (i.e., small immediate reward or large delayed reward) associated with each lever. Forced trials were identical to choice trials except that during forced trials, only a single lever was extended, and animals had a maximum of 10 sec to respond. During the first forced trial in a session, one of the levers was randomly inserted; thereafter, the inserted lever alternated with subsequent forced trials.

DD task training was divided into 2 phases. The first phase was the "zero-delays condition" in which each session included 10 forced trials and 40 choice trials with no delays. Two forced trials were issued at the beginning of the session, and 2 more were issued after every 8 choice trials. To prevent side bias for one lever over another and to ensure that all the animals were able to discriminate between reward magnitudes, the lever delivering the large reward was reversed every two weeks. This phase continued until the majority (greater than 80%) of choices were for the large reward (Anderson and Woolverton, 2005) and the animals were displaying fewer than 40% omissions toward the end of the sessions.

During the second phase of DD training, a delay preceded the presentation of the large reward. For this phase, the lever delivering the large reward was randomly assigned to either the left or right lever for each subject; this assignment did not change for the duration of the experiment. Each session was arranged into 5 blocks of 10 trials each (2 forced, 8 choice), with each block having a different delay to the large reward. To begin training, the 5 delays preceding the large reward were 1, 3, 6, 8, and 10 sec during each of the 5 10-trial blocks, respectively (Delay set 1). The delays were systematically increased over the training period in 3 delay sets. Delays were increased to the following delay set when choice percentages were stable via visual inspection. By the end of the training period, the delays were 3, 8, 15, 19 and 25 sec, respectively (Delay set 3). Delay values were informed by the methods from Evenden and Ryan (1999; 1996) and by our own experience with this preparation (Spencer et al., 2005). After choice percentages were deemed stable through visual inspection, training ended and the final experimental DD task began.

The final experimental DD task was comprised of data collected from the final week of Delay set 3. All conditions used in the final DD task were identical to those from Delay set 3 training (i.e., one operant session consisted of 10 forced trials and 40 choice trials for a total of 50 trials).

Statistical Analysis

All statistics were performed using SPSS Statistics (Version 19). The primary dependent variable was the percentage of choices for the large, delayed reward at each delay. A linear mixed model with delay as the within-subjects factor under compound symmetry covariance and line as the between-subjects factor was carried out for each delay set to test the main effects of delay and rat line and the delay $\times$ line interaction. Secondary dependent variables included the consumption of sucrose solution (ml) during the session and percent omissions (i.e., the proportion of trials during which the animal did not respond). Bonferroni corrections were used for all multiple comparisons. Heritability (h^2) was estimated by dividing the sum of squares between strains by the total sum of squares from a one-way ANOVA of the percent choice for the large reward for the final delay of Delay set 3 (Richards et al., 2013).

Results

Percent choice for the large reward

Prior to initiating delays, both lines exhibited a clear preference for the large sucrose reward over the small sucrose reward (Fig. 2A). Linear mixed model analysis showed no significant effect of rat line ($F_{1,10} = 0.83, p = 0.38$) or line $\times$ block interaction ($F_{4,40} = 0.15, p = 0.96$), indicating that both rat lines showed similar preference for the large reward throughout the session in the zero delays condition.

Delays preceding the presentation of the large reward were introduced over Delay sets 1–3 (Fig. 2B–D). Linear mixed-model analysis revealed a significant effect of delay during all 3 delay sets (Delay set 1, $F_{4,40} = 13.22, p < 0.001$) (Delay set 2, $F_{4,40} = 55.36, p < 0.001$) (Delay set 3, $F_{4,40} = 39.59, p < 0.001$), indicating that percent choice for the large reward

decreased as the delays increased. A significant effect of rat line was observed for all 3 delay sets (Delay set 1, $F_{1,10} = 13.82$, $p < 0.01$) (Delay set 2, $F_{1,10} = 17.18$, $p < 0.01$) (Delay set 3, $F_{1,10} = 12.15$, $p < 0.01$), with P rats choosing the large delayed reward significantly less often than NP rats.

A significant line $\times$ delay interaction was observed for all 3 delay sets (Delay set 1, $F_{4,40} = 6.97$, $p < 0.001$) (Delay set 2, $F_{4,40} = 12.02$, $p < 0.001$) (Delay set 3, $F_{4,40} = 5.87$, $p < 0.001$), indicating that the most pronounced differences in percent choice for the large reward between P and NP rat lines was present at the longest delays. Post-hoc, Bonferroni-adjusted, between-line comparisons of the estimated marginal means revealed that P rats consistently chose the large reward significantly less often than NP rats when the delay to the large reward was 10 sec or more (Fig. 2). The heritability of the DD phenotype was calculated for the highest delay in Delay set 3, $h^2 = 0.65$.

Trial omission

Linear mixed-model analysis revealed a significant effect of block in the zero-delays condition ($F_{4,40} = 19.67$, $p < 0.001$) but not of rat line ($F_{1,10} = 4.43$, $p = 0.06$) or a line $\times$ block interaction ($F_{4,40} = 1.9$, $p = 0.12$), indicating that omissions increased throughout the session equivalently in both lines (Fig. 3A). After implementing delays, the number of omitted trials increased more rapidly throughout the session in both rat lines; however, this effect was amplified in NP rats (Fig. 3B–D). There was a significant effect of delay for all delay sets (Delay set 1, $F_{4,40} = 41.99$, $p < 0.001$) (Delay set 2, $F_{4,40} = 36.74$, $p < 0.001$) (Delay set 3, $F_{4,40} = 45.54$, $p < 0.001$), indicating that omissions increased with increasing delay to the large reward. There was a significant effect of rat line (Delay set 1, $F_{1,10} = 13.57$, $p < 0.01$) (Delay set 2, $F_{1,10} = 43.99$, $p < 0.001$) (Delay set 3, $F_{1,10} = 38.25$, $p < 0.001$) and a line $\times$ block interaction (Delay set 1, $F_{4,40} = 7.81$, $p < 0.001$) (Delay set 2, $F_{4,40} = 14.82$, $p < 0.001$) (Delay set 3, $F_{4,40} = 25.42$, $p < 0.001$) for all delay sets, indicating that NP rats omitted a response more often than P rats and this difference was more pronounced at longer delays.

Consumption

Linear mixed model analysis revealed a main effect of delay set ($F_{3,30} = 47.71$, $p < 0.001$), and post-hoc analysis of the estimated marginal means indicated that both lines of rats consumed significantly less sucrose solution during Delay sets 2 ($p < 0.001$) and 3 ($p < 0.001$) compared to the zero-delays condition (Fig. 4). There was no significant difference in sucrose consumption between rat lines (line effect, $F_{1,10} = 3.66$, $p = 0.08$) during any delay set (line $\times$ delay set, $F_{3,30} = 0.55$, $p = 0.65$). Although P rats chose the large delayed reward significantly less often than NP rats, P rats also omitted significantly fewer trials. The combination of these behaviors resulted in P rats consuming a net quantity of sucrose similar to that consumed by NP rats.

Discussion

We hypothesized that P rats would exhibit higher levels of impulsive DD than NP rats; in other words, we postulated that the alleles associated with high ethanol consumption also

would be associated with high levels of impulsivity. We defined impulsive DD as attenuated preference for a large sucrose reward presented after a variable delay over a small sucrose reward presented immediately. In the current study, we found that preference for the large sucrose reward decreased as the delay to its presentation increased. This rate of decline was greater for the P line compared with the NP line during all of DD task training and the experimental DD task. When delays preceding the large reward's presentation during the experimental task were shorter (3 and 8 sec), the lines did not differ in their choice for the large reward, and both clearly preferred the large sucrose reward. However, as delays to the large reward became increasingly longer at 15, 19, and 25 sec, the P rats chose the small, immediate sucrose reward more frequently compared with the NP rats. In other words, the P rats discounted the value of the large, delayed reward to a greater extent than the NP rats.

These results suggest that compared with NP rats, P rats are more likely to choose immediate sucrose rewards than delayed ones, and therefore, P rats display higher levels of impulsive DD than NP rats. The current results also suggest that the alleles associated with the high alcohol preference phenotypes could also be associated with increased levels of DD, or impulsivity. The positive relationship between alcohol preference and impulsivity we observed is consistent with other animal studies (Oberlin and Grahame, 2009; Wilhelm et al., 2007; Wilhelm and Mitchell, 2008); however, this is the first study to examine DD impulsivity in P and NP rats.

The differences in impulsive DD observed between P and NP strains could be mediated by underlying differences in dopaminergic neurotransmission in the nucleus accumbens (NAc) shell. The maintenance of self-administration of ethanol is dependent on dopaminergic signaling in the NAc shell (Ding et al., 2014), and depletion of dopamine in the NAc shell increases ethanol consumption (Quarfordt et al., 1991). Notably, P rats show heightened sensitivity to ethanol self-administered directly into the NAc shell (Engleman et al., 2009) as well as a reduction in dopaminergic innervation of the NAc shell (Zhou et al., 1995). This relative reduction in dopaminergic signaling in the NAc shell in P rats may underlie their alcoholism-like phenotype. Moreover, a reduction in D_{2/3} dopamine receptors in the ventral striatum has been shown to be associated with increased trait impulsivity as well as augmented escalation of cocaine self-administration (Dalley et al., 2007), and dopaminergic neurotransmission has been shown to be associated with impulsivity in humans (Boettiger et al., 2007; Eisenberg et al., 2007; Jupp and Dalley, 2014). Thus, it is possible that the reduced dopaminergic signaling within in NAc shell in P rats could account for both the strain's augmented preference for ethanol as well as the trait impulsivity observed here.

In addition to observing differences in impulsivity for sucrose rewards between the P and NP lines, we also observed differences in number of completed trials between lines. The number of trials completed decreased as the delay to the reward increased, and this pattern was more evident in NP rats than P rats (Fig. 3). This finding is consistent with previous omissions-related observations in DD tasks. Lines bred to consume more ethanol generally have fewer omissions for saccharin or sucrose rewards than lines bred to consume less ethanol (Oberlin and Grahame, 2009). This difference may be related to the observation that rodents bred to consume large quantities of ethanol also tend to prefer more concentrated sweet solutions compared with animals that do not prefer large quantities of ethanol, a

relationship also observed in humans with a history of alcohol dependence (Kampov-Polevoy et al., 1999). Indeed, a heightened preference for sucrose has also been shown to be related to steeper discounting of delayed rewards (Weafer et al., 2014). Other investigators have suggested that the number of trials completed could reflect motivational differences between rat lines (Oberlin and Grahame, 2009), with P rats being more highly motivated for sucrose rewards than NP rats. The number of trials completed is not a standard measure of motivation; however, if this measure were to be accepted, then the difference in motivation for sucrose between P and NP rat lines could be a potential confound in the relationship between heritable alcohol preference and discounting of delayed rewards. However, a previous report in rats indicated that there was not an association between demand for sucrose and DD of a sucrose reward (Koffarnus and Woods, 2013). Given that demand is often interpreted as a measure of motivation (Amlung et al., 2012; Bentzley et al., 2014; Zimmer et al., 2012), differences in sucrose motivation between rat lines are unlikely to account for the relatively higher DD in P rats reported here.

Discounting of the delayed reward led to reduced sucrose consumption for both rat lines. DD (or greater impulsivity) resulted in less overall sipper tube access time and increased omissions, and consequently less overall reward consumption in delay set 3 compared to the zero-delays condition (Fig. 4). Thus, the inability to “wait” for large, delayed rewards yielded seemingly less-desirable consequences, i.e. less sucrose consumption. However, although consumption was similarly reduced in both P and NP rats, NP rats required fewer responses to obtain the same amount of reward as P rats, evidenced by a greater number of omissions for NP rats at the longer delays. Thus, P rats adopted a less efficient strategy than NP rats, a sign that a predisposition towards impulsivity can lead to maladaptive behavior.

In addition to providing insight into the role of impulsive DD in AUDs, this report also demonstrates use of a novel within-sessions DD procedure. As demonstrated here, within-sessions DD procedures measure degrees of discounting by arranging blocks of trials separated by a series of ascending or descending delays within a session, with reward magnitude kept constant throughout the experiment (Anderson and Woolverton, 2005; Cardinal et al., 2000; Evenden and Ryan, 1999; Evenden and Ryan, 1996). Our implementation of a within-sessions DD task is the first to employ sipper tubes for reward delivery. This novel application of within-sessions DD procedures demonstrates and validates this methodology, and it facilitates future sipper-tube DD studies by providing relevant delay and reward magnitude parameter ranges.

In conclusion, the current study revealed that alcohol-preferring rats are more impulsive than non-alcohol preferring rats for sucrose rewards, indicating that trait impulsivity prior to drug exposure may serve as an important endophenotype partially responsible for conferring genetic risk in the development of alcohol-use disorders. Moreover, we found that heightened DD in alcohol-preferring animals was behaviorally disadvantageous in that it resulted in an inefficient strategy of obtaining sucrose reward at longer delays. With respect to human impulsive decision-making, although impulsive choices have short-term utility, they may result in disadvantageous consequences when the immediate desire to self-administer a drug is favored over alternative, and more pro-social rewards, such as achieving success in one’s career or maintaining healthy interpersonal relationships.

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Within-Sessions Delay Discounting Task

Fig. 1.
Experimental procedure for each 60-sec DD task choice trial.

Fig. 2.

Percent choice for the large reward by rat line and delay to the large reward for the zero-delays condition (A) and delay sets 1 (B), 2 (C), and 3 (D). (A) Both P and NP rats displayed a clear preference for the large reward when delivered immediately, and no significant difference existed between rat lines for the percent choice for the large reward. (B–D) In contrast, increasing delays to the large reward resulted in significantly less preference for the large reward, and this effect was disproportionately large in P rats compared to NP rats. Each data point represents the percent choice for a single subject and the trend lines represent the means within each rat line. Filled symbols represent NP rats and open symbols represent P rats, and asterisks indicated significant differences between lines (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).

Fig. 3.

Number of omissions by rat line and delay to the large reward for the zero-delays condition (A) and delay sets 1 (B), 2 (C), and 3 (D). (A) Both P and NP rats omitted more responses during trials later in the session during the zero-delays condition, and no significant difference existed between rat lines. (B–D) Increasing delays to the large reward resulted in more omissions, and this effect was disproportionately large in NP rats compared to P rats. Each data point represents the average number of omissions (out of 10) for a single subject and the trend lines represent the means within each rat line. Filled symbols represent NP rats and open symbols represent P rats, and asterisks indicated significant differences between lines (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).

Fig. 4.

Consumption of sucrose solution throughout the session in both P and NP rats for the zero-delays condition and all delay sets. Compared to the zero-delays condition, consumption of sucrose was significantly less in delay sets 2 and 3 (** $p < 0.001$). There were no significant differences in consumption between rat lines for the zero-delays condition or any delay set.