### Title

Genetic Influences on Delayed Reward Discounting: A Genome-Wide Prioritized Subset Approach




### Journal

Experimental and Clinical Psychopharmacology, 27(1)

### ISSN

1064-1297



### Authors

MacKillop, James
Gray, Joshua C
Weafer, Jessica
et al.



### Publication Date

2019-02-01

### DOI

10.1037/pha0000227

Peer reviewed

Experimental and Clinical Psychopharmacology

# Genetic Influences on Delayed Reward Discounting: A Genome-Wide Prioritized Subset Approach

James MacKillop, Joshua C. Gray, Jessica Weafer, Sandra Sanchez-Roige, Abraham A. Palmer, and Harriet de Wit

Online First Publication, September 27, 2018. http://dx.doi.org/10.1037/pha0000227

American Psychological Association

Experimental and Clinical Psychopharmacology


1064-1297/18/$12.00

http://dx.doi.org/10.1037/pha0000227

# Genetic Influences on Delayed Reward Discounting: A Genome-Wide Prioritized Subset Approach

James MacKillop
McMaster University/St. Joseph's Healthcare Hamilton and Homewood Research Institute, Guelph, Ontario, Canada

Joshua C. Gray
University of Georgia and Brown University

Jessica Weafer
University of Chicago

Sandra Sanchez-Roige and Abraham A. Palmer
University of California, San Diego

Harriet de Wit
University of Chicago

Delayed reward discounting (DRD) is a behavioral economic measure of impulsivity that has been consistently associated with addiction. It has also been identified as a promising addiction endophenotype, linking specific sources of genetic variation to individual risk. A challenge in the studies to date is that levels of DRD are often confounded with prior drug use, and previous studies have also had limited genomic scope. The current investigation sought to address these issues by studying DRD in healthy young adults with low levels of substance use ($N = 986$; 62% female, 100% European ancestry) and investigating genetic variation genome-wide. The genome-wide approach used a prioritized subset design, organizing the tests into theoretically and empirically informed categories and apportioning power accordingly. Three subsets were used: (a) a priori loci implicated by previous studies; (b) high-value addiction (HVA) markers from the recently developed SmokeScreen array; and (c) an atheoretical genome-wide scan. Among a priori loci, a nominally significant association was present between DRD and rs521674 in *ADRA2A*. No significant HVA loci were detected. One statistically significant genome-wide association was detected (rs13395777, $p = 2.8 \times 10^{-8}$), albeit in an intergenic region of unknown function. These findings are generally not supportive of the previous candidate gene studies and suggest that DRD has a complex genetic architecture that will require considerably larger samples to identify genetic associations more definitively.

***Public Health Significance***

Steep discounting of future rewards has been substantially associated with addiction and other psychiatric disorders. Increasing evidence implicates genetic influences, but most previous studies have had relatively small sample sizes, limited genomic scope, and potentially confounding levels of previous substance use. This study addresses these issues and finds further evidence for one previously reported genetic association and a novel genome-wide association, further elucidating genetic contributions to this form of impulsivity.

*Keywords:* decision making, delayed reward discounting, genetics, genomics, impulsivity

*Supplemental materials:* http://dx.doi.org/10.1037/pha0000227.supp



James MacKillop, Peter Boris Centre for Addictions Research, McMaster University/St. Joseph's Healthcare Hamilton, and Homewood Research Institute, Guelph, Ontario, Canada; Joshua C. Gray, Department of Psychology, University of Georgia, and Department of Psychiatry and Human Behavior, Brown University; Jessica Weafer, Department of Psychiatry and Behavioral Neuroscience, University of Chicago; Sandra Sanchez-Roige, Department of Psychiatry, University of California, San Diego; Abraham A. Palmer, Department of Psychiatry and Institute for Genomic Medicine, University of California, San Diego; Harriet de Wit, Department of Psychiatry and Behavioral Neuroscience, University of Chicago.

These findings were previously reported at a symposium at the annual meeting of the American College of Neuropsychopharmacology.

All authors made substantive contributions to the research reported, and all authors have read and approved the final manuscript. The authors acknowledge the outstanding contributions of the research staff in executing the reported research including the bioinformatics support of Kyle Hernandez at the University of Chicago and are grateful for access to the SmokeScreen loci from James Baurley. This article was supported in part by National Institutes of Health Grant R01DA032015 and by the Peter Boris Chair in Addictions Research. The funding source had no other role other than financial support. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. No authors have potential conflicts of interest to declare, with the exception of James MacKillop who discloses that he is a principal in BEAM Diagnostics, Inc.

Correspondence concerning this article should be addressed to James MacKillop, Peter Boris Centre for Addictions Research, McMaster University/St. Joseph's Healthcare Hamilton, 100 West 5th Street, Hamilton Ontario L8P 3R2, Canada. E-mail: jmackill@mcmaster.ca

Delayed reward discounting (DRD) refers to the extent to which an individual devalues a reward based on its delay in time (Bickel & Marsch, 2001; Bickel, Johnson, Koffarnus, MacKillop, & Murphy, 2014). It is a behavioral economic measure of impulsivity, and is also referred to as impulsive choice, intertemporal choice, and capacity to delay gratification. Typically, DRD is operationally defined by how much a person prefers smaller immediate rewards versus larger delayed rewards on experimental tasks, with more precipitous devaluation of future rewards reflecting greater impulsivity. Numerous studies have shown that individuals with addictive disorders exhibit steeper DRD than controls (Bickel, Odum, & Madden, 1999; Coffey, Gudleski, Saladin, & Brady, 2003; MacKillop, Anderson, Castelda, Mattson, & Donovick, 2006; Madden, Petry, Badger, & Bickel, 1997; Petry, 2001). Significant associations have also been reported using dimensional (continuous) designs (MacKillop et al., 2010, 2014; Murphy & Garavan, 2011; Sweitzer et al., 2008). In addition, meta-analyses of both case–control and dimensional studies have revealed the link between DRD and addiction is robust across studies (Amlung et al., 2017; MacKillop et al., 2011). These relationships are distinct from other measures of impulsivity, as DRD tends to be weakly correlated with other behavioral or self-report measures of impulsivity (Caswell, Bond, Duka, & Morgan, 2015; Courtney et al., 2012; Cyders & Coskunpinar, 2011; MacKillop et al., 2014; Reynolds, Ortengren, Richards, & de Wit, 2006). This is consistent with the increasing recognition of impulsivity as a multifaceted construct comprising conceptually related domains that are quantitatively distinct (de Wit, 2009; Dick et al., 2010; Jentsch et al., 2014).

There is considerable evidence that genetic factors influence addiction (Agrawal & Lynskey, 2008; Goldman, Oroszi, & Ducci, 2005; Volkow & Baler, 2014), and impulsive discounting may contribute to this risk (MacKillop, 2013; Mitchell, 2011). Indeed, there is accumulating evidence that DRD is genetically influenced and shares heritability with addiction phenotypes. In preclinical studies, inbred rodent strains that are isogenic within strain but differ across strains exhibit systematic differences in DRD for food or water rewards (Anderson & Woolverton, 2005; Isles, Humby, Walters, & Wilkinson, 2004; Madden, Smith, Brewer, Pinkston, & Johnson, 2008; Richards et al., 2013; Stein, Pinkston, Brewer, Francisco, & Madden, 2012; Wilhelm & Mitchell, 2009). Furthermore, preclinical studies indicate that rat or mouse strains exhibiting more impulsive DRD exhibit higher preference for alcohol (Beckwith & Czachowski, 2014; Linsenbardt, Smoker, Janetsian-Fritz, & Lapish, 2017; Oberlin & Grahame, 2009; Perkel, Bentzley, Andrzejewski, & Martinetti, 2015; Wilhelm & Mitchell, 2008). Studies in humans comparing monozygotic and dizygotic twins have similarly revealed substantial levels of heritability (Anokhin, Grant, Mulligan, & Heath, 2015; Anokhin, Golosheykin, Grant, & Heath, 2011; Isen, Sparks, & Iacono, 2014; Sparks, Isen, & Iacono, 2014). In addition, greater DRD is associated with family history of addiction (Acheson, Vincent, Sorocco, & Lovallo, 2011; Dougherty et al., 2014; VanderBroek et al., 2016). Collectively, these studies suggest that DRD is both heritable and coaggregates with addiction propensity.

Molecular genetic studies on DRD suggest a role for catecholaminergic mechanisms. For example, DRD preferences in humans have been reported in relation to a locus in *ANKK1* (rs1800497; Eisenberg et al., 2007; MacKillop et al., 2015) that is proximal to the dopamine (DA) $D_2$ receptor gene, *DRD2*. Variation in DRD has also been reported in association with another DA-related locus in *COMT* (rs4680; Boettiger et al., 2007; Gianotti, Figner, Ebstein, & Knoch, 2012; MacKillop et al., 2015), which encodes catechol-O-methyl transferase, the enzyme involved in metabolizing DA in the prefrontal cortex (Chen et al., 2004; Tunbridge, Bannerman, Sharp, & Harrison, 2004). Finally, DRD has also been reported to be associated with variants in genes contributing to serotonergic and nor-adrenergic activity (Havranek, Hulka, & Tasiudi, 2017; Sonuga-Barke et al., 2011).

However, the existing literature on genetic correlates of DRD has a number of limitations. To start, the samples have typically been small, mainly permitting analyses focusing on single candidate genes or a few biologically related loci. Further, the samples have been heterogeneous. Across studies, samples have varied from the general population to individuals in recovery from alcohol use disorder, individuals with attention-deficit/hyperactivity disorder, gamblers, individuals with cocaine use disorder, and smokers. This heterogeneity is a problematic for several reasons. First, it means the study designs are not equivalent and not readily comparable. Second, the inclusion of individuals with addictive disorders makes it difficult to determine whether the elevated DRD was a predisposing factor or a result of the users' extended drug exposure. Although several studies suggest that impulsive DRD in humans predates addictive behavior (Audrain-McGovern et al., 2009; Fernie et al., 2013; Khurana et al., 2013; Kim-Spoon et al., 2015), there is also evidence that drug use itself induces more impulsive DRD (Mendez et al., 2010; Mitchell et al., 2014; Setlow, Mendez, Mitchell, & Simon, 2009; Simon, Mendez, & Setlow, 2007). Unsurprising consequences of these limitations are that the current literature is both genomically narrow and inconsistent in its findings.

The goal of the current study was to advance the investigation of genetic influences on DRD by addressing some of these issues. First, we recruited a sample of healthy young adults with low levels of psychoactive drug use to minimize the extent to which DRD preferences could be interpreted as a symptom or consequence of drug misuse. Second, we tested almost 1,000 individuals under controlled laboratory conditions, a sample substantially larger than most previous studies. Third, we expanded the scope of genetic associations with DRD preferences by examining genome-wide variation in single nucleotide polymorphisms (SNPs) and did so using a prioritized subset approach (Lin & Lee, 2010; Li, Li, Lange, & Watanabe, 2008; Schork et al., 2013; Sun, Craiu, Paterson, & Bull, 2006). Specifically, the study used three prioritized subsets: (a) a priori loci implicated by previous DRD molecular genetic studies, (b) high-value addiction (HVA) markers from the recently developed SmokeScreen array (Baurley, Edlund, Pardamean, Conti, & Bergen, 2016), a compilation of loci linked with diverse addiction-related phenotypes, and (c) an atheroetical genome-wide scan to identify loci not included in the two previous categories. Collectively, these strategies were intended to provide strong tests for previously reported associations in a larger and more stringently defined design, and to expand the scope of genetic variation under consideration substantially, but to do so in a biologically-informed and principled way.

# Method

## Participants

The sample and phenotypic data collection are described in detail in a report detailing phenotypic relationships among diverse measures of impulsivity (MacKillop et al., 2016). Briefly, participants were recruited at two sites (Athens, GA and Chicago, IL). Inclusion criteria were (a) English fluency (b) age 18–30, and (c) self-reported European ancestry and non-Hispanic ethnicity to control for population stratification (see below for genetic verification of racial homogeneity). Exclusion criteria were (a) ≥12 on the Alcohol Use Disorders Identification Test (AUDIT; Saunders, Aasland, Babor, de la Fuente, & Grant, 1993) or Drug Use Disorders Identification Test (DUDIT; Berman, Bergman, Palmstierna, & Schlyter, 2005), (b) addiction treatment in the last 12 months, and (c) self-reported presence of major depressive disorder, bipolar disorder, general anxiety disorder, social anxiety disorder, posttraumatic stress disorder, obsessive–compulsive disorder, panic attacks/disorder, phobia, schizophrenia, or eating disorders. Participant characteristics are provided in Table 1 and, per the study design, the sample can generally be characterized as healthy young adults reporting low levels of substance use. Other than sex, the two sites significantly differed such that the Chicago site was older, more educated, and lower income (see Table 1), reflecting a postcollegiate young adult sample. Institutional review board approval was obtained at both sites (University of Chicago #11–0549, University of Georgia, #10911, common title: "*Genetic basis of impulsive behavior in humans*").

## Procedure

Participants attended a single experimental session conducted in a laboratory under controlled conditions (i.e., no distractions, quiet environment, supervised task completion). They provided urine and breath samples to confirm abstinence from recent drug and alcohol use, and provided informed consent. Participants completed a computerized battery of self-report and behavioral tasks, including two measures of DRD (MacKillop et al., 2016; Inquisit 3.0.6.0, 2012; Survey Monkey [http://surveymonkey.com] or EPrime, Psychology Software Tools, Pittsburgh, PA). The task orders were counterbalanced to minimize order effects. Participants were given two 5-min breaks for refreshments (water, snacks) and/or to use the restroom. Samples of DNA were collected via a saliva sample in an Oragene DNA kit (DNA Genotek Inc., Kanata, ON, Canada).

Table 1
*Participant Characteristics (N = 986)*

| Variable | %/Mean (*SD*)/Median | Site 1 (*n* = 650) | Site 2 (*n* = 336) |
|---|---|---|---|
| Age | 21.68 (3.31) | 22.88 (3.26) | 19.38 (1.88) |
| Sex | 62.2% female | 61.3% female | 63.6% female |
| Income | $60,000–$89,999 | $30,000–$59,999 | $90,000–$119,999 |
| Education | 14.55* (2.22) | 15.36 (2.11) | 12.98 (1.45) |
| AUDIT | 4.26* (3.13) | 4.91 (2.88) | 3.00 (3.21) |
| DUDIT | 1.37* (2.2) | 1.79 (2.43) | .55 (1.34) |
| DDT | −2.370* (0.80) | −2.43 (0.82) | −2.25 (0.76) |
| MCQ-S[a] | −2.301* (0.66) | −2.355 (0.69) | −2.20 (0.58) |
| MCQ-M | −2.131* (0.69) | −2.191 (0.71) | −2.01 (0.62) |
| MCQ-L | −1.86* (0.68) | −1.92 (0.72) | −1.76 (0.58) |
| PCA-DRD[b] | 0.0* (1.00) | −0.09 (1.04) | 0.17 (0.88) |

*Note.* AUDIT = Alcohol Use Disorders Identification Test; DRD = Delayed reward discounting; DUDIT = Drug Use Disorders Identification Test; MCQ = Monetary Choice Questionnaire; PCA = principal components analysis; Site 1 = Chicago, IL; Site 2 = Athens, GA.
[a] Log-10 transformed. [b] Standardized via principal components analysis.
* $p < .05$.

## Measures

**Demographics and substance use.** Demographic characteristics, including sex, age, race, income, and education, were obtained. Alcohol use over the last year was measured using the Alcohol Use Disorders Identification Test (AUDIT), which contains 10 questions, scored from 0 to 4, pertaining to quantity, frequency, and consequences of drinking. Drug use over the last year was measured using the Drug Use Disorders Identification Test (DUDIT), which uses the same format as the AUDIT but with one additional question regarding frequency of polysubstance use.

**Delayed reward discounting.** Two tasks were used to measure DRD: a full iterative permuted delay discounting task and the Monetary Choice Questionnaire (MCQ; Kirby, Petry, & Bickel, 1999), which together provided four indices of DRD. Both tasks provided hyperbolic temporal discounting functions (*k*; Mazur, 1987). In the iterative task, a temporal discounting function is derived for each participant. Subjects are given 80 choices between smaller immediate rewards (i.e., $10.00, $20.00, $30.00, $40.00, $50.00, $60.00, $70.00, $80.00, $90.00, or $99.00) and a larger delayed reward of $100 with a delay of 1, 7, 14, 30, 60, 90, 180, or 365 days (Amlung, Sweet, Acker, Brown, & MacKillop, 2014). The amounts and delays were presented in mixed order. The MCQ (Kirby et al., 1999) consists of 27 choices between smaller immediate rewards and larger delayed rewards. The rewards range from $11 to $85, and the larger delayed rewards were available at varying intervals of delay from 1 week to 186 days (e.g., "Would you rather have $49.00 today or $60.00 in 89 days?"). The questions are presented in random order. The MCQ generates three *k* values for small ($M = $25), medium ($M = $55), and large ($M = $85) magnitude rewards. Ten control items provided choices between smaller versus larger rewards, both immediately available. A criterion of ≥80% correct was used to define adequate effort and attention. To maximize validity, performance on the two measures was consequated such that all participants received one in six chance to receive an outcome from their choices (value = $10–$100). Specifically, using Kirby et al.'s (1999) procedure, participants rolled a six-sided die following the tasks and those who rolled a six received the outcome for one of their choices (either immediately or at the specified delay). The actual choice received was randomly determined via the selection of one poker chip from a fishbowl containing chips pertaining to all of the items on the tasks.

## SNP Genotyping and Quality Control

Genotyping was performed using the Illumina PsychArray BeadChip platform, which calls ~600,000 markers and has optimized tag SNP content from the International HapMap Project to capture the maximum amount of common variation. Quality con-

trol filtering was implemented in PLINK v1.9 (Chang et al., 2015). Autosomal SNPs were filtered for call rates <98%, Hardy-Weinberg Equilibrium (HWE) violations of $p < 1 \times 10^{-6}$, MAF <5%, and invariance. After filtering, 437,652 SNPs remained for imputation, which was performed using IMPUTE2 v.2.3.1 (Howie, Donnelly, & Marchini, 2009) employing the 1000 Genomes Phase 3 b37 reference panel (Delaneau et al., 2014). Imputed SNPs were excluded if they provided an information score of < .3 (Marchini & Howie, 2010), MAF <5%, HWE violations of $p < 1 \times 10^{-6}$, missingness >5%, and multiallelic status. Imputed SNPs with confidence <.9 were set to missing.

## Data Analysis

The DRD task was analyzed using nonlinear regression and fitting the commonly used hyperbolic temporal discounting function (Mazur, 1987). To generate a single DRD index across delayed reward magnitudes and the task and MCQ, the four indices were consolidated using principal components analysis (PCA; oblique rotation [direct oblimin, $\delta = 0$]), as has been used successfully previously (Amlung & MacKillop, 2014; VanderBroek et al., 2016). Thus, the primary DRD phenotype in all subsequent analyses was the first principal component of the four *k* values. Given the established relevance of age and income to DRD (de Wit, Flory, Acheson, McCloskey, & Manuck, 2007; Green, Fry, & Myerson, 1994), both were included as a priori covariates. Two additional candidate covariates were explored, site and sex, and were only included if significantly associated with DRD. Phenotypic analyses were conducted using SPSS, v22.0 (IBM Corp., 2011).

Genetic analyses used Genome-wide Efficient Mixed Model Association (GEMMA) software (Zhou & Stephens, 2012) to conduct univariate linear mixed model associations between the loci from each subset (16 a priori loci, 12,990 HVA loci, and 4,883,968 genome-wide SNPs) and DRD performance. This approach accounts for cryptic relatedness among individuals, which is modeled out as a random effect (i.e., the genetic correlation between individuals). To maximize resolution of effects, an additive genetic effect model was used whereby participants were coded based on the number of minor alleles for each SNP (0–2). A priori loci were defined as SNPs that were previously reported in peer-reviewed publications to be significantly associated with DRD in populations of European ancestry. Two a priori loci were excluded for excessive missing values (>5%). Following quality control, 16 a priori loci, 12,990 of the 20,652 HVA SNPs, and 4,883,968 genome-wide SNPs were present for analysis. Type I error rate was apportioned according to the prioritized subset. For a priori tests, a nominal $\alpha \leq .05$ was used; for the HVA markers, a Benjamini-Hochberg (Benjamini & Hochberg, 1995) false discovery rate (FDR) correction was applied; for the atheoretical genome-wide scan, the standard genome-wide significance threshold was used ($p < 5 \times 10^{-8}$; Pe'er, Yelensky, Altshuler, & Daly, 2008; Panagiotou & Ioannidis, 2012). Statistical power was generated using Quanto software (Gauderman, 2002) and, at power = .80, the a priori tests had a minimum detectable effect (MDE) of .8% of variance, a small-to-medium effect size, depending on conventions. For the HVA markers, formal power analysis was not conducted because FDR correction is specific to empirical *p* values, but the genome-wide power analysis provides a conservative estimate for the HVA markers. For the genome-wide analyses, at power = .80, the MDE was 4.0% of variance, a large effect size.

# Results

## Preliminary Analyses

One thousand participants had valid genotyping data (call rates ≥98%, inbreeding coefficient absolute value ≤.02, concordant self-reported sex, and X-chromosome determined sex) and satisfied the inclusion/exclusion criteria. To verify and correct the misclassification of self-reported race, principal components analysis (PCA; Price et al., 2006) was conducted. Two population outliers were identified and removed by visual inspection of the principal components plot.

Eight participants were excluded for missing data, and two participants were excluded for invalid task performance (i.e., <80% on control items). Among valid participants, consistency on the control items was very high: $M = 98\%$; 91% = all correct responses, 8% = one error, 1% = two errors. Finally, participants were assessed for cryptic relatedness (Yang, Lee, Goddard, & Visscher, 2011) and two were removed for relatedness >.05, leaving the final sample of 986 participants (see Table 1).

Nonlinear modeling provided a good fit to the DRD task (median $R^2 = .86$). The resulting *k* values were positively skewed, as is typical, and were logarithmically transformed (base-10,) which substantially improved the distributions. Very high correlations among the individual magnitude *k* values (*r*s = .75–.86, *p*s < $10^{-130}$) supported the use of PCA and the resulting eigenvalue from the first component was 3.40 (all subsequent <.30), accounting for 85% of the variance among the four discounting indices. The component loadings were uniformly high: .90–.94. With regard to covariates, age was significantly associated with DRD, $r = .06$, $p = .05$, but income was not ($r = .03$ $p = .36$), although both were included in subsequent models given their a priori status. Site differences were present, $F(1, 983) = 15.02$, $p < .001$, but sex differences were not, $F(1, 983) = 1.17$, $p = .28$, so only site so site was included as an additional covariate.

## A Priori Loci

Of the a priori loci assessed, one locus was nominally significant (see Table 2). Specifically, the minor T allele of rs521674 and G allele of rs1800544 in *ADRA2A* were significantly associated with less impulsive DRD (*B*s = −.10, *SE*s = .05, *p*s = .046); identical values are reported because these loci were in total linkage disequilibrium ($R^2 = 1.0$). The inverse coefficients reflect possession of fewer minor alleles being associated with more impulsive DRD.

## High-Value Addiction Markers

Of the 12,990 HVA loci, none survived FDR correction. The top three strongest associations were for rs4986850 in breast cancer 1 (*BRCA1*) on chromosome 17 ($p = .000096$), rs1563119 in noncoding RNA on chromosome 2 ($p = .0002$), and rs10799790 in leucine zipper protein 1 (*LUZP1*) on chromosome 1 ($p = .0004$). Test statistics and other information for the top 50 most significant associations are in Supplemental Table 1.

Table 2
*Associations Between a Priori Loci and Delayed Reward Discounting Preferences*

| Chr | Locus | Gene | Missing | Minor allele | MAF | β | *SE* | *p* |
|---|---|---|---|---|---|---|---|---|
| 3 | rs3773678 | *DRD3* | 41 | A | .112 | .002 | .071 | .974 |
| 3 | rs7638876 | *DRD3* | 29 | C | .315 | .088 | .048 | .071 |
| 5 | rs464049 | *SLC6A3* | 0 | G | .446 | −.040 | .045 | .372 |
| 5 | rs12652860* | *SLC6A3* | 14 | A | .279 | .033 | .050 | .505 |
| 6 | rs1360780 | *FKBP5* | 14 | T | .306 | −.070 | .048 | .142 |
| 7 | rs10249982[a] | *DDC* | 4 | G | .241 | .058 | .050 | .250 |
| 7 | rs10244632[a] | *DDC* | 9 | T | .257 | .051 | .049 | .307 |
| 7 | rs1466163[a] | *DDC* | 4 | A | .116 | .023 | .070 | .747 |
| 7 | rs10499696[a] | *DDC* | 10 | G | .120 | .031 | .069 | .648 |
| **10** | **rs521674[b]** | ***ADRA2A*** | **23** | **T** | **.263** | **−.103** | **.052** | **.046** |
| **10** | **rs1800544[b]** | ***ADRA2A*** | **20** | **G** | **.263** | **−.102** | **.051** | **.046** |
| 10 | rs602618[b] | *ADRA2A* | 39 | C | .265 | −.076 | .051 | .142 |
| 10 | rs363338 | *SLC18A2* | 37 | C | .299 | .024 | .050 | .631 |
| 11 | rs1800497 | *ANKK1* | 0 | A | .185 | −.028 | .057 | .630 |
| 11 | rs1079597 | *DRD2* | 0 | T | .151 | −.037 | .062 | .550 |
| 22 | rs4680 | *COMT* | 0 | G | .480 | −.071 | .044 | .104 |

*Note.* COMT = catechol-O-methyltransferase; DRD = Delayed reward discounting; MAF = minor allele frequency; Just in case, Chr = chromosome. Bold text indicates nominally significant effects were identified ($p < .05$). Beta coefficients reflect number of minor alleles; letter superscripts reflect high linkage disequilibrium ($R^2 > .80$) among loci with common letters.
* Located near but not in the associated gene.

## Genome-Wide Association Analysis

The genome-wide analysis yielded one significant association on chromosome 2. Specifically, the minor (T) allele of rs13395777 was significantly positively associated with more impulsive DRD ($\beta = .27$, $SE = .05$, $p = 2.8 \times 10^{-8}$; MAF = .33). Figure 1 shows the results of the GWAS using both quantile-quantile (Q-Q) plots and Manhattan plots. The significant locus is intergenic and closest to *RNA5SP94* and *XR_940133.1*. To inform future studies, the top 50 most significant genome-wide associations are reported in Supplemental Table 2.

## Discussion

This study examined genetic influences on impulsive DRD, a psychological phenotype robustly associated with addiction, using a genome-wide prioritized subset approach. First, we examined a priori selected loci based on previously reported significant associations. Most of the previous associations were not replicated, although rs521674 and rs1800544, in *ADRA2A*, were nominally significant (the association would not have survived Type I error rate correction). *ADRA2A* encodes the α2 adrenoreceptor and this locus has previously been implicated in impulsive DRD among individuals with cocaine use disorders (Havranek et al., 2017). This association is consistent with preclinical pharmacological studies that found the noradrenaline-specific reuptake inhibitor atomoxetine reduces DRD (Robinson et al., 2008; Sun, Cocker, Zeeb, & Winstanley, 2012). However, it is notable that the pattern of association in healthy individuals was opposite the pattern in individuals with cocaine addiction, where possession of more minor alleles was associated with steeper discounting. With the potential exceptions of these loci, the current findings did not confirm previously reported associations. We cannot reach any firm conclusions about whether the previous findings were false positives or whether that those associations were moderated by methodological differences (e.g., differences between clinical groups and a healthy normative sample).

The second prioritized subset comprised a moderately sized set of markers specifically related to addiction. Although we predicted that this enriched marker set would reveal associations with DRD, no loci survived the Type I error correction and none showed promising trends given the number of tests conducted.

Interestingly, in the third prioritized subset, the genome-wide scan detected one significant association that exceeded the conventional threshold of $5 \times 10^{-8}$ (Panagiotou & Ioannidis, 2012; Pe'er et al., 2008). However, this locus is intergenic and nearby genes have no known relationships to the brain or behavior, making its functional role unclear. It is possible that this locus influences the regulation of distant genes (Krijger & de Laat, 2016), but, absent any evidence that this is the case, caution should be applied to this finding. Furthermore, the study did not include a replication sample to provide independent corroboration of the association. Further evidence in support of this association is needed.

These findings should be considered in the context of the study's strengths and weaknesses. In terms of strengths, the study had much wider genomic scope than most prior studies, and the prioritized subset design provided a principled framework for doing so. In addition, the study used a high-resolution latent DRD phenotype comprising four temporal discounting functions and incentivized procedure that maximized participant engagement and salience of the reward. Evidence in support of the characterization of the phenotype was present in terms of the very high performance on control items. However, the study had a number of limitations also. Although it was arguably the largest human laboratory study on DRD decision making to date, the sample size was modest in terms of genome-wide studies. Beyond the a priori tests, the study was only powered to detect relatively large effects. As such, an important corollary of these findings is that the study cannot speak to smaller effect size associations. Necessarily, if, as this study would suggest, the genetic architecture of DRD is in fact a function of numerous alleles with small effects, substantially larger sample sizes will be necessary for sufficient power to detect

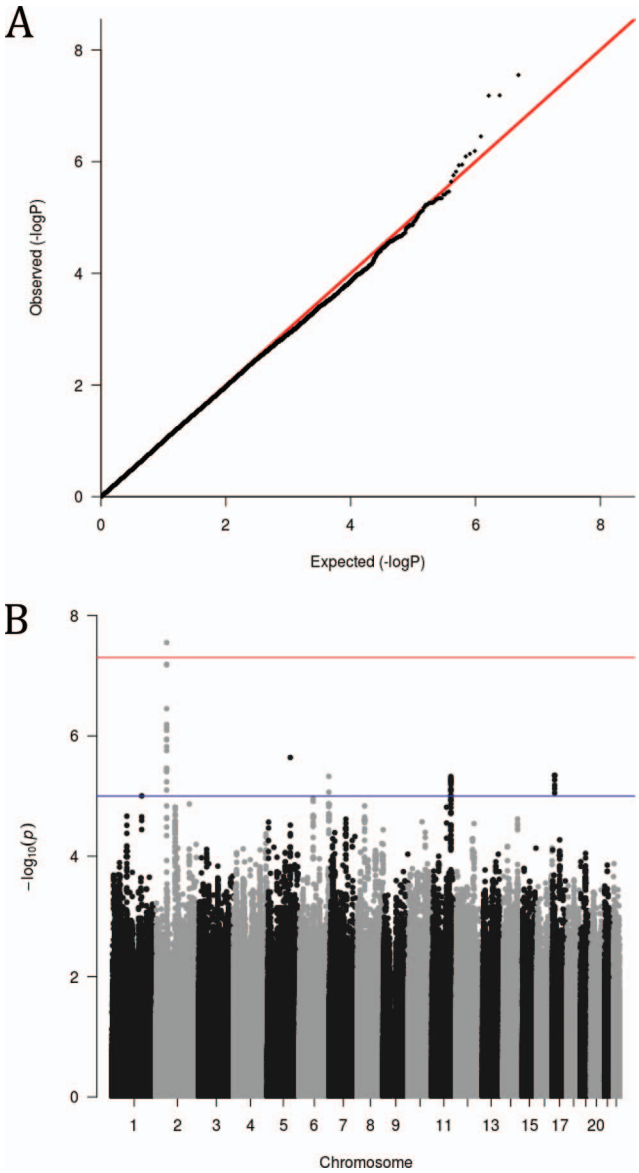


*Figure 1.* (A) Q-Q and (B) Manhattan plot of genome-wide associations for Delayed reward discounting (DRD) performance. Significance values were $-\log_{10}$ transformed to display the smaller $p$ values as larger in the figures. The Q-Q plot depicts the observed and expected $p$ values. The Manhattan plot displays level of significance for each single nucleotide polymorphism (SNP), organized by chromosomal position from chromosomes 1–22. The blue line (lower horizontal line) indicates suggestive significance ($p < 10^{-5}$), and the red line (upper horizontal line) indicates genome-wide significance ($p < 5 \times 10^{-8}$). See the online article for the color version of this figure.

them reliably. This is proving to be the case for clinical addiction phenotypes (e.g., Thorgeirsson et al., 2008) and other complex phenotypes (e.g., Okbay et al., 2016). Larger sample sizes would also permit the application of additional genome-wide methods (e.g., Yang et al., 2010). In addition, independent of sample size, a limitation to the current findings is that that they may not be generalizable beyond individuals of European ancestry. This has also been the case for virtually all of the previous studies in this area, albeit a small number, but it is no less a limitation because of it.

A feature of the current study that was both a strength and a potential limitation its inclusion criteria in terms of substance use. All participants reported relatively low levels of substance use during the prior year by self-report and were verified to have not recently used drugs or alcohol (with varying detection windows by test). This permitted the study to rule out recent drug involvement as a substantial determinant of DRD, either as a symptom or a neurocognitive consequences of heavy use. On the other hand, however, low substance use may have truncated the observed variability in the larger population. Moreover, epidemiologically, substance use and misuse peak in the age group recruited for the study (Courtney & Polich, 2009; Slutske, 2005), so low substance use may make this sample even less representative of the general population. Whether the exclusive focus on individuals with low levels of substance use increased or decreased resolution in this study cannot be addressed directly, but it is an important consideration for contextualizing the current findings.

At a broader level, it is worth considering the optimal experimental designs for investigating DRD (and other processes) as an endophenotype for addiction. Cases can be made for studies focusing on samples that either exclusively do not or do have heavy levels of substance use, but case–control or dimensional studies that are sufficiently powered and fully span the spectrum of severity (i.e., absence of problems to severe addiction) may maximize the capacity to detect differentially predictive loci. Furthermore, all the molecular genetic studies on DRD to date, including the current one, have been cross-sectional. This substantially limits the capacity for inferring causality (MacKillop & Munafò, 2017). Longitudinal designs that permit disentangling the interrelationships between genetic variation, DRD decision making, and addiction will be necessary to test causal pathways more definitively.

In sum, the current study investigated genetic associations with DRD preferences in three different domains. We found little support for previously reported associations, with the possible exception of *ADRA2A*, or an addiction-enriched marker set, but found one significant genome-wide association, warranting further study. The findings advance the understanding of genetic influences on DRD, both via the associations positively detected and the implication of DRD's genetic complexity and, in turn, the need for larger samples to identify its genetic underpinnings more conclusively.

## References

Acheson, A., Vincent, A. S., Sorocco, K. H., & Lovallo, W. R. (2011). Greater discounting of delayed rewards in young adults with family histories of alcohol and drug use disorders: Studies from the Oklahoma family health patterns project. *Alcoholism: Clinical and Experimental Research, 35,* 1607–1613.

Agrawal, A., & Lynskey, M. T. (2008). Are there genetic influences on addiction: Evidence from family, adoption and twin studies. *Addiction, 103,* 1069–1081. http://dx.doi.org/10.1111/j.1360-0443.2008.02213.x

Amlung, M., & MacKillop, J. (2014). Clarifying the relationship between impulsive delay discounting and nicotine dependence. *Psychology of Addictive Behaviors, 28,* 761–768. http://dx.doi.org/10.1037/a0036726

Amlung, M., Sweet, L. H., Acker, J., Brown, C. L., & MacKillop, J. (2014). Dissociable brain signatures of choice conflict and immediate

reward preferences in alcohol use disorders. *Addiction Biology, 19,* 743–753.

Amlung, M., Vedelago, L., Acker, J., Balodis, I., & MacKillop, J. (2017). Steep delay discounting and addictive behavior: A meta-analysis of continuous associations. *Addiction, 112,* 51–62.

Anderson, K. G., & Woolverton, W. L. (2005). Effects of clomipramine on self-control choice in Lewis and Fischer 344 rats. *Pharmacology, Biochemistry, and Behavior, 80,* 387–393. http://dx.doi.org/10.1016/j.pbb.2004.11.015

Anokhin, A. P., Golosheykin, S., Grant, J. D., & Heath, A. C. (2011). Heritability of delay discounting in adolescence: A longitudinal twin study. *Behavior Genetics, 41,* 175–183. http://dx.doi.org/10.1007/s10519-010-9384-7

Anokhin, A. P., Grant, J. D., Mulligan, R. C., & Heath, A. C. (2015). The genetics of impulsivity: Evidence for the heritability of delay discounting. *Biological Psychiatry, 77,* 887–894. http://dx.doi.org/10.1016/j.biopsych.2014.10.022

Audrain-McGovern, J., Rodriguez, D., Epstein, L. H., Cuevas, J., Rodgers, K., & Wileyto, E. P. (2009). Does delay discounting play an etiological role in smoking or is it a consequence of smoking? *Drug and Alcohol Dependence, 103,* 99–106. http://dx.doi.org/10.1016/j.drugalcdep.2008.12.019

Baurley, J. W., Edlund, C. K., Pardamean, C. I., Conti, D. V., & Bergen, A. W. (2016). Smokescreen: A targeted genotyping array for addiction research. *BMC Genomics, 17,* 145. http://dx.doi.org/10.1186/s12864-016-2495-7

Beckwith, S. W., & Czachowski, C. L. (2014). Increased delay discounting tracks with a high ethanol-seeking phenotype and subsequent ethanol seeking but not consumption. *Alcoholism: Clinical and Experimental Research, 38,* 2607–2614. http://dx.doi.org/10.1111/acer.12523

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate - a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society B: Statistical Methodology, 57,* 289–300.

Berman, A. H., Bergman, H., Palmstierna, T., & Schlyter, F. (2005). Evaluation of the Drug Use Disorders Identification Test (DUDIT) in criminal justice and detoxification settings and in a Swedish population sample. *European Addiction Research, 11,* 22–31. http://dx.doi.org/10.1159/000081413

Bickel, W. K., Johnson, M. W., Koffarnus, M. N., MacKillop, J., & Murphy, J. G. (2014). The behavioral economics of substance use disorders: Reinforcement pathologies and their repair. *Annual Review of Clinical Psychology, 10,* 641–677. http://dx.doi.org/10.1146/annurev-clinpsy-032813-153724

Bickel, W. K., & Marsch, L. A. (2001). Toward a behavioral economic understanding of drug dependence: Delay discounting processes. *Addiction, 96,* 73–86. http://dx.doi.org/10.1046/j.1360-0443.2001.961736.x

Bickel, W. K., Odum, A. L., Madden, G. J. (1999). Impulsivity and cigarette smoking: Delay discounting in current, never, and ex-smokers. *Psychopharmacol, 146,* 447–454. http://dx.doi.org/10.1007/PL00005490

Boettiger, C. A., Mitchell, J. M., Tavares, V. C., Robertson, M., Joslyn, G., D'Esposito, M., & Fields, H. L. (2007). Immediate reward bias in humans: Fronto-parietal networks and a role for the catechol-O-methyltransferase 158(Val/Val) genotype. *The Journal of Neuroscience, 27,* 14383–14391. http://dx.doi.org/10.1523/JNEUROSCI.2551-07.2007

Caswell, A. J., Bond, R., Duka, T., & Morgan, M. J. (2015). Further evidence of the heterogeneous nature of impulsivity. *Personality and Individual Differences, 76,* 68–74. http://dx.doi.org/10.1016/j.paid.2014.11.059

Chang, C. C., Chow, C. C., Tellier, L. C., Vattikuti, S., Purcell, S. M., & Lee, J. J. (2015). *Second-generation PLINK: Rising to the challenge of larger and richer datasets*. http://dx.doi.org/10.1186/s13742-015-0047-8

Chen, J., Lipska, B. K., Halim, N., Ma, Q. D., Matsumoto, M., Melhem, S., . . . Weinberger, D. R. (2004). Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): Effects on mRNA, protein, and enzyme activity in postmortem human brain. *American Journal of Human Genetics, 75,* 807–821. http://dx.doi.org/10.1086/425589

Coffey, S. F., Gudleski, G. D., Saladin, M. E., & Brady, K. T. (2003). Impulsivity and rapid discounting of delayed hypothetical rewards in cocaine-dependent individuals. *Experimental and Clinical Psychopharmacology, 11,* 18–25. http://dx.doi.org/10.1037/1064-1297.11.1.18

Courtney, K. E., Arellano, R., Barkley-Levenson, E., Gálvan, A., Poldrack, R. A., Mackillop, J., . . . Ray, L. A. (2012). The relationship between measures of impulsivity and alcohol misuse: An integrative structural equation modeling approach. *Alcoholism: Clinical and Experimental Research, 36,* 923–931. http://dx.doi.org/10.1111/j.1530-0277.2011.01635.x

Courtney, K. E., & Polich, J. (2009). Binge drinking in young adults: Data, definitions, and determinants. *Psychological Bulletin, 135,* 142–156. http://dx.doi.org/10.1037/a0014414

Cyders, M. A., & Coskunpinar, A. (2011). Measurement of constructs using self-report and behavioral lab tasks: Is there overlap in nomothetic span and construct representation for impulsivity? *Clinical Psychology Review, 31,* 965–982. http://dx.doi.org/10.1016/j.cpr.2011.06.001

Delaneau, O., Marchini, J., & the 1000 Genomes Project Consortium. (2014). Integrating sequence and array data to create an improved 1000 Genomes Project haplotype reference panel. *Nature Communications, 5,* 3934. http://dx.doi.org/10.1038/ncomms4934

de Wit, H. (2009). Impulsivity as a determinant and consequence of drug use: A review of underlying processes. *Addiction Biology, 14,* 22–31. http://dx.doi.org/10.1111/j.1369-1600.2008.00129.x

de Wit, H., Flory, J. D., Acheson, A., McCloskey, M., & Manuck, S. B. (2007). IQ and nonplanning impulsivity are independently associated with delay discounting in middle-aged adults. *Personality and Individual Differences, 42,* 111–121. http://dx.doi.org/10.1016/j.paid.2006.06.026

Dick, D. M., Smith, G., Olausson, P., Mitchell, S. H., Leeman, R. F., O'Malley, S. S., . . . Sher, K. (2010). Understanding the construct of impulsivity and its relationship to alcohol use disorders. *Addiction Biology, 15,* 217–226. http://dx.doi.org/10.1111/j.1369-1600.2009.00190.x

Dougherty, D. M., Charles, N. E., Mathias, C. W., Ryan, S. R., Olvera, R. L., Liang, Y., & Acheson, A. (2014). Delay discounting differentiates pre-adolescents at high and low risk for substance use disorders based on family history. *Drug and Alcohol Dependence, 143,* 105–111. http://dx.doi.org/10.1016/j.drugalcdep.2014.07.012

Eisenberg, D. T., Mackillop, J., Modi, M., Beauchemin, J., Dang, D., Lisman, S. A., . . . Wilson, D. S. (2007). Examining impulsivity as an endophenotype using a behavioral approach: A DRD2 TaqI A and DRD4 48-bp VNTR association study. *Behavioral and Brain Functions, 3,* 2. http://dx.doi.org/10.1186/1744-9081-3-2

Fernie, G., Peeters, M., Gullo, M. J., Christiansen, P., Cole, J. C., Sumnall, H., & Field, M. (2013). Multiple behavioural impulsivity tasks predict prospective alcohol involvement in adolescents. *Addiction, 108,* 1916–1923. http://dx.doi.org/10.1111/add.12283

Gauderman, W. J. (2002). Sample size requirements for association studies of gene-gene interaction. *American Journal of Epidemiology, 155,* 478–484. http://dx.doi.org/10.1093/aje/155.5.478

Gianotti, L. R. R., Figner, B., Ebstein, R. P., & Knoch, D. (2012). Why some people discount more than others: Baseline activation in the dorsal PFC mediates the link between COMT genotype and impatient choice. *Frontiers in Neuroscience, 6,* 54. http://dx.doi.org/10.3389/fnins.2012.00054

Goldman, D., Oroszi, G., & Ducci, F. (2005). The genetics of addictions: Uncovering the genes. *Nature Reviews Genetics, 6,* 521–532. http://dx.doi.org/10.1038/nrg1635

Green, L., Fry, A. F., & Myerson, J. (1994). Discounting of delayed rewards: A life-span comparison. *Psychological Science, 5,* 33–36. http://dx.doi.org/10.1111/j.1467-9280.1994.tb00610.x

Havranek, M. M., Hulka, L. M., Tasiudi, E., Eisenegger, C., Vonmoos, M., Preller, K. H., . . . Quednow, B. B. (2017). α2A-Adrenergic receptor polymorphisms and mRNA expression levels are associated with delay discounting in cocaine users. *Addiction Biology, 22,* 561–569. http://dx.doi.org/10.1111/adb.12324

Howie, B. N., Donnelly, P., & Marchini, J. (2009). A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. *PLoS Genetics, 5*(6), e1000529.

IBM Corp. (2011). *IBM SPSS statistics for windows* (Version 20.0). Armonk, NY: Author.

Isen, J. D., Sparks, J. C., & Iacono, W. G. (2014). Predictive validity of delay discounting behavior in adolescence: A longitudinal twin study. *Experimental and Clinical Psychopharmacology, 22,* 434–443. http://dx.doi.org/10.1037/a0037340

Isles, A. R., Humby, T., Walters, E., & Wilkinson, L. S. (2004). Common genetic effects on variation in impulsivity and activity in mice. *The Journal of Neuroscience, 24,* 6733–6740. http://dx.doi.org/10.1523/JNEUROSCI.1650-04.2004

Jentsch, J. D., Ashenhurst, J. R., Cervantes, M. C., Groman, S. M., James, A. S., & Pennington, Z. T. (2014). Dissecting impulsivity and its relationships to drug addictions. *Annals of the New York Academy of Sciences, 1327,* 1–26.

Khurana, A., Romer, D., Betancourt, L. M., Brodsky, N. L., Giannetta, J. M., & Hurt, H. (2013). Working memory ability predicts trajectories of early alcohol use in adolescents: The mediational role of impulsivity. *Addiction, 108,* 506–515. http://dx.doi.org/10.1111/add.12001

Kim-Spoon, J., McCullough, M. E., Bickel, W. K., Farley, J. P., & Longo, G. S. (2015). Longitudinal associations among religiousness, delay discounting, and substance use initiation in early adolescence. *Journal of Research on Adolescence, 25,* 36–43. http://dx.doi.org/10.1111/jora.12104

Kirby, K. N., Petry, N. M., & Bickel, W. K. (1999). Heroin addicts have higher discount rates for delayed rewards than non-drug-using controls. *Journal of Experimental Psychology: General, 128,* 78–87. http://dx.doi.org/10.1037/0096-3445.128.1.78

Krijger, P. H. L., & de Laat, W. (2016). Regulation of disease-associated gene expression in the 3D genome. *Nature Reviews Molecular Cell Biology, 17,* 771–782. http://dx.doi.org/10.1038/nrm.2016.138

Li, C., Li, M., Lange, E. M., & Watanabe, R. M. (2008). Prioritized subset analysis: Improving power in genome-wide association studies. *Human Heredity, 65,* 129–141. http://dx.doi.org/10.1159/000109730

Lin, W.-Y., & Lee, W.-C. (2010). Incorporating prior knowledge to facilitate discoveries in a genome-wide association study on age-related macular degeneration. *BMC Research Notes, 3,* 26. http://dx.doi.org/10.1186/1756-0500-3-26

Linsenbardt, D. N., Smoker, M. P., Janetsian-Fritz, S. S., & Lapish, C. C. (2017). Impulsivity in rodents with a genetic predisposition for excessive alcohol consumption is associated with a lack of a prospective strategy. *Cognitive, Affective & Behavioral Neuroscience, 17,* 235–251.

MacKillop, J. (2013). Integrating behavioral economics and behavioral genetics: Delayed reward discounting as an endophenotype for addictive disorders. *Journal of the Experimental Analysis of Behavior, 99,* 14–31. http://dx.doi.org/10.1002/jeab.4

MacKillop, J., & Munafò, M. R. (2017). Commentary: Delay discounting and smoking: Robust correlation, but uncertain causation. *International Journal of Epidemiology, 46,* 870–871. http://dx.doi.org/10.1093/ije/dyw303

MacKillop, J., Amlung, M. T., Few, L. R., Ray, L. A., Sweet, L. H., & Munafò, M. R. (2011). Delayed reward discounting and addictive behavior: A meta-analysis. *Psychopharmacology, 216,* 305–321. http://dx.doi.org/10.1007/s00213-011-2229-0

MacKillop, J., Anderson, E. J., Castelda, B. A., Mattson, R. E., & Donovick, P. J. (2006). Divergent validity of measures of cognitive distortions, impulsivity, and time perspective in pathological gambling. *Journal of Gambling Studies, 22,* 339–354. http://dx.doi.org/10.1007/s10899-006-9021-9

MacKillop, J., Gray, J. C., Bidwell, L. C., Bickel, W. K., Sheffer, C. E., & McGeary, J. E. (2015). Genetic influences on delay discounting in smokers: Examination of a priori candidates and exploration of dopamine-related haplotypes. *Psychopharmacology, 232,* 3731–3739. http://dx.doi.org/10.1007/s00213-015-4029-4

MacKillop, J., Miller, J. D., Fortune, E., Maples, J., Lance, C. E., Campbell, W. K., & Goodie, A. S. (2014). Multidimensional examination of impulsivity in relation to disordered gambling. *Experimental and Clinical Psychopharmacology, 22,* 176–185. http://dx.doi.org/10.1037/a0035874

MacKillop, J., Miranda, R., Jr., Monti, P. M., Ray, L. A., Murphy, J. G., Rohsenow, D. J., . . . Gwaltney, C. J. (2010). Alcohol demand, delayed reward discounting, and craving in relation to drinking and alcohol use disorders. *Journal of Abnormal Psychology, 119,* 106–114. http://dx.doi.org/10.1037/a0017513

MacKillop, J., Weafer, J. C., Gray, J., Oshri, A., Palmer, A., & de Wit, H. (2016). The latent structure of impulsivity: Impulsive choice, impulsive action, and impulsive personality traits. *Psychopharmacology, 233,* 3361–3370. http://dx.doi.org/10.1007/s00213-016-4372-0

Madden, G. J., Petry, N. M., Badger, G. J., & Bickel, W. K. (1997). Impulsive and self-control choices in opioid-dependent patients and non-drug-using control patients: Drug and monetary rewards. *Experimental and Clinical Psychopharmacology, 5,* 256–262. http://dx.doi.org/10.1037/1064-1297.5.3.256

Madden, G. J., Smith, N. G., Brewer, A. T., Pinkston, J. W., & Johnson, P. S. (2008). Steady-state assessment of impulsive choice in Lewis and Fischer 344 rats: Between-condition delay manipulations. *Journal of the Experimental Analysis of Behavior, 90,* 333–344. http://dx.doi.org/10.1901/jeab.2008.90-333

Marchini, J., & Howie, B. (2010). Genotype imputation for genome-wide association studies. *Nature Reviews Genetics, 11,* 499–511. http://dx.doi.org/10.1038/nrg2796

Mazur, J. E. (1987). An adjusting procedure for studying delayed reinforcement. In M. L. Commons, J. E. Mazur, & J. A. Nevin (Eds.), *The effect of delay and of intervening event on reinforcement value: Quantitative analyses of behavior* (pp. 55–73). Hillsdale, NJ: Erlbaum.

Mendez, I. A., Simon, N. W., Hart, N., Mitchell, M. R., Nation, J. R., Wellman, P. J., & Setlow, B. (2010). Self-administered cocaine causes long-lasting increases in impulsive choice in a delay discounting task. *Behavioral Neuroscience, 124,* 470–477. http://dx.doi.org/10.1037/a0020458

Mitchell, M. R., Weiss, V. G., Ouimet, D. J., Fuchs, R. A., Morgan, D., & Setlow, B. (2014). Intake-dependent effects of cocaine self-administration on impulsive choice in a delay discounting task. *Behavioral Neuroscience, 128,* 419–429. http://dx.doi.org/10.1037/a0036742

Mitchell, S. H. (2011). The genetic basis of delay discounting and its genetic relationship to alcohol dependence. *Behavioural Processes, 87,* 10–17. http://dx.doi.org/10.1016/j.beproc.2011.02.008

Murphy, P., & Garavan, H. (2011). Cognitive predictors of problem drinking and AUDIT scores among college students. *Drug and Alcohol Dependence, 115,* 94–100. http://dx.doi.org/10.1016/j.drugalcdep.2010.10.011

Oberlin, B. G., & Grahame, N. J. (2009). High-alcohol preferring mice are more impulsive than low-alcohol preferring mice as measured in the delay discounting task. *Alcoholism: Clinical and Experimental Research, 33,* 1294–1303. http://dx.doi.org/10.1111/j.1530-0277.2009.00955.x

Okbay, A., Beauchamp, J. P., Fontana, M. A., Lee, J. J., Pers, T. H., Rietveld, C. A., . . . the LifeLines Cohort Study. (2016). Genome-wide

association study identifies 74 loci associated with educational attainment. *Nature, 533,* 539–542. http://dx.doi.org/10.1038/nature17671

Panagiotou, O. A., Ioannidis, J. P. A., & the Genome-Wide Significance Project. (2012). What should the genome-wide significance threshold be? Empirical replication of borderline genetic associations. *International Journal of Epidemiology, 41,* 273–286. http://dx.doi.org/10.1093/ije/dyr178

Pe'er, I., Yelensky, R., Altshuler, D., & Daly, M. J. (2008). Estimation of the multiple testing burden for genomewide association studies of nearly all common variants. *Genetic Epidemiology, 32,* 381–385. http://dx.doi.org/10.1002/gepi.20303

Perkel, J. K., Bentzley, B. S., Andrzejewski, M. E., & Martinetti, M. P. (2015). Delay discounting for sucrose in alcohol-preferring and nonpreferring rats using a sipper tube within-sessions task. *Alcoholism: Clinical and Experimental Research, 39,* 232–238. http://dx.doi.org/10.1111/acer.12632

Petry, N. M. (2001). Delay discounting of money and alcohol in actively using alcoholics, currently abstinent alcoholics, and controls. *Psychopharmacology, 154,* 243–250. http://dx.doi.org/10.1007/s002130000638

Price, A. L., Patterson, N. J., Plenge, R. M., Weinblatt, M. E., Shadick, N. A., & Reich, D. (2006). Principal components analysis corrects for stratification in genome-wide association studies. *Nature Genetics, 38,* 904–909. http://dx.doi.org/10.1038/ng1847

Reynolds, B., Ortengren, A., Richards, J. B., & de Wit, H. (2006). Dimensions of impulsive behavior: Personality and behavioral measures. *Personality and Individual Differences, 40,* 305–315. http://dx.doi.org/10.1016/j.paid.2005.03.024

Richards, J. B., Lloyd, D. R., Kuehlewind, B., Militello, L., Paredez, M., Solberg Woods, L., & Palmer, A. A. (2013). Strong genetic influences on measures of behavioral-regulation among inbred rat strains. *Genes, Brain & Behavior, 12,* 490–502. http://dx.doi.org/10.1111/gbb.12050

Robinson, E. S. J., Eagle, D. M., Mar, A. C., Bari, A., Banerjee, G., Jiang, X., . . . Robbins, T. W. (2008). Similar effects of the selective noradrenaline reuptake inhibitor atomoxetine on three distinct forms of impulsivity in the rat. *Neuropsychopharmacology, 33,* 1028–1037. http://dx.doi.org/10.1038/sj.npp.1301487

Saunders, J. B., Aasland, O. G., Babor, T. F., de la Fuente, J. R., & Grant, M. (1993). Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption—II. *Addiction, 88,* 791–804. http://dx.doi.org/10.1111/j.1360-0443.1993.tb02093.x

Schork, A. J., Thompson, W. K., Pham, P., Torkamani, A., Roddey, J. C., Sullivan, P. F., . . . the Tobacco and Genetics Consortium, & the Bipolar Disorder Psychiatric Genomics Consortium, & the Schizophrenia Psychiatric Genomics Consortium. (2013). All SNPs are not created equal: Genome-wide association studies reveal a consistent pattern of enrichment among functionally annotated SNPs. *PLOS Genetics, 9,* e1003449. http://dx.doi.org/10.1371/journal.pgen.1003449

Setlow, B., Mendez, I. A., Mitchell, M. R., & Simon, N. W. (2009). Effects of chronic administration of drugs of abuse on impulsive choice (delay discounting) in animal models. *Behavioural Pharmacology, 20,* 380–389. http://dx.doi.org/10.1097/FBP.0b013e3283305eb4

Simon, N. W., Mendez, I. A., & Setlow, B. (2007). Cocaine exposure causes long-term increases in impulsive choice. *Behavioral Neuroscience, 121,* 543–549. http://dx.doi.org/10.1037/0735-7044.121.3.543

Slutske, W. S. (2005). Alcohol use disorders among U.S. college students and their non-college-attending peers. *Archives of General Psychiatry, 62,* 321–327. http://dx.doi.org/10.1001/archpsyc.62.3.321

Sonuga-Barke, E. J. S., Kumsta, R., Schlotz, W., Lasky-Su, J., Marco, R., Miranda, A., . . . Faraone, S. V. (2011). A functional variant of the serotonin transporter gene (SLC6A4) moderates impulsive choice in attention-deficit/hyperactivity disorder boys and siblings. *Biological Psychiatry, 70,* 230–236. http://dx.doi.org/10.1016/j.biopsych.2011.01.040

Sparks, J. C., Isen, J. D., & Iacono, W. G. (2014). Preference on cash-choice task predicts externalizing outcomes in 17-year-olds. *Behavior Genetics, 44,* 102–112. http://dx.doi.org/10.1007/s10519-013-9638-2

Stein, J. S., Pinkston, J. W., Brewer, A. T., Francisco, M. T., & Madden, G. J. (2012). Delay discounting in Lewis and Fischer 344 rats: Steady-state and rapid-determination adjusting-amount procedures. *Journal of the Experimental Analysis of Behavior, 97,* 305–321. http://dx.doi.org/10.1901/jeab.2012.97-305

Sun, H., Cocker, P. J., Zeeb, F. D., & Winstanley, C. A. (2012). Chronic atomoxetine treatment during adolescence decreases impulsive choice, but not impulsive action, in adult rats and alters markers of synaptic plasticity in the orbitofrontal cortex. *Psychopharmacology, 219,* 285–301. http://dx.doi.org/10.1007/s00213-011-2419-9

Sun, L., Craiu, R. V., Paterson, A. D., & Bull, S. B. (2006). Stratified false discovery control for large-scale hypothesis testing with application to genome-wide association studies. *Genetic Epidemiology, 30,* 519–530. http://dx.doi.org/10.1002/gepi.20164

Sweitzer, M. M., Donny, E. C., Dierker, L. C., Flory, J. D., & Manuck, S. B. (2008). Delay discounting and smoking: Association with the Fagerstrom Test for Nicotine Dependence but not cigarettes smoked per day. *Nicotine & Tobacco Research, 10,* 1571–1575. http://dx.doi.org/10.1080/14622200802323274

Thorgeirsson, T. E., Geller, F., Sulem, P., Rafnar, T., Wiste, A., Magnusson, K. P., . . . Stefansson, K. (2008). A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. *Nature, 452,* 638–642. http://dx.doi.org/10.1038/nature06846

Tunbridge, E. M., Bannerman, D. M., Sharp, T., & Harrison, P. J. (2004). Catechol-o-methyltransferase inhibition improves set-shifting performance and elevates stimulated dopamine release in the rat prefrontal cortex. *The Journal of Neuroscience, 24,* 5331–5335. http://dx.doi.org/10.1523/JNEUROSCI.1124-04.2004

VanderBroek, L., Acker, J., Palmer, A. A., de Wit, H., & MacKillop, J. (2016). Interrelationships among parental family history of substance misuse, delay discounting, and personal substance use. *Psychopharmacology, 233,* 39–48.

Volkow, N. D., Baler, R. D. (2014). Addiction science: Uncovering neurobiological complexity. *Neuropharmacology 76*(Part B), 235–49. http://dx.doi.org/10.1016/j.neuropharm.2013.05.007

Wilhelm, C. J., & Mitchell, S. H. (2008). Rats bred for high alcohol drinking are more sensitive to delayed and probabilistic outcomes. *Genes, Brain & Behavior, 7,* 705–713. http://dx.doi.org/10.1111/j.1601-183X.2008.00406.x

Wilhelm, C. J., & Mitchell, S. H. (2009). Strain differences in delay discounting using inbred rats. *Genes, Brain & Behavior, 8,* 426–434. http://dx.doi.org/10.1111/j.1601-183X.2009.00484.x

Yang, J., Benyamin, B., McEvoy, B. P., Gordon, S., Henders, A. K., Nyholt, D. R., . . . Visscher, P. M. (2010). Common SNPs explain a large proportion of the heritability for human height. *Nature Genetics, 42,* 565–569. http://dx.doi.org/10.1038/ng.608

Yang, J., Lee, S. H., Goddard, M. E., & Visscher, P. M. (2011). *GCTA: A tool for genome-wide complex trait analysis*. http://dx.doi.org/10.1016/j.ajhg.2010.11.011

Zhou, X., & Stephens, M. (2012). Genome-wide efficient mixed-model analysis for association studies. *Nature Genetics, 44,* 821–824. http://dx.doi.org/10.1038/ng.2310

Received February 23, 2018
Revision received June 22, 2018
Accepted June 26, 2018 ■