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 adenyl 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).

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 (Keber 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; Munafò 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 x environment interaction (G x E), in which genetic vulnerabilities are thought to occasion negative outcomes (e.g. psychological pathology) mainly in individuals who are also disadvantaged by adverse circumstance (Manuck, 2010; Manuck and McCaffery, 2010). Another form of ordinal G x 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 disorderly 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 (Boyle and Ellis, 2005; Belsky and Fluess, 2009). Whether ‘differential susceptibility’ defines a common form of G x 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 (Bovba 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 Tripplett, 2009) and is both heritable (h²≈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 x 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 (Genta Systems, Minneapolis, MN, USA). The DRD4 exon 3 VNTR was genotyped by polymerase chain reaction amplification using the primers F-5’-GCGACTAGTGTTCACTCG-3’ and R-5’-AGGACCTCATGGCGCTTG-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, 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 (\(< 2.3 \times 10^{-4}\)). 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 for each delay interval were presented in randomized order, and immediate rewards were presented in randomized order, and in 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

<table>
<thead>
<tr>
<th>Allele</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>2</td>
<td>100 (9.2)</td>
</tr>
<tr>
<td>3</td>
<td>42 (3.9)</td>
</tr>
<tr>
<td>4</td>
<td>723 (66.2)</td>
</tr>
<tr>
<td>5</td>
<td>12 (1.1)</td>
</tr>
<tr>
<td>6</td>
<td>7 (0.6)</td>
</tr>
<tr>
<td>7</td>
<td>197 (18.0)</td>
</tr>
<tr>
<td>8</td>
<td>9 (0.8)</td>
</tr>
<tr>
<td>10</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Total</td>
<td>1092 (100.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genotype (where frequency &gt; 1%)</th>
<th>n (%)</th>
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</thead>
<tbody>
<tr>
<td>2,2</td>
<td>6 (1.1)</td>
</tr>
<tr>
<td>2,4</td>
<td>66 (12.1)</td>
</tr>
<tr>
<td>2,7</td>
<td>14 (2.6)</td>
</tr>
<tr>
<td>3,4</td>
<td>28 (5.1)</td>
</tr>
<tr>
<td>3,7</td>
<td>6 (1.1)</td>
</tr>
<tr>
<td>4,4</td>
<td>243 (44.5)</td>
</tr>
<tr>
<td>4,5</td>
<td>9 (1.6)</td>
</tr>
<tr>
<td>4,7</td>
<td>125 (22.9)</td>
</tr>
<tr>
<td>7,7</td>
<td>23 (4.2)</td>
</tr>
<tr>
<td>Other, 7</td>
<td>6 (1.1)</td>
</tr>
<tr>
<td>All other</td>
<td>20 (3.7)</td>
</tr>
<tr>
<td>Total</td>
<td>546 (100.0)</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Characterization of genotypes by presence of the 7-repeat allele</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-repeat present</td>
<td>174 (31.9)</td>
</tr>
<tr>
<td>7-repeat absent</td>
<td>372 (68.1)</td>
</tr>
<tr>
<td>Total</td>
<td>546 (100.0)</td>
</tr>
</tbody>
</table>

**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 through 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 ± 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 ± 3.4 years; mothers: M = 12.6 ± 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 Ps > 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, r² partial = 0.016). When tested in separate models, adulthood SES did not predict future discounting in similar interaction with DRD4 genotype (B = −0.160, s.e. = 0.08, t = −1.76, P = 0.08, r² partial = 0.006) nor did IQ (B = −0.046, s.e. = 0.09, t = −0.55, P = 0.58, r² 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, r² 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, r² 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, r² 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, r² 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, r² partial = 0.016), but again, no significant association among
individuals of other DRD4 genotype ($B = -0.004$, s.e. = 0.05, $t = -0.081$, $P = 0.94$, $r_{\text{partial}}^2 = 0.000$).

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 $\pm 1$ 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, $t = 2.966$, $P = 0.003$, $r_{\text{partial}}^2 = 0.016$), but exhibited comparatively shallower discounting if raised under conditions of mild socioeconomic advantage ($B = -0.296$, s.e. = 0.118, $t = -2.507$, $P = 0.012$, $r_{\text{partial}}^2 = 0.012$).

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, $t = -2.17$, $P = 0.031$, $r_{\text{partial}}^2 = 0.007$) and education ($B = -2.63$, s.e. = 0.087, $t = -3.03$, $P = 0.003$, $r_{\text{partial}}^2 = 0.017$). Adding the quadratic interaction likewise proved significant for parental occupation ($B = 0.208$, s.e. = 0.087, $t = 2.39$, $P = 0.017$, $r_{\text{partial}}^2 = 0.011$) and approached significance for parental education ($B = 0.112$, s.e. = 0.058, $t = 1.93$, $P = 0.054$, $r_{\text{partial}}^2 = 0.007$). Plots of the quadratic interactions were nearly identical to our composite measure of childhood SES, with the regression lines crossing over at $\pm 0.5$ 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 ($F = 17.4, df = 1.534, P < 0.0001, \eta_{\text{partial}}^2 = 0.032$). 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 ($F = 8.2, df = 1.262, P = 0.005, \eta_{\text{partial}}^2 = 0.030$) and women ($F = 9.3, df = 1.269, P = 0.002, \eta_{\text{partial}}^2 = 0.034$).

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 ($F = 5.0, df = 10.387, P = 0.026, \eta_{\text{partial}}^2 = 0.013$), as it was also in a model including only persons with 0 or 1 ($n = 151$) 7-repeat allele ($F = 13.7, df = 1.515, P < 0.0001, \eta_{\text{partial}}^2 = 0.026$).

**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...
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 pro-social 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 activation and connectivity among prefrontal regions implicated in others, as indicated by lower parental education, showed reduced of the present findings. First, Gianaros and colleagues recently reported et al. 2010 for a review) and that individual differences in delay discounting in tests of intertemporal choice (McClure et al. et al. 2004; Carter 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 parent and sibling 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 × 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 test-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


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