doi:10.1093/scan/nss020 SCAN (2013) 8, 499–508

Polymorphic variation in the dopamine D4 receptor predicts delay discounting as a function of childhood socioeconomic status: evidence for differential susceptibility

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Inconsistent or null findings among studies associating behaviors on the externalizing spectrum—addictions, impulsivity, risk-taking, novelty-seeking traits—with presence of the 7-repeat allele of a common length polymorphism in the gene encoding the dopamine D4 receptor (*DRD4*) may stem from individuals' variable exposures to prominent environmental moderators (gene × environment interaction). Here, we report that relative preference for immediate, smaller rewards over larger rewards delayed in time (delay discounting), a behavioral endophenotype of impulsive decision-making, varied by interaction of *DRD4* genotype with childhood socioeconomic status (SES) among 546 mid-life community volunteers. Independent of age, sex, adulthood SES and IQ, participants who were both raised in families of distinctly low SES (low parental education and occupational grade) and carried the *DRD4* 7-repeat allele discounted future rewards more steeply than like-reared counterparts of alternate *DRD4* genotype. In the absence of childhood socioeconomic disadvantage, however, participants carrying the 7-repeat allele discounted future rewards *less* steeply. This bidirectional association of *DRD4* genotype with temporal discounting, conditioned by participants' early life circumstances, accords with a recently proposed developmental model of gene × environment interaction ('differential susceptibility') that posits genetically modulated sensitivity to both adverse and salubrious environmental influences.

Keywords: gene–environment interaction; differential susceptibility; delay discounting; *DRD4*; childhood socioeconomic status; impulsivity

INTRODUCTION

One of the most extensively studied polymorphisms in psychiatric and behavioral genetics consists of a variable number of tandem repeats (VNTR) in exon 3 of the gene encoding the dopamine D4 receptor (*DRD4*), located on chromosome 11p15.5. This VNTR contains 10 known variants of a 48-base pair (bp) repeat sequence in the region coding for the receptor's third cytoplasmic loop. Although allele frequencies vary by ethnicity and geographic region, alleles of 2, 4 and 7 repeats account for over 90% of variation in most populations (Wang *et al.*, 2004). The DRD4 protein is expressed in many brain areas, including prefrontal and subcortical regions implicated in executive functioning, reward processing and emotion (Oak *et al.*, 2000). Activation of this G protein-linked receptor attenuates intracellular signaling by inhibiting adenylyl cyclase coupling, with consequent reduction in second messenger [cyclic adenosine monophosphate (cAMP)] synthesis. This inhibitory effect is blunted, however, in cell lines expressing the 7-repeat variant of the VNTR, with greater dopamine stimulation required to achieve levels of receptor-mediated cAMP reduction equivalent to the ancestral 4-repeat allele (Asghari *et al.*, 1995). Additionally, the 7-repeat allele may modify *DRD4* expression, as seen in an *in vitro* assay system, via mechanisms affecting RNA stability or translational efficiency (Schoots and Van Tol, 2003).

Received 26 October 2011; Accepted 7 February 2012
Advance Access publication 15 February 2012

Support for this research was provided by the National Institutes of Health [PO1 HL040962 and RO1 HL065137 to S. B. Manuck]. M. Sweitzer was supported by a National Science Foundation Integrative Graduate Education and Research Training grant [DGE-0549352] and the University of Pittsburgh Center for the Neural Basis of Cognition.

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Numerous studies associate risk for attention deficit/hyperactivity disorder (ADHD) with presence of the 7-repeat allele, a relationship confirmed in several meta-analyses (Faraone *et al.*, 2001; Li *et al.*, 2006; Gizer *et al.*, 2009). Genotypes containing the 7-repeat variant moderately increase ADHD risk, both overall and in studies of European–Caucasian and South American populations separately; yet paradoxically, the same allele appears modestly protective in the few studies of Middle Eastern cohorts (Nikolaidis and Gray, 2010). In smaller literatures involving other phenotypes of self-regulation, the 7-repeat allele has been associated with addictive behaviors, such as cigarette smoking (Laucht *et al.*, 2005; Le Foll *et al.*, 2009), cue-elicited craving (Hutchison *et al.*, 2002; but see also van den Wildenberg *et al.*, 2007) and pathological gambling (Perez de Castro *et al.*, 1997; Comings *et al.*, 2001), as well as laboratory measures of financial risk taking and inhibitory motor control (e.g. Congdon *et al.*, 2008; Dreber *et al.*, 2009; Kuhnen and Chiao, 2009; Eisenegger *et al.*, 2010). Contrary findings (e.g. greater response inhibition) in college students carrying the 7-repeat allele (Kramer *et al.*, 2009) have been reported too, however, and neuropsychological studies of attentional processes and executive functioning among children with ADHD have found the 7-repeat variant variously associated with superior performance (Swanson *et al.*, 2000a; Manor *et al.*, 2002; Bellgrove *et al.*, 2005; Johnson *et al.*, 2008), null effects (Barkley *et al.*, 2006) or impaired responding (Waldman, 2005; Kieling *et al.*, 2006; Laucht *et al.*, 2007), relative to other *DRD4* genotypes (Kebir *et al.*, 2009).

Notably, the *DRD4* exon 3 VNTR was the first gene polymorphism prominently associated with a human personality trait, Novelty Seeking (Cloninger, 1987). In initial reports, persons who tested high for Novelty Seeking (characterized by high-appetitive motivation and

sensitivity to signals of reward, exploratory activity and impulsive disposition) were more likely to carry long (principally 7-repeat) *DRD4* alleles than lower scoring individuals (Benjamin *et al*., 1996; Ebstein *et al*., 1996). However, this association proved inconclusive in later research, and in some studies, *DRD4* alleles were related to Novelty Seeking in an opposite direction. Meta-analytic reviews corroborated this lack of clear association, yet also revealed nonrandom (true) heterogeneity of study outcomes attributable to unknown moderators (Kluger *et al*., 2002; Schinka *et al*., 2002; Munafo *et al*., 2008). One potential environmental moderator, early life stress, was suggested subsequently when *DRD4* genotype predicted Novelty Seeking only among individuals who had experienced hostile or emotionally distant maternal rearing (Keltikangas-Jarvinen *et al*., 2004). In other studies and against similar developmental adversities [e.g. parenting deficiencies, maternal insensitivity, low socioeconomic status (SES)], the *DRD4* 7-repeat allele was found associated also with several unfavorable child outcomes, such as disorganized infant attachment, heightened sensation seeking and various externalizing behaviors, including aggressive conduct (Bakermans-Kranenburg and van Ijzendoorn, 2006; Van Ijzendoorn and Bakermans-Kranenburg, 2006; Nobile *et al*., 2007; Sheese *et al*., 2007). In contrast, study phenotypes were unrelated to *DRD4* genotype among children raised in the absence of such adversities.

The foregoing observations generally accord with 'diathesis–stress' models of gene × environment interaction (G × E), in which genetic vulnerabilities are thought to occasion negative outcomes (e.g. psychopathology) mainly in individuals who are also disadvantaged by adverse circumstance (Manuck, 2010; Manuck and McCaffery, 2010). Another form of ordinal G × E may be postulated as well ('vantage sensitivity'), in which benefits accrued in a favorable environment are also modulated by genetic variation. For instance, children carrying the *DRD4* 7-repeat allele were found more likely to exhibit *prosocial* behaviors (e.g. sharing) as a function of maternal *positivity* or when encouraged in this direction experimentally, relative to children of other *DRD4* genotypes (Knafo, 2009; Bakermans-Kranenburg and van Ijzendoorn, 2011; Knafo *et al*., 2011). Similarly, therapeutic intervention to enhance positive parenting reduced oppositional behavior in children with externalizing problems, but again, only among those possessing the 7-repeat allele (Bakermans-Kranenburg *et al*., 2008). Overall, these studies suggest that the same *DRD4* genotype may potentiate positive outcomes in propitious environments and negative outcomes in adverse environments. The term 'differential susceptibility' was applied recently to disordinal interactions of this type, in which a genetic variant predicts both higher and lower values of a given phenotype at opposite poles of an environmental gradient, compared to alternate genotypes of the same polymorphism (Boyce and Ellis, 2005; Belsky and Pluess, 2009). Whether 'differential susceptibility' defines a common form of G × E remains uncertain, however, as in many studies potential moderators may not be assessed over a sufficiently broad range of (unfavorable to favorable) environmental variation (Belsky *et al*., 2009) and, with respect to *DRD4*, most supporting evidence is limited to relatively small studies of child traits or behaviors.

A common attribute of many phenotypes previously examined in relation to *DRD4* is the capacity to regulate motivated behavior, particularly where alternative courses of action entail trade-offs between proximal rewards and distal consequences. One index of such behavior is termed delay discounting, which reflects an individual's relative preference for smaller, immediate rewards over larger rewards delayed in time (Green and Myerson, 2004). The discounting of future outcomes underlies much of human decision-making and figures prominently in many overlapping psychological constructs, such as self-regulation, impulse-control, delayed gratification and intertemporal choice (Manuck *et al*., 2003). Notably, a marked preference for immediate over deferred rewards of larger value (steeper discounting) associates with many of the same behaviors implicated in studies of *DRD4* variation, including addictions [substance use (Kirby *et al*., 1999; Coffey *et al*., 2003; Kollins, 2003), alcohol dependence (Bobova *et al*., 2009), pathological gambling (Alessi and Petry, 2003; Reynolds, 2006), cigarette smoking (Bickel *et al*., 1999; Mitchell, 1999; Reynolds *et al*., 2004; Ohmura *et al*., 2005; Sweitzer *et al*., 2008; Audrain-McGovern *et al*., 2009)] and antisocial behavior (Petry, 2002), and among children or adolescents, substance use (Wulfert *et al*., 2002), conduct problems (Krueger *et al*., 1996) and ADHD (Scheres *et al*., 2006, 2010). Moreover, delay discounting is a stable dimension of individual differences (albeit steeper in youth than among adults; Green *et al*., 1994, 1996; Beck and Triplett, 2009) and is both heritable ($h^2 \approx 30$–50%) (Anokhin *et al*., 2010) and influenced by early and later socioeconomic conditions (wherein socioeconomic disadvantage is associated with steeper discounting; Green et al., 1996; de Wit *et al*., 2007; Sweitzer *et al*., 2008; Anokhin *et al*., 2010;).

Discounting is typically assessed using behavioral tasks that require choices between multiple immediate (either actual or hypothetical) rewards that vary in value and a constant, larger reward (e.g. $100) available after varying intervals of delay (e.g. a day, week, month, 3 months, etc.). For each delay interval, an 'indifference' point is computed as the value of immediately available reward that an individual deems equally desirable to the larger, delayed reward. A hyperbolic curve is then commonly fitted to indifference points for the several delay intervals, and a free parameter, *k*, is calculated to index steepness of discounting (Mitchell, 1999; Richards *et al*., 1999; de Wit *et al*., 2007). In previous work, for instance, we found this measure of discounting associated with adult cigarette smoking and nicotine dependence, trait impulsivity, and reward-dependent activation of the ventral striatum (a key metric in the mesocorticolimbic circuitry of reward processing; Hariri *et al*., 2006; de Wit *et al*., 2007; Sweitzer *et al*., 2008). Steeper discounting was predicted, in turn, by variability in socioeconomic circumstances, as referenced to personal (adult) income and educational attainments and, independently, to childhood (parental socioeconomic) environments (de Wit *et al*., 2007; Sweitzer *et al*., 2008). To further explore determinants of this potential endophenotype of impulsive decision-making, the purposes of the present study were to: (i) examine whether repeat length variants of the *DRD4* VNTR predict delay discounting in the same midlife community sample and (ii) test whether any genetic association may be moderated by adult or early life socioeconomic indicators, in accordance with contrasting G × E models.

MATERIAL AND METHODS

Participants

Study data were derived from a sample of 648 non-Hispanic Caucasian men and women (50% female) who were administered a computerized delay discounting task during their participation in the University of Pittsburgh Adult Health and Behavior (AHAB) project between 2001 and 2005. The AHAB project provides a registry of behavioral and biological measurements, plus DNA for genetic analysis of registry phenotypes, on mid-life community volunteers recruited via mass-mail solicitation from communities of southwestern Pennsylvania (principally Allegheny County; Halder *et al*., 2007, 2010; Bleil *et al*., 2008; Manuck *et al*., 2010, 2011). AHAB participants were 30–54 years of age, with no clinical history of atherosclerotic cardiovascular disease, chronic kidney or liver disease, cancer treatment within the preceding year or major neurologic disorders, schizophrenia or other psychotic illness. Other AHAB study exclusions included pregnancy and use of insulin, glucocorticoid, antiarrhythmic, psychotropic or

prescription weight-loss medications. Data collection occurred over multiple laboratory sessions, and informed consent was obtained in accordance with approved guidelines of the University of Pittsburgh Institutional Review Board.

Although the AHAB registry includes measurements on a small proportion of African Americans, study analyses were limited to the larger Caucasian cohort to mitigate effects of sample heterogeneity, race/ethnic differences in allele frequencies of the *DRD4* VNTR and unknown extent and variability of European genetic admixture among African American participants (Wang *et al.*, 2004; Halder *et al.*, 2009). Since parental SES comprised a principal study variable, as well as to avoid confounding of study results by variation or change in family (parental) composition during early childhood, we also restricted our analyses to individuals who had been raised in two-parent families for at least the first 13 years of life. This resulted in exclusion of 63 participants whose parents had divorced (49) or who suffered loss of a parent by death or had only ever lived with a single parent (14). An additional 11 participants were excluded for missing data on one or more other nongenetic study variables to yield a working sample of 585 men and women.

Genotyping

Genomic DNA was isolated from peripheral white blood cells using the PureGene kit (Gentra Systems, Minneapolis, MN, USA). The *DRD4* exon 3 VNTR was genotyped by polymerase chain reaction amplification using the primers F-5′-GCGACTACGTGGTCTACTCG-3′ and R-5′-AGGACCCTCATGGCCTTG-3′ following the method of Lichter *et al.* (1993), and the fragments resolved on 2% agarose gel and visualized under UV illumination with ethidium bromide. Genotypes were assigned by direct comparison to controls of known genotype. Overall, 95.1% of the individuals were genotyped successfully to yield a final study sample of 546 participants. The common 2-, 4- and 7-repeat variants together accounted for >93% of alleles, with respective frequencies of 9.2, 66.2, and 18.0%. The distribution of *DRD4* genotypes conformed to Hardy–Weinberg Equilibrium ($P = 0.58$) and, for purposes of analysis, genotypes were grouped by presence of any 7-repeat allele ($n = 174$) *vs* all other allele combinations ($n = 372$; Table 1).

Since genetic data derived from individuals of common race/ethnicity may still exhibit stratification, we tested for possible genetic substructure in this sample. Fifteen additional, genome-spanning single nucleotide polymorphisms (SNPs; rs1022106, rs1335995, rs1439564, rs1502812, rs1860300, rs548146, rs705388, rs715994, rs720517, rs733743, rs730899, rs734204, rs9059966, rs1328994 and rs1485405) were genotyped for analysis using the program STRUCTURE (Pritchard *et al.*, 2000; Falush *et al.*, 2003). A model with admixture, uncorrelated allele frequencies, individual alpha parameters and independent *F*-statistic (fixation index) for all subpopulations was run separately assuming 1, 2 or 3 subpopulations. For each model, we used a burn-in of 40 000 simulations, followed by 80 000 repetitions and compared the likelihood of models fitting the data. Evidence of stratification could be inferred if the likelihood of data fitting a model with ≥ 2 subpopulations was greater than that of a model with 1 population. However, no evidence of genetic substructure was detected, with a single-population probability of 0.99 and a negligible probability of more than one population ($<2.3 \times 10^{-49}$). Therefore, no further adjustments were made for stratification.

Delay discounting

Participants completed a computerized delay-discounting task as a component of the AHAB protocol. As described elsewhere (de Wit *et al.*, 2007), subjects chose between hypothetical amounts of money available the same day ($0.10–105.00) and $100 available after a delay of 0, 7, 30, 90, 180, 365 or 1825 days. All combinations of delays and immediate rewards were presented in randomized order, and indifference points for each delay interval were calculated, as described by Mitchell (1999), as the midpoint value (in dollars) between the lowest immediate reward ($0.10–105.00) selected by the subject and the next lowest immediate reward in sequence (i.e. the value of immediate reward at which the participant began consistently to select the standard $100 delayed reward). Since paired values of immediate reward and delay interval were presented in random order, choice preferences sometimes alternated briefly in the sequence of declining immediate rewards before establishing a clear delayed-reward preference. Following Mitchell (1999), in this case, we defined the shift in preference as having occurred when the subject rejected two successive (adjacent) values of immediate reward, again calculating the indifference point as the mid-point between the values of the lowest immediate reward chosen and the (rejected) next lowest immediate reward. A hyperbolic function was then fit to the seven indifference points by the following formula: $V = A/(1 + kD)$, where V is the value of the delayed outcome (i.e. the indifference value), A is the fixed $100 delayed reward, D is the length of the delay, and the magnitude of k expresses the steepness (low to high) with which an individual is discounting delayed rewards (Mazur, 1987; Myerson and Green, 1995; Richards *et al.*, 1999). k-values were log normalized for statistical analysis, and an R^2 was calculated for each individual indicating how well data points fit the hyperbolic function. The median R^2 for the present sample (0.92) was identical to the larger AHAB cohort of Caucasian and African American participants from which this sample was derived ($n = 743$; AHAB data registry).

Table 1. Frequencies of *DRD4* exon 3 VNTR alleles and genotypes, and categorization of genotypes by presence of the 7-repeat allele

	n (%)
Allele	
2	100 (9.2)
3	42 (3.9)
4	723 (66.2)
5	12 (1.1)
6	7 (0.6)
7	197 (18.0)
8	9 (0.8)
10	2 (0.2)
Total	1092 (100.0)
Genotype (where frequency > 1%)	
2,2	6 (1.1)
2,4	66 (12.1)
2,7	14 (2.6)
3,4	28 (5.1)
3,7	6 (1.1)
4,4	243 (44.5)
4,5	9 (1.6)
4,7	125 (22.9)
7,7	23 (4.2)
Other, 7	6 (1.1)
All other	20 (3.7)
Total	546 (100.0)
Characterization of genotypes by presence of the 7-repeat allele	
7-repeat present	174 (31.9)
7-repeat absent	372 (68.1)
Total	546 (100.0)

SES

Childhood SES was estimated by the two-factor Hollingshead Index (Hollingshead, unpublished manuscript, Yale University, 1975),

based on highest parental education and occupational grade. Parental education was coded over seven levels of attainment (ranging from 8th grade or less to completion of graduate or professional training), and parental occupations were coded according to the nine Hollingshead grades (from manual labor and menial service work though large-business proprietorship and high-level professions). The highest value for either parent on each indicator was used in determining childhood SES. Since parental information was available at both ages 5 and 10 years of the participants, values were averaged over these two ages. The age-mean values were then weighted according to the Hollingshead algorithm to yield the Index (HI) score, and the resulting distribution was standardized to a mean of 0.0 and standard deviation (s.d.) of 1.0.

Adulthood SES could not be estimated identically to our measure of childhood SES, as not all participants were employed and, among those who were married, we lacked occupational information on spouses. Accordingly, we indexed adulthood SES by two conventional indicators, personal educational attainment and annual (pretax) family income. Highest level of educational attainment was coded on the same scale as parental education, and income was graded over six bracketed ranges from <$25 000 to >$80 000. As in prior reports (Manuck *et al.*, 2004; Petersen *et al.*, 2008; Manuck and McCaffery, 2010), we computed a composite SES variable by averaging standardized (*z*-score) values of the two index variables for each individual. Like childhood SES, this measure was then re-standardized to a mean (s.d.) of 0.0 (1.0). Finally, because individual differences in cognitive abilities often covary with socioeconomic indicators, such as education, and are known to predict delay discounting (de Wit *et al.*, 2007; Shamosh and Gray, 2008; Bobova *et al.*, 2009), we also estimated participants' IQ using the two-subtest (matrix reasoning, vocabulary) short-form of the Wechsler Abbreviated Scale of Intelligence (WASI), which has been validated against the full-scale Wechsler Adult Scale of Intelligence-III ($r = 0.87$; PsychCorp, San Antonio, TX, USA).

Data analysis

In preliminary analyses, we examined bivariate associations, by Pearson correlation and *t*-test, between individual differences in delay discounting (normalized *k*-values) and subject characteristics (age, sex and estimated IQ), *DRD4* genotype and childhood and adulthood SES. Ordinary least squares (OLS) regression was then used to determine whether any effects of sociodemographic predictors on discounting were moderated by *DRD4* genotype (G × E), controlling for subject age and sex. Genotype was coded 1 or 0 for presence or absence, respectively, of any 7-repeat allele, and both childhood and adulthood SES were entered as standardized variables to reduce multi-collinearity between predictors and their interaction product. Where an interaction was observed between genotype and a given socioeconomic indicator (e.g. childhood SES), a further model was run controlling for correlated variation in the alternate indicator and IQ. Possible nonlinearity of association was examined by inclusion of quadratic terms in final regression models.

RESULTS

Sample characteristics

Participants averaged 45.6 ±6.5 years of age, and the sample included a nearly equal number of men ($n = 270$) and women ($n = 276$). Most were married at the time of participation (71%), and most were employed full- or part-time (79%). Estimated IQ was relatively high in the sample ($M = 117.1 \pm 10.2$), as was average years of schooling (16.1 ± 2.7). Nonetheless, participants varied appreciably in SES. Hence, level of education ranged from high school completion or less (16%) through graduate or professional training (25%). Median income fell in the $50–65 000 range, and varied from <$25 000/year (14%) to >$80 000/year (28%). Consistent with secular trends, participants reported their parents having fewer years of schooling than themselves (fathers: $M = 12.9 \pm 3.4$ years; mothers: $M = 12.6 \pm 2.7$ years). Eight percent came from families in which neither parent completed high school, while at the high end of educational attainment, 11% had at least one parent with a professional or graduate degree. Similarly, highest parental employment was limited to manual or semi-skilled labor in 14% of the subjects, while a nearly equal proportion (13%) were raised in families at the highest occupational grade (e.g. high-level professional or large business owner/proprietor).

Our index of childhood SES extended over the full range of potential HI values (8–66), and the median HI score (39) fell close to the computational mid-point of the index (37). Across subjects, the two HI components, highest parental education and occupational grade, covaried strongly ($r = 0.70$, $P < 0.0001$) and the HI score itself correlated modestly with both our composite index of adulthood SES ($r = 0.27$, $P < 0.0001$) and participants' estimated IQ ($r = 0.32$, $P < 0.0001$). The components of adulthood SES, personal educational attainment and income, covaried modestly as well ($r = 0.23$, $P < 0.0001$) and our index of adulthood SES correlated moderately with participants' estimated IQ ($r = 0.43$, $P < 0.0001$). Neither childhood nor adulthood SES varied significantly by presence/absence of the *DRD4* 7-repeat allele ($t = 0.011$, *ns* and $t = -1.84$, ns, respectively).

Predictors of delay discounting

Bivariate associations

As expected, delay discounting was modestly predicted by participants' SES both in childhood ($r = -0.23$, $P < 0.0001$) and as adults ($r = -0.26$, $P < 0.0001$), such that lower socioeconomic position on each index was associated with higher *k*-values (indicating steeper discounting). Differences in estimated IQ also correlated inversely with delay discounting ($r = -0.33$, $P < 0.0001$), whereas discounting was unrelated to age or sex (both P's > 0.10) and did not differ by main effect of *DRD4* genotype ($t = -0.565$, *ns*).

Gene × environment interactions

In a regression model testing for genotype-dependent interaction, *DRD4* variation moderated the association of childhood SES with delay discounting ($B = -0.265$, s.e. $= 0.09$, $t = 2.96$, $P = 0.003$, $r^2_{\text{partial}} = 0.016$). When tested in separate models, adulthood SES did neither predict future discounting in similar interaction with *DRD4* genotype ($B = -0.160$, s.e. $= 0.08$, $t = -1.76$, $P = 0.08$, $r^2_{\text{partial}} = 0.006$) nor did IQ ($B = -0.046$, s.e. $= 0.09$, $t = -0.55$, $P = 0.58$, $r^2_{\text{partial}} = 0.001$). The interaction of childhood SES and *DRD4* variation remained significant, moreover, when adulthood SES and IQ were included as covariates in the regression model ($B = -0.224$, s.e. $= 0.09$, $t = -2.60$, $P = 0.01$, $r^2_{\text{partial}} = 0.012$). Follow-up analyses, again controlling for both adulthood SES and IQ, showed lower HI scores (lower childhood SES) associated with steeper delay discounting among individuals carrying the 7-repeat allele ($B = -0.285$, s.e. $= 0.08$, $t = -3.83$, $P < 0.001$, $r^2_{\text{partial}} = 0.027$), but unrelated to discounting among those of alternate genotype ($B = -0.061$, s.e. $= 0.05$, $t = -1.24$, $P = 0.22$, $r^2_{\text{partial}} = 0.003$). Further, on testing for potential nonlinearity, the interaction of childhood SES and *DRD4* genotype was qualified by a significant quadratic trend ($B = 0.190$, s.e. $= 0.08$, $t = 2.34$, $P = 0.02$, $r^2_{\text{partial}} = 0.010$). Consistent with associations seen in linear interaction, here follow-up analyses showed a quadratic relationship between childhood SES and delay discounting among subjects carrying the 7-repeat allele ($B = 0.186$, s.e. $= 0.06$, $t = 2.92$, $P = 0.004$, $r^2_{\text{partial}} = 0.016$), but again, no significant association among

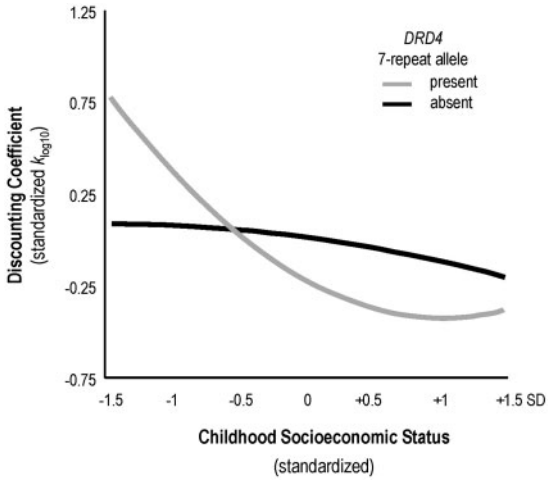

Fig. 1 Delay discounting as a function of *DRD4* genotype (presence or absence of any 7-repeat allele) and childhood SES, adjusted for age, sex, adulthood SES and IQ. The discounting coefficient is the log-normalized *k*-value derived from curve fitting of indifference points to a hyperbolic function (standardized as *z*-score); higher values denote steeper delay discounting.

individuals of other *DRD4* genotype ($B = -0.004$, s.e. $= 0.05$, $t = -0.081$, $P = 0.94$, $r^2_{\text{partial}} = 0.000$).

The quadratic interaction of childhood SES and genotype is plotted in Figure 1. We note that participants carrying the 7-repeat allele discounted future rewards more steeply than those lacking this allele if raised by parents of very low SES, but appeared to do so less steeply if raised by parents of more advantaged SES. Since regression lines shown in Figure 1 'cross over' at about 0.5 s.d. below the average childhood SES for the sample, we tested for the difference in estimated *k* coefficient between *DRD4* genotypes at −1.5 and +0.5 s.d. from the mean HI score (i.e. thus centering contrasts at ±1 s.d. from the approximate intersection of the regression lines). Results of these analyses corroborated the observed visual trend. Subjects carrying the 7-repeat allele discounted more steeply than their counterparts of alternate *DRD4* genotype in the context of very low childhood SES ($B = 0.607$, s.e. $= 0.205$, $t = 2.966$, $P = 0.003$, $r^2_{\text{partial}} = 0.016$), but exhibited comparatively shallower discounting if raised under conditions of mild socioeconomic advantage ($B = -0.296$, s.e. $= 0.118$, $t = -2.507$, $P = 0.012$, $r^2_{\text{partial}} = 0.012$).

Secondary analyses

To examine the generality of these associations, we ran parallel regression analyses on the two components of the HI, highest parental occupation and education, again controlling for age, sex, adulthood SES and IQ. The linear interaction with *DRD4* genotype was significant for both parental occupation ($B = -0.187$, s.e. $= 0.086$, $t = -2.17$, $P = 0.031$, $r^2_{\text{partial}} = 0.007$) and education ($B = -.263$, s.e. $= 0.087$, $t = -3.03$, $P = 0.003$, $r^2_{\text{partial}} = 0.017$). Adding the quadratic interaction likewise proved significant for parental occupation ($B = 0.208$, s.e. $= 0.087$, $t = 2.39$, $P = 0.017$, $r^2_{\text{partial}} = 0.011$) and approached significance for parental education ($B = 0.112$, s.e. $= 0.058$, $t = 1.93$, $P = 0.054$, $r^2_{\text{partial}} = 0.007$). Plots of the quadratic interactions were nearly identical to our composite measure of childhood SES, with the regression lines crossing over at ∼0.5 s.d. below the sample mean on each parental indicator. To aid in interpretation, scaled values under this threshold correspond to a highest parental occupation as semi-skilled laborer and a highest parental education of less than high school.

To further explore the interaction of *DRD4* variation and childhood SES on delay discounting, we dichotomized the sample by presence or absence of socioeconomic disadvantage in childhood. Here, we defined early disadvantage as having parents whose highest occupational grade did not exceed semi-skilled laborer and/or highest parental education averaged less than high school completion. The normalized *k* coefficient of discounting was then subjected to analysis of covariance (ANCOVA) with three between-subjects factors [childhood socioeconomic disadvantage (yes, no); *DRD4* genotype; sex] and covariates of age, adulthood SES and IQ. As in prior regression analyses, the ANCOVA revealed a highly significant interaction of childhood socioeconomic disadvantage and *DRD4* genotype ($F = 17.4$, $df = 1.534$, $P < 0.0001$, $\eta^2_{\text{partial}} = 0.032$). Subsequent pairwise contrasts among group means by Students' Neuman–Keuls (SNK) test (Glantz and Slinker, 2001) showed the 7-repeat allele associated with significantly steeper discounting among subjects raised in socioeconomically disadvantaged families ($P < 0.01$) and, conversely, with shallower discounting among those raised in the absence of such disadvantage ($P < 0.05$). To illustrate, Figure 2 depicts the mean discounting curves (indifference values, as a function of delay interval) among subjects partitioned by childhood socioeconomic disadvantage and *DRD4* genotype. Finally, the two-way interaction of disadvantage and genotype was not qualified by sex of participant, and in fact, sex-stratified analyses showed this interaction significant independently in both men ($F = 8.2$, $df = 1.262$, $P = 0.005$, $\eta^2_{\text{partial}} = 0.030$) and women ($F = 9.3$, $df = 1.269$, $P = 0.002$, $\eta^2_{\text{partial}} = 0.034$).

Finally, we note that the paucity of participants homozygous for the 7-repeat variant ($n = 23$) limits our ability to detect potential additive effects at this locus and that, with respect to the interaction with childhood SES, only five individuals in the group defined as disadvantaged carried two 7-repeat alleles. Nonetheless, average discounting coefficients (*z*-scores) of participants with 0, 1 and 2 7-repeat alleles suggest some additivity, with corresponding means of +0.17, +0.97 and +1.26, respectively, among individuals reared in socioeconomically disadvantaged families and, absent disadvantage, −0.02, −0.22 and −0.37. Thus, 7-repeat homozygotes showed the steepest discounting when participants were reared in adverse circumstances and the shallowest discounting otherwise. It is notable, too, that the interaction of childhood socioeconomic disadvantage and *DRD4* genotype was significant even in an ANCOVA model including just persons with 0 ($n = 372$) or 2 ($n = 23$) 7-repeat alleles ($F = 5.0$, $df = 10.387$, $P = 0.026$, $\eta^2_{\text{partial}} = 0.013$), as it was also in a model including only persons with 0 or 1 ($n = 151$) 7-repeat allele ($F = 13.7$, $df = 1.515$, $P < 0.0001$, $\eta^2_{\text{partial}} = 0.026$).

DISCUSSION

In this study, relative preference for immediate, smaller rewards over larger rewards delayed in time varied inversely with both the childhood and adulthood socioeconomic circumstances of 546 mid-life men and women. In addition, childhood (but not adulthood) SES covaried with delay discounting as a function of *DRD4* genotype. This interaction, which persisted across childhood socioeconomic indicators (composite HI, parental education and occupation) was independent of age, IQ or adulthood SES, was similar in men and women, and was qualified by significant nonlinear (quadratic) trend. Regarding the latter finding, individuals with at least one copy of the *DRD4* 7-repeat allele and raised to adolescence in families of particularly low SES (e.g. having parents who lacked high school education or did not work beyond semi-skilled or manual labor) discounted future rewards more steeply than like-reared counterparts of alternate *DRD4* genotype. And conversely, among the majority of participants with a more socioeconomically advantaged upbringing, those having any 7-repeat allele discounted future rewards *less* steeply. As illustrated in the discounting curves plotted in Figure 2, for instance, subjects from

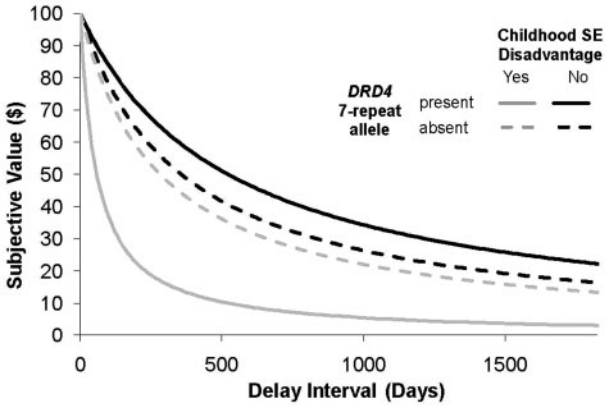

Fig. 2 Hyperbolic discounting curves for subject groups differing by *DRD4* genotype (7-repeat allele present, absent) and by exposure (yes, no) to an early family environment of socioeconomic disadvantage. Functions were fitted to median indifference values across seven delay intervals for each group.

socioeconomically disadvantaged families who carried the 7-repeat allele were willing, on average, to exchange a deferred $100 reward, whatever the interval of delay, for an immediate reward of far less value than would persons of similar rearing environment but different *DRD4* genotype. Among individuals raised in the absence of socioeconomic disadvantage, in contrast, future discounting was less steep overall and least pronounced in participants carrying the 7-repeat allele.

This bidirectional genetic association, moderated by childhood SES, supports predictions from differential susceptibility, a form of G × E described recently by several developmental psychologists (Belsky and Pluess, 2009; Bakermans-Kranenburg and van Ijzendoorn, 2011; Ellis *et al.*, 2011). Differential susceptibility posits variability in individuals' sensitivity, or responsiveness, to environmental influences, whether positive or negative. These theorists argue that much G × E research may be misinterpreted through adherence to a dominant model of illness or trait vulnerability that assumes ordinal interactions between genetic variation and environmental adversities (diathesis–stress). Noting that this default representation of G × E neglects the potential genetic modulation of beneficial effects of salubrious environments, it is suggested that genotypes promoting negative outcomes under adversity might also potentiate positive outcomes in favorable circumstances if environmental exposures were indexed over a sufficiently broad range of unfavorable-to-favorable exposures.

In practice, differential susceptibility is said to exist when regression lines reflecting associations between a phenotype and an environmental factor intersect (i.e. 'cross over') when plotted for different variants of a susceptibility marker (polymorphism; Manuck, 2010). In such instances, the line of greater slope (plasticity) predicts both higher and lower phenotype values at opposing ends of an environmental gradient, compared to the line of shallower slope (lesser plasticity). Since few have tested this model explicitly, evidence for differential susceptibility remains indefinite. Nonetheless, some genotypes associated with negative outcomes in adverse circumstances have elsewhere been related to positive outcomes in good environments, identifying these genotypes as candidate markers of differential susceptibility. For instance, developmental studies of common dopamine (DA)-regulating gene polymorphisms and their interactions with environmental factors, both positive and negative, were recently examined in meta-analysis by Bakermans-Kranenburg and van Ijzendoorn (2011). Here, putative susceptibility alleles were associated with positive outcomes among studies involving supportive environments and with adverse outcomes in studies of unsupportive environments, with near-equal effect size. Moreover, most of these studies examined the same *DRD4* variation studied here, with the 7-repeat allele predicting fewer externalizing problems and more prosocial behavior in conjunction with supportive parental attributes or interventions and, conversely, with more externalizing problems and early attachment difficulties in association with negative parenting environments.

We believe the present findings offer the most direct evidence of differential susceptibility, as related to the *DRD4* exon 3 VNTR. Here, in the same study sample and along the same environmental gradient (childhood SES), presence of the 7-repeat allele predicted steeper delay discounting against backgrounds of socioeconomic disadvantage and shallower discounting in the absence of such disadvantage. It is noteworthy, too, that the interaction of *DRD4* genotype with early family circumstances predicted this behavioral phenotype even when measured in adulthood, and then also, net correlated variation in adulthood SES, which is itself a robust predictor of discounting. This suggests an instance of differential susceptibility that is both rooted in childhood and consistent with developmental literature concerning interactions of *DRD4* variation and early parenting environments on children's externalizing problems—behaviors likewise associated with problems of impulse control and preference for immediate over delayed rewards (Scheres *et al.*, 2006; Bobova *et al.*, 2009; Scheres *et al.*, 2010). There is also precedent in this literature for the nonlinear association we observed between genotype and childhood SES. Hence, Nobile *et al.* (2007) reported preadolescent aggressive behavior predicted by an interaction *DRD4* genotype and parental occupation, with occupational grade similarly indexed on the Hollingshead scale and dichotomized (low *vs* intermediate/high) at the same occupational threshold suggested by our findings. Interestingly, behavioral correlates of the *DRD4* VNTR may interact not only with environmental factors (G × E), but with other sources of genetic variation as well (i.e. gene × gene interaction, or epistasis). Thus, Nobile *et al.* (2007) also found *DRD4* genotype associated with child externalizing behaviors in interaction with regulatory variation in the serotonin transporter, and in a prior study of delay discounting among college students, *DRD4* genotypes containing any long (principally 7-repeat) allele predicted steeper discounting on interaction with a second DA polymorphism (*DRD2* Taq1 A; Eisenberg *et al.*, 2007).

How might carrying the 7-repeat allele augment preference for immediate rewards against a background of socioeconomic disadvantage, yet otherwise favor shallower discounting? Any answer to this question is speculative at present, but would likely entail environmental and genetic effects on neural components of reward processing and self-regulation. The canonical circuitry of reward-based decision-making encompasses both striatal regions of the basal ganglia and networked prefrontal structures, including dorsal, lateral, medial, anterior cingulate, and inferior parietal cortices, as well modulatory DA-releasing neurons projecting from the midbrain ventral tegmental area. By one model of intertemporal choice, delay discounting is supported by functional interactions between striatal and prefrontal regions, in which activation of the nucleus accumbens (and of the ventral striatum broadly) abets sensitivity to immediate reward, while the various prefrontal regions mediate deliberative or reflective processes supporting the formulation of more distant aims, as by computing reward probabilities, maintaining reward-related information in working memory, representing future goals, and, via pathways of corticostriatal connectivity, effecting executive control of reward-dependent behaviors (McClure *et al.*, 2004; Carter *et al.*, 2010). Experimental evidence suggests that striatal and prefrontal regions are differentially engaged when individuals select rewards of varying value and delay (smaller/immediate or larger/delayed rewards)

in tests of intertemporal choice (McClure *et al.*, 2004; Carter *et al.*, 2010 for a review) and that individual differences in delay discounting covary with the magnitude of activation elicited in these regions by cues signaling monetary gain (Hariri *et al.*, 2006).

Two related observations may bear specifically on the interpretation of the present findings. First, Gianaros and colleagues recently reported that midlife adults who were raised in families of lower SES than others, as indicated by lower parental education, showed reduced activation and connectivity among prefrontal regions implicated in self-regulation and impulse control, as well as reduced effective, or directional (top-down), connectivity between dorsomedial prefrontal cortex and the ventral striatum in response to reward-related stimuli (Gianaros *et al.*, 2010). Since these findings were not accounted for by adulthood SES or other potential confounders, they conceivably reflect developmental influences on the corticostriatal circuitry of reward processing arising from early socioeconomic circumstances, with potential long-term consequences for self-regulatory capacity and tolerance for delayed gratification. Also noteworthy in this context, the prefrontal brain systems that process rewards and support reward-based decision-making undergo a prolonged and vulnerable developmental trajectory, and an impaired capacity of these prefrontal systems to regulate subcortical structures (particularly striatal regions of the basal ganglia) is implicated in risky, impulsive and otherwise disadvantageous decision-making from childhood through later life (for review, Fareri *et al.*, 2008). Hence, speculatively, perhaps certain proximal correlates of rearing in advantaged socioeconomic environments (e.g. more frequent and consistent exposure to supportive parenting practices and parent–child interactions; more frequent home and school exposures to adult modeling of adaptive decision-making) favorably influence—and in their absence, impede—the assembly and long-term functionality of brain systems supporting top-down or regulatory control functions that, in turn, bias individuals toward less impulsive decision-making (Hackman and Farah, 2009; Hackman *et al.*, 2010).

The second observation bearing on interpretation of the present findings is that individuals with the *DRD4* 7-repeat allele exhibit greater activation of the ventral striatum in response to reward-related stimuli than subjects lacking this allele (Forbes *et al.*, 2009). With respect to the present study, a heightened responsivity of the ventral striatum in persons carrying the 7-repeat allele would be consistent with a stronger preference for immediate over delayed rewards (steeper discounting), and this effect might be potentiated, or perhaps only seen, when accompanied by diminished prefrontal inhibitory control, as demonstrated by Gianaros *et al.* (2010) in connection with low parental education.

Conversely, the more strongly networked prefrontal areas involved in goal setting, reward valuation, and other executive processes seen in association with higher parental education, along with enhanced top-down connectivity between prefrontal cortex and ventral striatum, might conduce to a longer 'time horizon' and less inclination to discount future rewards (Gianaros *et al.*, 2010). It is less clear why, in this context, the 7-repeat allele of the *DRD4* polymorphism would actually predict shallower discounting, as we observed. Conceivably, the attenuated D4-receptor binding efficiency conferred by the 7-repeat allele might pleiotropically *enhance* some cognitive control processes in ways that diminish future discounting. If so, such an outcome might be detected more readily when opposing effects of the same genotype on sensitivity to immediate rewards is constrained, as through the more robust connectivity between prefrontal and striatal regions that Gianaros *et al.* (2010) observed in relation to higher childhood SES. As noted previously, there is some, albeit mixed, evidence that among children with ADHD, presence of the 7-repeat allele predicts better neurocognitive functioning (e.g. on tests of attention or executive processing), even though the 7-repeat allele also contributes to risk for ADHD (e.g. Swanson *et al.*, 2000b; Manor *et al.*, 2002; Bellgrove *et al.*, 2005; Johnson *et al.*, 2008; Kebir *et al.*, 2009). Genotypes containing the same allele have been found associated with greater response inhibition in a nonpatient, college population as well (Kramer *et al.*, 2009). Such findings might be explained by the inhibitory actions of the D4 receptor on glutamatergic efferents from the prefrontal cortex (Asghari *et al.*, 1995), such that attenuation of these effects by the 7-repeat allele may occasion improved top-down cortical signaling. In this regard, animal studies have shown improved performance on working memory and set-shifting tasks resulting from antagonism of the prefrontal D4 receptor (Zhang *et al.*, 2004; Floresco *et al.*, 2006), and mice lacking the D4 receptor show superior reward learning, compared to wild-type mice, under some experimental conditions (Nemirovsky *et al.*, 2009). In sum, we speculate that the *DRD4* 7-repeat allele may be associated with both a heightened responsivity to immediate rewards *and* better prefrontal regulatory control. Moreover, the extent to which either of these effects modulates delay discounting in humans may vary with differences in integrated corticostriatal functionality, differences that may arise developmentally and in relation to the presence or absence of early life socioeconomic (or associated) adversities.

Whatever mechanisms underlie the present findings, it may be asked whether our observations represent a true interaction of genetic and environmental factors. Although socioeconomic position is often treated as a sentinel index of the environment, biometric analyses show components of SES (education, income) both substantially heritable and correlated with IQ, with much of the correlated variation in socioeconomic indicators and cognitive ability accounted for by shared genetic effects (Rowe *et al.*, 1999). To the extent that parental social standing may partly reflect genetic influences that are transmissible to offspring—possibly via genetic contribution to the covariation of childhood SES and IQ—some portion of the interaction seen here between *DRD4* genotype and childhood socioeconomic circumstance could conceivably entail interaction with other genes (epistasis), rather than strictly environmental factors. It is noteworthy, however, that statistical adjustment for both IQ and correlated differences in adult SES did not mitigate interacting genetic and childhood socioeconomic effects on delay discounting. Nonetheless, should there exist in this sample any other heritable, but unmeasured, correlate of parental social standing (also shared by parents and offspring), our index of childhood SES would merit at least a partly genetic interpretation (Lichtenstein and Pedersen, 1997). Where genetic and nongenetic influences on putative environmental measurements cannot be partitioned by study design (as may be achieved in certain twin and adoption studies), therefore, inferring $G \times E$ remains somewhat ambiguous (Uher and McGuffin, 2008; Manuck and McCaffery, 2010).

Finally, we acknowledge several methodological and interpretive limitations of this study. First, in a developmental context, our cross-sectional data are less informative than longitudinal observations would prove, and our reliance on self-reported childhood SES (though indexed to objective markers of parental education and occupation) may be less reliable than contemporaneous family measurements. This study is also limited by assessment of delay discounting on a single occasion. In addition to imperfect retest reliability, known situational influences on discounting include transient variations in mood, motivational states and blood glucose levels (Wilson and Daly, 2004; Hirsh *et al.*, 2010; Wang and Dvorak, 2010;). Our findings are restricted as well to observations on non-Hispanic Caucasian men and women examined in midlife, so that their generalizability to other populations and age cohorts remains unknown. These considerations suggest directions for future research, including prospective studies

extending from early life, repeated assessment of discounting and other measures of impulsive decision-making, and broader participant sampling. At present, though, we believe our findings afford initial evidence that childhood socioeconomic disadvantage and its absence moderate effects of *DRD4* genotype on temporal discounting and do so in a manner consistent with the G × E model of differential susceptibility.

Conflict of Interest

None declared.

REFERENCES

Alessi, S.M., Petry, N.M. (2003). Pathological gambling severity is associated with impulsivity in a delay discounting procedure. *Behavioural Processes*, *64*(3), 345–54.

Anokhin, A.P., Golosheykin, S., Grant, J.D., Heath, A.C. (2010). Heritability of delay discounting in adolescence: a longitudinal twin study. *Behavior Genetics*, *41*(2), 175–83.

Asghari, V., Sanyal, S., Buchwaldt, S., et al. (1995). Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. *Journal of Neurochemistry*, *65*(3), 1157–65.

Audrain-McGovern, J., Rodriguez, D., Epstein, et al. (2009). Does delay discounting play an etiological role in smoking or is it a consequence of smoking? *Drug and Alcohol Dependence*, *103*(3), 99–106.

Bakermans-Kranenburg, M.J., van Ijzendoorn, M.H. (2006). Gene-environment interaction of the dopamine D4 receptor (DRD4) and observed maternal insensitivity predicting externalizing behavior in preschoolers. *Developmental Psychobiology*, *48*(5), 406–9.

Bakermans-Kranenburg, M.J., van Ijzendoorn, M.H. (2011). Differential susceptibility to rearing environment depending on dopamine-related genes: new evidence and a meta-analysis. *Developmental Psychopathology*, *23*(1), 39–52.

Bakermans-Kranenburg, M.J., van Ijzendoorn, M.H., Pijlman, F.T., Mesman, J., Juffer, F. (2008). Experimental evidence for differential susceptibility: dopamine D4 receptor polymorphism (DRD4 VNTR) moderates intervention effects on toddlers' externalizing behavior in a randomized controlled trial. *Developmental Psychology*, *44*(1), 293–300.

Barkley, R.A., Smith, K.M., Fischer, M., Navia, B. (2006). An examination of the behavioral and neuropsychological correlates of three ADHD candidate gene polymorphisms (DRD4 7+, DBH TaqI A2, and DAT1 40 bp VNTR) in hyperactive and normal children followed to adulthood. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *141B*(5), 487–98.

Beck, R.C., Triplett, M.F. (2009). Test-retest reliability of a group-administered paper-pencil measure of delay discounting. *Experimental and Clinical Psychopharmacology*, *17*(5), 345–55.

Bellgrove, M.A., Hawi, Z., Lowe, N., et al. (2005). DRD4 gene variants and sustained attention in attention deficit hyperactivity disorder (ADHD): effects of associated alleles at the VNTR and -521 SNP. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *136B*(1), 81–6.

Belsky, J., Jonassaint, C., Pluess, , et al. (2009). Vulnerability genes or plasticity genes? *Molecular Psychiatry*, *14*(8), 746–54.

Belsky, J., Pluess, M. (2009). Beyond diathesis stress: differential susceptibility to environmental influences. *Psychological Bulletin*, *135*(6), 885–908.

Benjamin, J., Li, L., Patterson, C., et al. (1996). Population and familial association between the D4 dopamine receptor gene and measures of Novelty Seeking. *Nature Genetics*, *12*(1), 81–4.

Bickel, W.K., Odum, A.L., Madden, G.J. (1999). Impulsivity and cigarette smoking: delay discounting in current, never, and ex-smokers. *Psychopharmacology*, *146*(4), 447–54.

Bleil, M.E., Gianaros, P.J., Jennings, J.R., Flory, J.D., Manuck, S.B. (2008). Trait negative affect: toward an integrated model of understanding psychological risk for impairment in cardiac autonomic function. *Psychosomatic Medicine*, *70*(3), 328–37.

Bobova, L., Finn, P.R., Rickert, M.E., Lucas, J. (2009). Disinhibitory psychopathology and delay discounting in alcohol dependence: personality and cognitive correlates. *Experimental and Clinical Psychopharmacology*, *17*(1), 51–61.

Boyce, W.T., Ellis, B.J. (2005). Biological sensitivity to context: I. An evolutionary-developmental theory of the origins and functions of stress reactivity. *Development and Psychopathology*, *17*(2), 271–301.

Carter, R.M., Meyer, J.R., Huettel, S.A. (2010). Functional neuroimaging of intertemporal choice models: a review. *Journal of Neuroscience, Psychology, and Economics*, *3*(1), 27–45.

Cloninger, C.R. (1987). A systematic method for clinical description and classification of personality variants. A proposal. *Archives of General Psychiatry*, *44*(6), 573–588.

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*(1), 18–25.

Comings, D.E., Gade-Andavolu, R., Gonzalez, N., et al. (2001). The additive effect of neurotransmitter genes in pathological gambling. *Clinical Genetics*, *60*(2), 107–16.

Congdon, E., Lesch, K.P., Canli, T. (2008). Analysis of DRD4 and DAT polymorphisms and behavioral inhibition in healthy adults: implications for impulsivity. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *147B*(1), 27–32.

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*, 111–21.

Dreber, A., Apicella, C.L., Eisenberg, D.T., et al. (2009). The 7R polymorphism in the dopamine receptor D4 gene (DRD4) is associated with financial risk taking in men. *Evolution and Human Behavior*, *30*(2), 85–92.

Ebstein, R.P., Novick, O., Umansky, R., et al. (1996). Dopamine D4 receptor (D4DR) exon III polymorphism associated with the human personality trait of Novelty Seeking. *Nature Genetics*, *12*(1), 78–80.

Eisenberg, D.T., Mackillop, J., Modi, M., et al. (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.

Eisenegger, C., Knoch, D., Ebstein, R.P., et al. (2010). Dopamine receptor D4 polymorphism predicts the effect of L-DOPA on gambling behavior. *Biological Psychiatry*, *67*(8), 702–6.

Ellis, B.J., Boyce, W.T., Belsky, J., Bakermans-Kranenburg, M.J., van Ijzendoorn, M.H. (2011). Differential susceptibility to the environment: an evolutionary: neurodevelopmental theory. *Development and Psychopathology*, *23*(1), 7–28.

Falush, D., Stephens, M., Pritchard, J.K. (2003). Inference of population structure using multilocus genotype data: linked loci and correlated allele frequencies. *Genetics*, *164*(4), 1567–87.

Faraone, S.V., Doyle, A.E., Mick, E., Biederman, J. (2001). Meta-analysis of the association between the 7-repeat allele of the dopamine D(4) receptor gene and attention deficit hyperactivity disorder. *American Journal of Psychiatry*, *158*(7), 1052–1057.

Fareri, D.S., Martin, L.N., Delgado, M.R. (2008). Reward-related processing in the human brain: developmental considerations. *Development and Psychopathology*, *20*(4), 1191–211.

Floresco, S.B., Magyar, O., Ghods-Sharifi, S., Vexelman, C., Tse, M.T. (2006). Multiple dopamine receptor subtypes in the medial prefrontal cortex of the rat regulate set-shifting. *Neuropsychopharmacology*, *31*(2), 297–309.

Forbes, E.E., Brown, S.M., Kimak, M., Ferrell, R.E., Manuck, S.B., Hariri, A.R. (2009). Genetic variation in components of dopamine neurotransmission impacts ventral striatal reactivity associated with impulsivity. *Molecular Psychiatry*, *14*(1), 60–70.

Gianaros, P.J., Manuck, S.B., Sheu, L.K., et al. (2010). Parental education predicts corticostriatal functionality in adulthood. *Cerebral Cortex*, *21*(4), 896–910.

Gizer, I.R., Ficks, C., Waldman, I.D. (2009). Candidate gene studies of ADHD: a meta-analytic review. *Human Genetics*, *126*(1), 51–90.

Glantz, S.A., Slinker, B.K. (2001). *Primer of Applied Regression and Analysis of Variance*. New York: McGraw-Hill.

Green, A.E., Fry, A., Myerson, J. (1994). Discounting of delayed rewards: a lifespan comparison. *Psychological Science*, *5*(1), 33–6.

Green, L., Myerson, J. (2004). A discounting framework for choice with delayed and probabilistic rewards. *Psychological Bulletin*, *130*(5), 769–92.

Green, L., Myerson, J., Lichtman, D., Rosen, S., Fry, A. (1996). Temporal discounting in choice between delayed rewards: the role of age and income. *Psychology and Aging*, *11*(1), 79–84.

Hackman, D.A., Farah, M.J. (2009). Socioeconomic status and the developing brain. *Trends in Cognitive Sciences*, *13*(2), 65–73.

Hackman, D.A., Farah, M.J., Meaney, M.J. (2010). Socioeconomic status and the brain: mechanistic insights from human and animal research. *Nature Reviews Neuroscience*, *11*(9), 651–9.

Halder, I., Marsland, A.L., Cheong, J., et al. (2010). Polymorphisms in the CRP gene moderate an association between depressive symptoms and circulating levels of C-reactive protein. *Brain, Behavior, and Immunity*, *24*(1), 160–7.

Halder, I., Muldoon, M.F., Ferrell, R.E., Manuck, S.B. (2007). Serotonin receptor 2A (HTR2A) gene polymorphisms are associated with blood pressure, central adiposity, and the metabolic syndrome. *Metabolic Syndrome and Related Disorders*, *5*(4), 323–30.

Halder, I., Yang, B.Z., Kranzler, H.R., et al. (2009). Measurement of admixture proportions and description of admixture structure in different U.S. populations. *Human Mutatation*, *30*(9), 1299–309.

Hariri, A.R., Brown, S.M., Williamson, D.E., et al. (2006). Preference for immediate over delayed rewards is associated with magnitude of ventral striatal activity. *Journal of Neuroscience*, *26*(51), 13213–7.

Hirsh, J.B., Guindon, A., Morisano, D., Peterson, J.B. (2010). Positive mood effects on delay discounting. *Emotion*, *10*(5), 717–21.

Hutchison, K.E., LaChance, H., Niaura, R., Bryan, A., Smolen, A. (2002). The DRD4 VNTR polymorphism influences reactivity to smoking cues. *Journal of Abnormal Psychology*, *111*(1), 134–43.

Johnson, K.A., Kelly, S.P., Robertson, I.H., et al. (2008). Absence of the 7-repeat variant of the DRD4 VNTR is associated with drifting sustained attention in children with ADHD but not in controls. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *147B*(6), 927–37.

Kebir, O., Tabbane, K., Sengupta, S., Joober, R. (2009). Candidate genes and neuropsychological phenotypes in children with ADHD: review of association studies. *Journal of Psychiatry and Neuroscience*, *34*(2), 88–101.

Keltikangas-Jarvinen, L., Raikkonen, K., Ekelund, J., Peltonen, L. (2004). Nature and nurture in novelty seeking. *Molecular Psychiatry*, *9*(3), 308–11.

Kieling, C., Roman, T., Doyle, A.E., Hutz, M.H., Rohde, L.A. (2006). Association between DRD4 gene and performance of children with ADHD in a test of sustained attention. *Biological Psychiatry*, *60*(10), 1163–5.

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*(1), 78–87.

Kluger, A.N., Siegfried, Z., Ebstein, R.P. (2002). A meta-analysis of the association between DRD4 polymorphism and novelty seeking. *Molecular Psychiatry*, *7*(7), 712–17.

Knafo, A. (2009). Prosocial development: The intertwined roles of children's genetics and their parental environment. *Biennial Meeting of the Society for Research in Child Development*. Denver, CO.

Knafo, A., Israel, S., Ebstein, R.P. (2011). Heritability of children's prosocial behavior and differential susceptibility to parenting by variation in the dopamine receptor D4 gene. *Development and Psychopathology*, *23*(1), 53–67.

Kollins, S.H. (2003). Delay discounting is associated with substance use in college students. *Addictive Behaviors*, *28*(6), 1167–73.

Kramer, U.M., Rojo, N., Schule, R., et al. (2009). ADHD candidate gene (DRD4 exon III) affects inhibitory control in a healthy sample. *BMC Neuroscience*, *10*, 150.

Krueger, R.F., Caspi, A., Moffitt, T.E., White, J., Stouthamer-Loeber, M. (1996). Delay of gratification, psychopathology, and personality: is low self-control specific to externalizing problems? *Journal of Personality*, *64*(1), 107–129.

Kuhnen, C.M., Chiao, J.Y. (2009). Genetic determinants of financial risk taking. *Public Library of Science One*, *4*(2), e4362.

Laucht, M., Becker, K., Blomeyer, D., Schmidt, M.H. (2007). Novelty seeking involved in mediating the association between the dopamine D4 receptor gene exon III polymorphism and heavy drinking in male adolescents: results from a high-risk community sample. *Biological Psychiatry*, *61*(1), 87–92.

Laucht, M., Becker, K., El-Faddagh, M., Hohm, E., Schmidt, M.H. (2005). Association of the DRD4 exon III polymorphism with smoking in fifteen-year-olds: a mediating role for novelty seeking? *Journal of the American Academy of Child & Adolescent Psychiatry*, *44*(5), 477–84.

Le Foll, B., Gallo, A., Le Strat, Y., Lu, L., Gorwood, P. (2009). Genetics of dopamine receptors and drug addiction: a comprehensive review. *Behavioural Pharmacology*, *20*(1), 1–17.

Li, D., Sham, P.C., Owen, M.J., He, L. (2006). Meta-analysis shows significant association between dopamine system genes and attention deficit hyperactivity disorder (ADHD). *Human Molecular Genetics*, *15*(14), 2276–84.

Lichtenstein, P., Pedersen, N.L. (1997). Does genetic variance for cognitive abilities account for genetic variance in educational achievement and occupational status? A study of twins reared apart and twins reared together. *Society of Biology*, *44*(1–2), 77–90.

Lichter, J.B., Barr, C.L., Kennedy, J.L., et al. (1993). A hypervariable segment in the human dopamine receptor D4 (DRD4) gene. *Human Molecular Genetics*, *2*(6), 767–73.

Manor, I., Tyano, S., Eisenberg, J., et al. (2002). The short DRD4 repeats confer risk to attention deficit hyperactivity disorder in a family-based design and impair performance on a continuous performance test (TOVA). *Molecular Psychiatry*, *7*(7), 790–4.

Manuck, S.B. (2010). The reaction norm in gene x environment interaction. *Molecular Psychiatry*, *15*(9), 881–2.

Manuck, S.B., Craig, A.E., Flory, J.D., Halder, I., Ferrell, R.E. (2011). Reported early family environment covaries with menarcheal age as a function of polymorphic variation in estrogen receptor-alpha. *Development and Psychopathology*, *23*(1), 69–83.

Manuck, S.B., Flory, J.D., Ferrell, R.E., Muldoon, M.F. (2004). Socio-economic status covaries with central nervous system serotonergic responsivity as a function of allelic variation in the serotonin transporter gene-linked polymorphic region. *Psychoneuroendocrinology*, *29*(5), 651–68.

Manuck, S.B., Flory, J.D., Muldoon, M.F., Ferrell, R.E. (2003). A neurobiology of intertemporal choice. In: Loewenstein, G., Read, D., Baumeister, R.F., editors. *Time and Decision: Economic and Psychological Perspectives on Intertemporal Choice*. New York: Russell Sage Foundation, pp. 139–72.

Manuck, S.B., McCaffery, J.M. (2010). Genetics of stress: Gene-stress correlation and interaction. In: Septoe, A., editor. *Handbook of Behavioral Medicine*. New York: Springer, pp. 455–78.

Manuck, S.B., Phillips, J.E., Gianaros, P.J., Flory, J.D., Muldoon, M.F. (2010). Subjective socioeconomic status and presence of the metabolic syndrome in midlife community volunteers. *Psychosomatic Medicine*, *72*(1), 35–45.

Mazur, J.E. (1987). An adjusting procedure for studying delayed reinforcement. In: Commons, M.L., Mazur, J.E., Nevin, J.A., Rachlin, H., editors. *Quantitative Analysis of Behavior: The Effect of Delay and of Intervening Events on Reinforcement Value*, Vol. 5, Hillsdale, NJ: Erlbaum, pp. 55–73.

McClure, S.M., Laibson, D.I., Loewenstein, G., Cohen, J.D. (2004). Separate neural systems value immediate and delayed monetary rewards. *Science*, *306*(5695), 503–7.

Mitchell, S.H. (1999). Measures of impulsivity in cigarette smokers and non-smokers. *Psychopharmacology*, *146*(4), 455–64.

Munafo, M.R., Yalcin, B., Willis-Owen, S.A., Flint, J. (2008). Association of the dopamine D4 receptor (DRD4) gene and approach-related personality traits: meta-analysis and new data. *Biological Psychiatry*, *63*(2), 197–206.

Myerson, J., Green, L. (1995). Discounting of delayed rewards: Models of individual choice. *Journal of the Experimental Analysis of Behavior*, *64*(3), 263–76.

Nemirovsky, S.I., Avale, M.E., Brunner, D., Rubinstein, M. (2009). Reward-seeking and discrimination deficits displayed by hypodopaminergic mice are prevented in mice lacking dopamine D4 receptors. *Synapse*, *63*(11), 991–7.

Nikolaidis, A., Gray, J.R. (2010). ADHD and the DRD4 exon III 7-repeat polymorphism: an international meta-analysis. *Social Cognitive and Affective Neuroscience*, *5*(2–3), 188–93.

Nobile, M., Giorda, R., Marino, C., et al. (2007). Socioeconomic status mediates the genetic contribution of the dopamine receptor D4 and serotonin transporter linked promoter region repeat polymorphisms to externalization in preadolescence. *Development and Psychopathology*, *19*(4), 1147–60.

Oak, J.N., Oldenhof, J., Van Tol, H.H. (2000). The dopamine D(4) receptor: one decade of research. *European Jounal of Pharmacology*, *405*(1–3), 303–327.

Ohmura, Y., Takahashi, T., Kitamura, N. (2005). Discounting delayed and probabilistic monetary gains and losses by smokers of cigarettes. *Psychopharmacology*, *182*(4), 508–15.

Perez de Castro, I., Ibanez, A., Torres, P., Saiz-Ruiz, J., Fernandez-Piqueras, J. (1997). Genetic association study between pathological gambling and a functional DNA polymorphism at the D4 receptor gene. *Pharmacogenetics*, *7*(5), 345–8.

Petersen, K.L., Marsland, A.L., Flory, J., et al. (2008). Community socioeconomic status is associated with circulating interleukin-6 and C-reactive protein. *Psychosomatic Medicine*, *70*(6), 646–652.

Petry, N.M. (2002). Discounting of delayed rewards in substance abusers: relationship to antisocial personality disorder. *Psychopharmacology*, *162*(4), 425–32.

Pritchard, J.K., Stephens, M., Donnelly, P. (2000). Inference of population structure using multilocus genotype data. *Genetics*, *155*(2), 945–59.

Reynolds, B. (2006). A review of delay-discounting research with humans: relations to drug use and gambling. *Behavioural Pharmacology*, *17*(8), 651–67.

Reynolds, B., Richards, J.B., Horn, K., Karraker, K. (2004). Delay discounting and probability discounting as related to cigarette smoking status in adults. *Behavioural Processes*, *65*(1), 35–42.

Richards, J.B., Zhang, L., Mitchell, S.H., de Wit, H. (1999). Delay or probability discounting in a model of impulsive behavior: effect of alcohol. *Journal of the Experimental Analysis of Behavior*, *71*(2), 121–43.

Rowe, D.C., Vesterdal, W.J., Rodgers, J.L. (1999). Herrnstein's syllogism: genetic and shared environmental influences on IQ, education, and income. *Intelligence*, *26*, 405–23.

Scheres, A., Dijkstra, M., Ainslie, E., et al. (2006). Temporal and probabilistic discounting of rewards in children and adolescents: effects of age and ADHD symptoms. *Neuropsychologia*, *44*(11), 2092–103.

Scheres, A., Tontsch, C., Thoeny, A.L., Kaczkurkin, A. (2010). Temporal reward discounting in attention-deficit/hyperactivity disorder: the contribution of symptom domains, reward magnitude, and session length. *Biological Psychiatry*, *67*(7), 641–8.

Schinka, J.A., Letsch, E.A., Crawford, F.C. (2002). DRD4 and novelty seeking: results of meta-analyses. *American Journal of Medical Geneics*, *114*(6), 643–8.

Schoots, O., Van Tol, H.H. (2003). The human dopamine D4 receptor repeat sequences modulate expression. *The Pharmacogenomics Journal*, *3*(6), 343–8.

Shamosh, N.A., Gray, J.R. (2008). Delay discounting and intelligence: a meta-analysis. *Intelligence*, *36*(4), 289–305.

Sheese, B.E., Voelker, P.M., Rothbart, M.K., Posner, M.I. (2007). Parenting quality interacts with genetic variation in dopamine receptor D4 to influence temperament in early childhood. *Development and Psychopathology*, *19*(4), 1039–46.

Swanson, J., Oosterlaan, J., Murias, M., et al. (2000a). Attention deficit/hyperactivity disorder children with a 7-repeat allele of the dopamine receptor D4 gene have extreme behavior but normal performance on critical neuropsychological tests of attention. *Proceedings of the National Academy of Sciences USA*, *97*(9), 4754–9.

Swanson, J.M., Flodman, P., Kennedy, J., et al. (2000b). Dopamine genes and ADHD. *Neuroscience and Biobehavioral Reviews*, *24*(1), 21–5.

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 and Tobacco Research*, *10*(10), 1571–5.

Uher, R., McGuffin, P. (2008). The moderation by the serotonin transporter gene of environmental adversity in the aetiology of mental illness: review and methodological analysis. *Molecular Psychiatry*, *13*(2), 131–46.

van den Wildenberg, E., Janssen, R.G., Hutchison, K.E., van Breukelen, G.J., Wiers, R.W. (2007). Polymorphisms of the dopamine D4 receptor gene (DRD4 VNTR) and

cannabinoid CB1 receptor gene (CNR1) are not strongly related to cue-reactivity after alcohol exposure. *Addiction Biology*, *12*(2), 210–20.

van Ijzendoorn, M.H., Bakermans-Kranenburg, M.J. (2006). DRD4 7-repeat polymorphism moderates the association between maternal unresolved loss or trauma and infant disorganization. *Attachment and Human Development*, *8*(4), 291–307.

Waldman, I.D. (2005). Statistical approaches to complex phenotypes: evaluating neuropsychological endophenotypes for attention-deficit/hyperactivity disorder. *Biological Psychiatry*, *57*(11), 1347–56.

Wang, E., Ding, Y.C., Flodman, P., et al. (2004). The genetic architecture of selection at the human dopamine receptor D4 (DRD4) gene locus. *The American Journal of Human Genetics*, *74*(5), 931–44.

Wang, X.T., Dvorak, R.D. (2010). Sweet future: fluctuating blood glucose levels affect future discounting. *Psychological Science*, *21*(2), 183–8.

Wilson, M., Daly, M. (2004). Do pretty women inspire men to discount the future? *Proceedings of the Royal Society B: Biological Sciences*, *271*(Suppl. 4), S177–9.

Wulfert, E., Block, J.A., Santa Ana, E., Rodriguez, M.L., Colsman, M. (2002). Delay of gratification: impulsive choices and problem behaviors in early and late adolescence. *Journal of Personality*, *70*(4), 533–52.

Zhang, K., Grady, C.J., Tsapakis, E.M., et al. (2004). Regulation of working memory by dopamine D4 receptor in rats. *Neuropsychopharmacology*, *29*(9), 1648–55.