GENETIC AND ENVIRONMENTAL INFLUENCES ON IMPULSIVITY AND COPING MOTIVES FOR ALCOHOL ACROSS EMERGING AND YOUNG ADULTHOOD

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The undersigned, appointed by the dean of the Graduate School, have examined the dissertation entitled

GENETIC AND ENVIORNMENTAL INFLUENCES ON IMPULSIVITY AND COPING MOTIVES FOR ALCOHOL ACROSS EMERGING AND YOUNG ADULTHOOD

presented by Andrew Littlefield,

a candidate for the degree of doctor of philosophy,

and hereby certify that, in their opinion, it is worthy of acceptance.

Professor Kenneth J. Sher

Professor Matthew P. Martens

Professor Denis M. McCarthy

Professor Timothy J. Trull

Professor Phillip K. Wood

I would like to dedicate this dissertation to…

Tim and Mary Littlefield,

My parents,

For your constant support and love.

&

Amelia Talley,

My love,

For your everything.

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GENETIC AND ENVIRONMENTAL INFLUENCES ON IMPULSIVITY AND COPING MOTIVES FOR ALCOHOL ACROSS EMERGING AND YOUNG ADULTHOOD

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ABSTRACT

Variation in the gene encoding the dopamine D4 receptor (DRD4) may moderate the influence of environments on personality traits and motives associated with alcohol use disorders. This project examines whether variation in DRD4 moderates the environmental influence of childhood adversity on personality (including replication attempts of reported GXE) as well as coping motives. Primary analyses were conducted in the Alcohol, Health, and Behavior (AHB; for current analyses *ns*=236-252) dataset, a prospective, high-risk sample of college students who were assessed seven times from ages 18-35. Replication analyses were conducted in the Missouri Adolescent Female Twin Study (MOAFTS, for current analyses *n*s =1,017-1476), a study of a birth cohort of female like-sex twin pairs. Analyses involving DRD4 2- and 5- repeat allele carries vs. others yielded findings inconsistent with the existing GXE personality studies. Although results varied, 7-repeat carriers appeared to be more susceptible to environmental influences on novelty seeking, and to a lesser extent impulsivity, in the AHB data; this finding largely failed to replicate in MOAFTS. No GXE on coping motives were identified. These findings provide limited support that DRD4 status modifies the influence of childhood adversity on personality and have implications for replication-focused research involving GXE.

Introduction

Problematic alcohol involvement (PAI), including alcohol use disorders (AUDS), is both prevalent and problematic in the United States and elsewhere (Goetzel et al., 2003; Grant et al., 2004; Roy-Byrne et al., 2000; Sanderson & Andrews, 2002; Stewart et al., 2003; World Health Organization, 2003). Heavy alcohol use and related problems are associated with significant consequences for the drinker as well as the drinker's family, community, and society (Sher, Martinez, & Littlefield, 2011), including medical morbidity and mortality (e.g., Rehm et al., 2003), marital dissatisfaction (e.g., Kearns-Bodkin & Leonard, 2005), physical assaults, vandalism, and decreased quality of life proportionate to drinking rates of heavily alcohol-involved communities (e.g., college campuses; Wechsler et al., 2002), as well as billions of dollars of economic costs to the United States (Harwood, 1998). Therefore, problematic alcohol involvement inflicts an overwhelming, though possibly preventable, burden (Grant et al., 2004).

AUDs: Genetically Influenced Developmental Disorders

Understanding the etiology of AUDs is important, as it can inform preventative and treatment efforts addressing alcohol related problems. Notably, AUDs appear to be both genetically-influenced and developmentally-limited disorders. AUDs are considered a moderately to highly heritable psychiatric disease (see Ducci & Goldman, 2008 for a review), with heritability increasing substantially with age (see van Beek et al., 2012) and hertiability coefficients of more than .5 in adulthood (Goldman et al., 2005). Developmentally, peak hazards and prevalence of AUDs occur in emerging adulthood (roughly age 18-25; Arnett, 2000) and rapidly decrease in both onset and prevalence in the later part of the third decade of life (Hasin, Stinson, Ogburn, & Grant, 2007; see

O'Malley, 2004-2005, for a review). The so-called "maturing out" (Winick, 1962) of PAI has led to the suggestion that AUDs should be considered developmental disorders in the sense that their appearance and resolution appear to correspond with developmental transitions into environmental settings (e.g., adult roles including spouse/partner, parent) considered to be incompatible with a heavy drinking lifestyle (Kandel, 1980; Yamaguchi & Kandel, 1985; see Sher & Gotham, 1999).

Accordingly, etiological models of AUDs should incorporate both relevant genetic influences and environmental factors within a longitudinal framework to address, among other things, how risk associated with susceptibility genes for AUDs manifests across young to mid-adulthood and interacts with environmental influences (Dick et al., 2009). Several studies have examined how genotypes related to neurotransmitter (e.g., dopamine) functioning and environmental factors (e.g., childhood adversity), as well as their interactions (e.g., *GABRA2* and marriage; Dick et al., 2006), influence AUDs, (see Ducci & Goldman, 2008; Goldman et al., 2005; van der Zwaluw & Engels, 2009 for reviews). However, it is only recently that specific genetic effects and their interplay with moderating environmental factors have been studied regarding prospective data of externalizing behavior related to PAI. For example, Dick et al. (2009) found that individuals with trajectories characterized by relatively high levels of externalizing behavior from ages 12-22 were more likely to carry the *GABRA2* genotype (which has been associated with adult alcohol dependence, e.g., Edenberg et al., 2004) and that this association was attenuated by high levels of parental monitoring reported at age 11. Park, Sher, Todorov, and Heath (2011) showed that individuals with seven or more tandem repeats for dopamine receptor 4 (*DRD4*) were more susceptible to environmental

influences and these influences varied with age. These findings highlight the importance of examining genetic influences that incorporates environmental influences and prospective data. Further, the finding that genotypes associated with AUDs also are linked to the development of general externalizing behaviors suggests that it might be profitable to look for genes contributing to the etiology of other phenotypes associated with AUDs (see Goldman et al., 2005), especially phenotypes that have been genetically and developmentally linked to AUDs and corresponding environmental factors.

Personality Traits: Genetic and Prospective Covariates of AUDs

One broad class of phenotypes empirically associated with both the genetic risk and developmental changes in AUDs are personality characteristics, especially approach-related traits (e.g., novelty seeking, impulsivity). Noting several theories of the etiology of AUDs which suggest that the genetic diathesis for AUDs is mediated by personality (Cloninger, 1987a; Tarter, 1988; Tarter et al., 1985; Zuckerman, 1987), Slutske et al. (2002) examined the extent to which genetic risk for alcohol dependence overlapped with genetic factors contributing to variation in dimensions of personality in over three thousand adult male and female twin pairs. Specifically, genetic influences contributing to variation in behavioral undercontrol (a broad construct related to impulsivity) accounted for approximately 40% of the genetic variation in alcohol dependence. More recently, Littlefield et al. (2011) found that AUD symptoms showed significant genetic overlap with several personality dimensions, including control (i.e., reverse-scaled impulsivity). Overall, these findings suggest that genetic factors that contribute to variation in personality dimensions (especially traits associated with impulsivity) account for a significant proportion of the genetic diathesis for alcohol dependence. Although

results have been inconsistent (suggesting possible gene-environment interactions; South & Krueger, 2008; see also McCrae, Scally, Terracciano, Abecasis, & Costa, 2010, for discussion/demonstration that personality traits are influenced by the additive effects of many genetic variants), several potential genetic factors of personality have also been identified and reviewed (see Ebstein, 2006; Ebstein & Israel, 2009), including genotypes related to the functioning of dopamine neurotransmitters thought to be relevant to variation in alcohol involvement.

Further, personality has long been considered an important predictor of alcohol involvement (especially impulsivity/behavioral undercontrol and to a lesser extent neuroticism/negative emotionality and extraversion; see Sher & Littlefield, 2008; Sher et al., 2005, for a review). In fact, more recent evidence suggests changes in impulsivity (and neuroticism) correlate with changes in alcohol problems across emerging and young adulthood (Littlefield, Sher, & Wood, 2009). Several theories suggest motivations act as a proximal influence on substance use through which more distal influences, such as personality, are mediated (e.g., Cooper et al., 1995; Cox & Klinger, 1988, 1990; Kuntsche et al., 2008; Stewart & Devine, 2000), and changes in coping motives appear to mediate the relation between changes in impulsivity and neuroticism with changes in alcohol problems (Littlefield, Sher, & Wood, 2011). These findings suggest PAI, specific personality traits, and coping motives are linked both cross-sectionally and across time.

Additional evidence suggests that coping motives may also show genetic overlap with certain personality traits and PAI. Drinking motives involving coping with negative moods appear to be heritable (Agrawal et. al., 2008; Prescott et al., 2004) and a substantial portion of genetic variation in AUDs appears to overlap with drinking to

manage mood states (Prescott et al., 2004). Littlefield et al. (2011) showed that variation in coping motives explained a signification portion of the genetic overlap between several personality traits and AUD symptoms. Although coping motives are heritable, no studies have identified reliable genetic markers associated with this construct (see Armeli, Conner, Covalut, Tennen, & Kranzler, 2008; Kristjansson et al., 2012). Further, to my knowledge, no studies have tested whether certain specific genetic factors and their interactions with environmental influences (i.e., gene-environment interactions; GXE) influence coping motives. Regardless, traits related to impulsivity, coping motives, and PAI appear to be genetically and prospectively linked.

DRD4: Moderator of Environmental Influences?

Although the etiology and course of personality, drinking motives, and alcohol problems may be influenced by similar genetic and environmental factors as well as GXE interactions, the extant literature (involving measured genes and environments) prohibits any firm conclusion regarding this proposition. More specifically, several studies to date suggest GXE involving hypothesized alcohol-relevant genetic factors (i.e., DRD4) and alcohol relevant environmental risk factors (e.g., negative childhood family environments) influence approach-related personality traits (i.e., novelty seeking; Keltikangas-Järvinen et al., 2004; Lahti et al., 2005). However, these studies compared individuals with 2- and 5-repeats (i.e., 2r and 5r) on the DRD4 VNTR to individuals with who do not have 2r and 5r on either allele for DRD4. This classification is inconsistent with biological studies linking variation in number of repeats to dopamine functioning (which suggest that 7-repeats [7r] have less efficient dopamine functioning compared to individuals with other numbers of repeats; Jovanovic, Guan, & Van Tol, 1999) as well as

the larger literature suggesting that 7r are generally more susceptible to environmental influences (e.g., Bakermans-Kranenburg & van Ijzendoorn, 2011; Creswell et al., 2012). Further, these findings await replication, which is being increasingly recognized as an essential part of genetically-informed research (see Duncan & Keller, 2011, for a thorough discussion regarding issues with replication in GXE studies and Hewitt, 2012 for proposed guidelines involving replicability for GXE studies). Finally, it is unclear if this specific GXE impact on approach-related personality traits is consistent across time or is developmentally limited. For example, the extent to which DRD4 status moderates the influence of childhood stressors on approach-related personality traits may be persistent rather than time-limited, given that childhood abuse relates to heightened impulsivity during the thirties (Brodsky, Oquendo, Ellis, Haas, Malone, & Mann, 2001). On the other hand, given the increasing recognition that GXE may vary by age through numerous mechanisms (e.g., Park et al., 2011; see Lenroot & Giedd, 2011, for a detailed discussion), DRD4 status may only moderate the relation between childhood adversity on novelty seeking/impulsivity at certain ages. Thus, though similar GXE may relate to PAI and the related phenotypes of personality and drinking motives, this has yet to be reliably demonstrated.

In sum, PAI has been genetically and longitudinally linked to personality traits and coping motives. Dopamine functioning as indexed by variation in the number of repeats in DRD4 has been shown to moderate the influence of several environmental influences on a range of outcomes. More specifically, variation in DRD4 has been shown to moderate the influence of aversive environments (e.g., harsh parenting, history of abuse) on both measures indexing alcohol dependence (Park et al., 2011) and traits

related to impulsivity (Keltikangas-Järvinen et al., 2004). However, inconsistent classification involving DRD4 and lack of evidence for replication casts doubt on the current robustness of these existing findings. Further, though coping motives have been genetically linked to both PAI and certain personality characteristics (Littlefield et al., 2011), it remains unknown whether GXE that relate to PAI (Park et al., 2011) and specific personality traits (Keltikangas-Järvinen et al., 2004) also predicts variation in coping motives.

Given these issues and the importance of demonstrating replicability regarding GXE findings, the primary aims of this paper are to: 1) test the robustness of G (i.e., DRD4 2r and 5r vs. all others) X E (i.e., aversive childhood environments) findings involving approach-related personality traits (e.g., novelty seeking, impulsivity) found in the current literature, 2) test if GXE involving codings of DRD4 consistent with the larger literature (i.e., DRD4 7r vs. all others and aversive childhood environments) relate to variation in novelty seeking/impulsivity and coping motives and if this relation various by age, 3) examine the extent to which any common GXE contributes to overlap among personality, motives, and PAI, and 4) attempt to replicate any significant findings in an independent dataset.

Methods

Primary Analysis: AHB. Primary analyses were conducted in the Alcohol, Health, and Behavior (AHB) dataset. The target population of the AHB dataset was a subsample of the 1987 entering class of first-time college students at the University of Missouri-Columbia (see Sher et al., 1991). The data are a prospective sample of 489 college students over sampled for family history of alcoholism (FH; 51%). Students completed a

battery of questionnaire and semi-structured interviews during their first year college (i.e., Wave 1; mean age = 18.2, SD = .7) and then again at (roughly) age 19, 20, 21, 25, 29, and 35 (i.e., Waves 2-7). Sample retention is good, with over 84% of participants retained over the first 11 years of the study, and over 78% retained through Year 16 (mean age = 34.5; see Sher et al., 1991 for more details).

Replication Analysis: MOAFTS. Replication analyses were conducted in the Missouri Adolescent Female Twin Study (MOAFTS) sample. MOAFTS is a prospective study of a birth cohort of female like-sex twin pairs, first assessed in adolescence, with follow-up in young adulthood, using structured diagnostic telephone interviews. Parents of female twin pairs born between 1975 and 1985 in the state of Missouri were identified and traced through birth records and contacted regarding participation. Data collection from the twins began with the baseline interview in 1995-1999, when twins were median age 15 (n= 3,266, mean age = 15.5, SD = 2.4; range: 12-23 years). Data for the current project will be primarily drawn from baseline data and Wave 4 data, which was conducted between 2000 and 2005, on average 5 years after the baseline assessment (for individuals with non-missing on DRD4, n = 1,493, mean age = 21.65, SD = 2.63, range 18-28 years). Sample retention is good, with interview information from at least one family member from better than 93% of families of European/Other Ancestry families, and better than 90% of African-American families (this latter group representing the sole sizeable minority group for the sample; see Heath et al., 2002, for more details).

Measures

Personality. In AHB, novelty seeking was assessed using short-form of the Tridimensional Personality Questionnaire (Short-TPQ; Sher, Wood, Crews, & Vandiver,

1995) at ages 18, 25, 29, and 35. A narrower measure of impulsivity (which generally reflects lack of precontemplation) used in recent studies based on AHB data (e.g., Littlefield et al., 2009) consisted of a sum of 10 items and was used to assess impulsivity at ages 18, 25, 29, and 35. Six of these items (e.g., "I often follow my instincts, hunches, or intuition without thinking through all the details") were drawn from the short-form of the Tridimensional Personality Questionnaire and the remaining four items (e.g., "I often do things on the spur of the moment") were taken from the Eysenck Personality Inventory (EPI; Eysenck & Eysenck, 1968). In MOAFTS, novelty seeking was assessed with items from the Tridimensional Personality Questionnaire (TPQ; Cloninger, 1987b). Control, a subscale of constraint, was also assessed in MOAFTS with items from the Multidimensional Personality Questionnaire (Tellegen A., 1982 unpublished data).

Drinking motives. Coping motives were assessed using items derived from a tension-reduction drinking motives composite developed by Sher et al. (1991; see also Sher et al., 2004, for more details), with items adapted from those used by Cahalan, Cisin, and Crossley (1969). Coping included four items (e.g., "I drink to forget my worries"). Composites were created for coping motives using the sum of the items (coefficient alphas ≥ .84; Littlefield et al., 2010). In MOAFTS, coping motives were assessed using the Drinking Motive Questionnaire-Revised (Cooper, 1994). This scale has good internal validity (alpha > .80; Kuntsche, Stewart, & Cooper, 2008) and was scored by summing responses (ranging 1 to 5) across the 5 items per scale and then dividing the summed items by 5, resulting in scores that ranged from 1 to 5 for each scale.

Childhood adversity. To measure experiences of verbal, physical, emotional, and sexual abuse, abandonment and neglect prior to the age of 18 in AHB, 15 items were

administered retrospectively at the mean age of 25 as part of a structured interview of the Childhood Life Events (Sher, Gershuny, Peterson, & Raskin, 1997). Trained, Masters-level clinical interviewers used strategies to improve accuracy of retrospective self-reports, such as providing recognition cues and responding sensitively to respondents' emotional status (Brewin et al., 1993). This variable was scaled as a three-level categorical variable such that 0 = no endorsement of adversity, 1 = endorsing 1 or 2 adversity items, and 2 = endorsing 3 or more adversity items. To increase comparability to measures available in MOAFTS, a narrower measure involving four items assessing physical and sexual abuse was also used. This variable was scaled as a three-level categorical variable such that 0 = no items endorsed, 1 = endorsing 1 physical/sexual abuse item, and 2 = endorsing 2 or more items. In MOAFTS, a measure involving four items assessing physical and sexual abuse was used and scored identically to the aforementioned AHB measure. Additionally, a more stringent measure of physical abuse based on four items was also included in analyses involving MOAFTS data to be consistent with recent work exploring GXE (i.e., Argawal et al., 2012) in this dataset. Exposure to childhood physical abuse in MOAFTS was coded dichotomously such that 0 = no physical abuse and 1 = endorsement of at least one of the four physical abuse items.

Dopamine D4 receptor (DRD4) gene polymorphism. . Participants AHB sample who had not actively withdrawn from the study were invited to provide genetic data. A tube for blood sampling and instructions for phlebotomists were provided to those who expressed interest in participating (n = 435; mean age = 35; 89% of the baseline sample). Blood samples drawn at participants' preferred locations were returned to research staff via mail. Blood samples were collected and genotyped; the current analyses involved genetic

data from 252 participants. As described in Park et al., (2011), genotyping the DRD4 polymorphism of 48-base pair Variable Number of Tandem Repeat (VNTR) in Exon 3 was performed as described by LaHoste et al. (1996). DRD4 status was coded in two ways. Consistent with existing GXE involving personality, individuals with dichotomized into 2r and 5r carriers (i.e., at least one allele with 2 or 5 repeats, *n* = 60) or non-2r/5r (N25r, *n* = 192) carriers (i.e., neither allele with 2 or 5 repeats). Participants were also dichotomized into 7r carriers (i.e., at least one allele with 7 repeats, *n* = 90) or non-seven repeat (N7r, *n* = 162). Identical coding approaches were implemented in MOAFTS (2r and 5r *n* = 261, N25r *n* = 1,232; 7r *n* = 555, N7r *n* = 938). Chi-square tests comparing observed and expected genotype frequencies based Hardy-Weinberg equilibrium (HWE) assumptions suggested HWE was not violated.

Analytic Approach

Moffitt and colleagues (2005; 2006) outlined seven steps when investigating measured GXE in psychopathology "to encourage careful, deliberate GXE hypothesis testing" (Moffitt et al., 2006, p. 9). For the current project, the first four of these steps (i.e., consulting quantitative behavioral genetic models of the disorder, identifying the candidate environmental pathogen for the disorder, optimizing measurement of environmental risk, identifying susceptibility genes) have been considered in the review above. As outlined by Moffitt et al. (2005; 2006), the fifth step, testing for an interaction, a longitudinal cohort sampling design is considered as the "most informative design for testing GXE" (Moffitt et al., 2006, p. 15). If a GXE is found, the sixth step, evaluating whether a GXE extends beyond the initially hypothesized triad of gene, environmental pathogen, and disorder, is conducted by systematically replacing one variable in the triad

while holding the other two constant to examine if the interaction remains significant. Specifically to this project, this step can be utilized to examine if potential GXE found for a specific study construct (e.g., impulsivity) extends to other constructs (e.g., drinking motives). The seventh step, replication and meta-analysis, will be partially addressed by the replication analyses conducted in MOAFTS sample.

In order to determine the extent that environmental and genetic factors predict personality and coping motives, factor models involving novelty seeking, impulsivity and coping motives were estimated. Given that novelty seeking and impulsivity were assessed at only four time points (roughly at ages 18, 25, 29, 35), an overall "trait" with four manifest variables as congeneric indicators was respectively estimated for these personality measures. Follow-up analyses were conducted to determine if any significant GXE were age dependent (by testing interactions between GXE and time in SAS PROC MIXED; SAS Institute Inc. 2008). For coping motives, which was assessed at all seven time points, the fit of an overall "trait" model (i.e., one factor with seven motive indicators) was compared to a correlated two-factor model (where an "emerging adulthood" factor comprised of four manifest coping variables from ages 18-21 is correlated with a "young adulthood" factor comprised of three coping variables from ages 25-35) as well as a hierarchical factor model (Schmid & Leiman, 1957) to determine the necessity of developmentally-specific factors. When employed in longitudinal data, hierarchical factors models can decompose variability into an overall, cross-temporal trait and developmentally-specific residual variation. Thus, within in this framework, coping motives can be modeled, using AHB data, across distinct developmental periods (i.e., emerging adulthood [age 18-21] and young adulthood [age 25-35]) as well as overall

levels of coping motives across the entire timeframe. Given the MOAFTS data in the current analysis are cross-sectional, age interactions were included in all tests of GXE. If GXE influences on personality or motives were found, the extent to which these factors account for the respective relation between PAI, personality, and motives was examined. All structural equation models were estimated in *Mplus* version 6.11 (Muthén & Muthén, 1998 - 2013); full-information maximum likelihood (FIML) estimation was used for missing data.

Threats of Population Stratification. To guard against the potential compound of population stratification, two separate analytic strategies were employed. In one set of models, non-Caucasian participants (based on self-reported ancestry) were removed (in AHB, n=16; in MOAFTS, n = 170). In a second set of models, self-reported ancestry was included as a statistical covariate (given the relative homogeneity of both AHB and MOAFTS this variable was coded dichotomously as Caucasian vs. all other ancestry groups). This approach has been shown to protect against threats of population stratification and show nearly identical overlap to more complicated approaches (i.e., genetic cluster analysis; Tang et al., 2005).

Comparability. Although all measures are described above (see *Measures* section above), it bears mentioning that there were several levels of "comparability" to consider involving outcome measures (i.e., personality and coping motives), DRD4 status, and childhood adversity. To be consistent as possible with the existing GXE personality literature, measures of novelty seeking were included in both AHB and MOAFTS; to be consistent with previous work involving measures of impulsivity drawn from AHB data (e.g., Littlefield et al., 2009), a measures of impulsivity (detailed above) were also

modeled in AHB and control was included in MOAFTS analyses. To test the robustness of existing GXE involving novelty seeking, DRD4 was coded with 2r and 5r vs. all other repeats; to maintain consistency with the larger literature, DRD4 was also coded with 7r vs. all other repeats. Consistent with previous conceptualizations of childhood adversity using AHB data (i.e., Park et al., 2011), a relatively broad measure of abuse was used in analyses; to enhance comparability to measures available in MOAFTS a narrower measure involving physical and sexual abuse was also used. A more stringent measure of physical abuse was also included in analyses involving MOAFTS data to be consistent with recent work exploring GXE in MOAFTS data (i.e., Argawal et al., 2012). In AHB, there were three outcomes (i.e., novelty seeking, impulsivity, coping motives), two codings of DRD4 status (used to examine replicability of existing personality GXE; only one coding [7r vs 7Nr] was used for models involving coping motives), two measures of childhood adversity, and two ways to handle threats to population stratification (i.e., removing minorities vs. adjusting for ethnic/racial status), resulting in 20 primary models using AHB data. In MOAFTS, there were three primary outcomes (i.e., novelty seeking, control, coping motives), two codings of DRD4 status (again, only 7r vs 7Nr was examined for motives), two measures of childhood adversity, and two approaches to population stratification, which resulted in 20 primary models using MOAFTS data (see *Measures* section above for more details).

Results

Factor Models of Novelty Seeking/Impulsivity in AHB. Before exploring the analyses described above, the fit of factor models involving novelty seeking and impulsivity was evaluated. The fit of the single factor model of novelty seeking (i.e., $\chi^2(2, n = 252) =$

5.33, p = .07, Comparative Fit Index (CFI) = .99, Root Mean Square Error of Approximation (RMSEA) = .08) and impulsivity $\chi^2(2, n = 252) = 2.99$, p = .22, CFI = 1.0, RMSEA = .04) with congeneric indicators was adequate. The fit of a model that assumed tau-equivalence for novelty seeking (i.e., $\chi^2(5, n = 252) = 12.53$, p = .03, CFI = .98, RMSEA = .08) also exhibited adequate fit to the data and fit the data equally well as the congeneric model based on model fit comparisons involving χ^2, CFI, and RMSEA (Chen, 2007; Cheung & Rensvold, 2002). However, the fit of a model that assumed tau-equivalence for impulsivity $\chi^2(5, n = 252) = 20.97$, $p < .01$, CFI = .95, RMSEA = .11) exhibited significantly poorer fit compared to the congeneric model (i.e., χ^2 difference test $p < .01$, CFI difference > .01; RMSEA difference > .015). To maintain comparability between models involving novelty seeking and impulsivity, results involving congeneric factor models are presented in described henceforth; notably, tau-equivalent models involving novelty seeking yielded nearly identical results compared to the presented findings.

Factor Models of Coping Motives. The fit of the single factor model (i.e., $\chi^2(14, n = 252) = 86.18$, $p < .001$, CFI = .90, RMSEA = .14) exhibited poor fit to the data whereas the correlated two-factor model (i.e., $\chi^2(13, n = 252) = 28.65$, $p < .01$, CFI = .98, RMSEA = .07) exhibited adequate fit to the data. However, the hierarchical factor model exhibited the best fit to the data (i.e., $\chi^2(14, n = 252) = 10.84$, p = .21, CFI = 1.0, RMSEA = .04) and was thus used in subsequent models to test GXE. Factor loadings are presented in Table 1.

Testing GXE. For each model, main effects of DRD4 and childhood adversity, and their interaction, were estimated. To probe any significant interaction, factor scores were

plotted as a function of genotype and childhood adversity. In AHB, n = 252 for all analyses that adjusted for ethnicity/race and n = 236 for analyses that removed minorities. In MOAFTS, ns ranged (depending on the measures used in a particular analysis) from 1121-1476 for all analyses that adjusted for ethnicity/race and ns ranged from 1017-1141 for analyses that removed minorities. All analyses in AHB adjusted for sex.

AHB: Novelty Seeking. For each model, potential multivariate outliers were examined by using Mahalanobis distance and the corresponding p-value (by specifying SAVE = MAHALANOBIS option in *M*plus). A multivariate outlier can be defined as a case that is associated with a Mahalanobis distance greater than a critical distance typically specified by $p < .001$ (Tabachnick & Fidell, 2006; see Ullman, 2006). Only one observation met this criterion and this was limited to models involving the broad childhood adversity variable and codings of DRD4 involving 7r vs 7Nr; this observation was removed from all relevant analyses. Results from analyses testing GXE are shown in Table 2. First, codings of DRD4 consistent with the extant GXE personality literature (i.e., 2r/5r vs. all others; Keltikangas-Järvinen et al., 2004; Lahti et al., 2005) were tested. When DRD4 was coded as 2r/5r vs. N25r, significant (p<.05) interactions with childhood adversity (i.e., a GXE) were observed on trait novelty seeking, regardless of which abuse variable was used or the approach for handling ethnic/racial heterogeneity. However, plots of novelty seeking factor scores by genotype and abuse suggested findings were in the *opposite* direction to previous research; novelty seeking scores were *lower* for 2r/5r in the presence of childhood adversity compared to N25r (see Figure 1 for an example involving childhood adversity and adjusting for race/ethnicity). Second, codings of DRD4 consistent with the larger literature (i.e., 7r vs. 7Nr) were tested. Regardless of the

approach for handling ethnic/racial status, the interaction between DRD4 and childhood adversity approached statistical significance (p = .07) when using the broader childhood adversity variable but not the narrower physical and sexual abuse variable (ps = .33 and .17 for models adjusting for ethnicity/race and dropping racial minorities, respectively). Plots of the models using the broader childhood adversity variable (see Figure 2 for the model that adjusted for ethnic/racial status) suggested that 7r allele carriers had a stronger relation between childhood adversity and novelty seeking; this plot also suggested that 7r with no childhood adversity showed the *lowest* levels of trait impulsivity. Follow-up analyses conducted in SAS PROC MIXED involving the manifest novelty seeking variables suggested this GXE was not moderated by time. Although the interaction was statistically non-significant, the interactions in the models involving the narrower abuse measure showed the same pattern as described above (see Table 2).

AHB: Impulsivity. Only one observation met the criterion as an influential multivariate outlier; this individual was an ethnic/racial minority and thus only impacted models that adjusted for ethnic/racial status. This observation was removed from all relevant analyses. As with novelty seeking, codings of DRD4 consistent with the extant GXE personality literature (i.e., 2r/5r vs. N25r,; Keltikangas-Järvinen et al., 2004; Lahti et al., 2005) were first tested. Identical to the findings with novelty seeking, significant (p<.05) interactions with childhood adversity (i.e., a GXE) were observed on trait impulsivity across all models. Also identical to the models involving novelty seeking, a plots of these interactions (not shown) suggested findings were in the *opposite* direction to previous research; impulsivity scores were *lower* for 2r/5r in the presence of childhood adversity compared to N25r. Second, codings of DRD4 consistent with the larger literature (i.e., 7r

vs. 7Nr) were tested. No interactions were statistically significant though the model involving the broader measure of childhood adversity and excluding minorities approached statistical significance ($p = .07$; $p = .11$ for the interaction in the parallel model that adjusted for racial/ethnic status). Although not statistically significant, parameters from these models showed the same pattern as those for novelty seeking (i.e., there was a stronger relation between childhood adversity and trait impulsivity among 7r compared to 7NR). A plot of the interaction that approached statistical significance (see Figure 3) suggested a similar pattern to that found with novelty seeking; however, it appeared that 7r who experienced any level of childhood adversity showed very similar levels of impulsivity. Indeed, in follow-up analyses that dichotomized the childhood adversity variable (i.e., no childhood adversity vs. all others), the interaction between DRD4 status and adversity became statistically significant ($p = .02$).

AHB: Coping Motives. Regardless of approach or which motive factor was considered, there was no evidence of a significant GXE predicting coping motives (see Table 2 for estimates on the overall coping motives trait).

MOAFTS Replication. All analyses were conducted in SAS PROC MIXED (SAS Institute Inc., 2008) in order to account for the nested twin data. For all models, three-way interactions among genotype, environment, and age were first examined; non-significant three-way interactions were trimmed and subsequent models testing GXE (without interactions with age) were tested. Further, potential influential observations were identified by using Cook's Distance (1977); observation's with distance (D) values greater than $4/n$ (Bollen & Jackman, 1990) were removed and analyses were reran to determine the impact of these observations on interaction estimates. The only significant

(p = .03) three-way interaction involved novelty seeking as an outcome, DRD4 coded as 7r vs. 7Nr, and the physical abuse item used in Argawal et al. (2012) in the model that removed minorities; the three-way interaction in the parallel model that adjusted for minority status approached significance (p = .08). Plots of this interaction (not shown) suggested that, among younger participants, 7r carriers showed a stronger relation between physical abuse and novelty seeking though this GXE was not as pronounced among older participants. However, follow-up analyses that removed forty-five observations with above threshold D values resulted in a non-significant three-way interaction (p = .45) as well as two-way GXE. After trimming the non-significant three-way interactions, no GXE were statistically significant at $p < .05$. However, an interaction between DRD4 and physical/sexual abuse on novelty seeking approached significance (p = .09) in the model that removed minorities (p = .12 for interaction in the parallel model that adjusted for ethnic/minority status). Consistent of findings in AHB, plots of this interaction (not shown) suggested that there was a stronger relation between physical/sexual abuse and novelty seeking among 7r carriers. However, removing thirty-three observations with above threshold D values resulted in p = .40 for the interaction. Across all models, there was no evidence of significant interactions when DRD4 status was coded as 2r/5r vs. N25r or when constraint and coping motives were the outcome of interest; these findings were consistent in models that removed above threshold D values.

Covariance Accounted for by GXE. At first glance, findings that showed 7r have a more pronounced relation between childhood adversity and trait novelty seeking are consistent with previous findings using data from AHB (i.e., Park et al., 2011) involving alcohol dependence items. However, as documented in Footnote 1 of Park et al., ancillary

analyses that dropped carriers of rare alleles and compared 7r to N7r (as opposed to comparing "long vs. short" allele carriers) did not show that DRD4 status significantly moderated the influence of childhood adversity on alcohol dependence. Indeed, supplementary analyses conducted as part of the current project that did not drop rare carriers and compared 7r to 7Nr also failed to find a significant interaction between DRD4 status and childhood adversity in predicting alcohol dependence. Nevertheless, to determine the extent to which this GXE contributed to overlap between novelty seeking and items tapping alcohol dependence (see Park et al., 2011, for more details), two models were compared. The first model consisted of trait novelty seeking and alcohol dependence (modeled as a hierarchical fashion identical to the approach used in Park et al.); the overall correlation between trait novelty seeking and alcohol dependence factors was .46. The second model included childhood adversity, DRD4 status, and their interaction; the correlation between the factors was minimally reduced (r = .44). Thus, the current GXE does not appear to explain much of the overlap between these constructs.

Discussion

DRD4 status has been shown to moderate environmental influences on a number of outcomes, including problematic alcohol involvement (Park et al., 2011) and specific personality traits (Keltikangas-Järvinen et al., 2004; Lahti et al., 2005). Inconsistent with existing GXE involving novelty seeking (i.e., Keltikangas-Järvinen et al., 2004; Lahti et al., 2005), there was no evidence those individuals with 2- and 5-repeats for DRD4 VNTR showed higher levels of novelty seeking or impulsivity in the presence of aversive childhood environments. This is not entirely surprising, given the 2- and 5-repeat coding

approach seems to be limited to very few studies (e.g., Keltikangas-Järvinen et al., 2004; Lahti et al., 2005) and is inconsistent with the much larger literature involving DRD4 that focuses on 7-repeat carriers (e.g., Bakermans-Kranenburg & Ijzendoorn, 2011).

However, in the AHB dataset, there was some evidence that 7r were more sensitive to the impact of childhood adversity on personality throughout emerging and young adulthood, though no analyses revealed significant GXE at $p < .05$ when multivariate outliers were removed. Plots of these findings were seemingly consistent with the larger literature suggesting that individuals with 7-repeats for DRD4 VNTR may actually have "better" outcomes in the presence of adaptive environmental factors/lack of aversive environmental factors (e.g., Bakermans-Kranenburg & Ijzendoorn, 2011; Creswell et al., 2012). Notably, though relatively higher levels of novelty seeking and impulsivity have been linked to PAI, especially low levels of novelty seeking/impulsivity should not necessarily be considered as a "better" outcome compared to more average levels of these traits, given that extremely low levels of impulsivity may reflect excessive "overcontrol".

With few exceptions the findings involving 7r did not replicate in the MOAFTS dataset and these exceptions are further qualified in follow-up analyses that found no statistically significant GXE when potential impactful observations (as indexed by Cook's *D*) were removed. This lack of replication may reflect, among other possibilities, a) the AHB findings reflect false positives, a potentially common outcome involving measured genotypes and psychiatric phenotypes (Duncan & Keller, 2011), b) differences in sample characteristics (e.g., MOAFTS is comprised of all females and is relatively age heterogeneous compared to AHB; however, follow-up analyses on the GXE did not

suggest these interactions were moderated by sex), c) differences in measures across the two samples, d) increased reliability (and thus increased statistical power) in AHB by utilizing multiple measures of impulsivity across time.

Perhaps this lack of replication is not too surprising given there were several findings that suggested reliably detecting interactions between DRD4 status and childhood adversity is difficult, even within the *same* dataset. Although several of the findings were robust across approaches to handle population stratification and conceptualizations/codings of abuse, there was also evidence of varying results as a function of approach and coding procedure. More specifically, evidence for GXE (i.e., statistically-significant interactions) in AHB data varied, to some extent, by a) approach to account for racial/ethnic heterogeneity, b) outcome (even when outcomes are ostensibly tapping similar constructs and include overlapping items; i.e., novelty seeking and impulsivity), c) conceptualizations of childhood adversity/abuse, d) if influential observations were included or excluded from the analyses, and e) scoring approach (e.g., dichotomous vs. trichotomous classifications of abuse).

These disparate findings have implications for replication efforts. The importance of replicable findings appears to be increasingly recognized; in fact, a recent special issue in *Perspectives on Psychological Science* was dedicated to the topic of replicability (see Pashler & Wagenmakers, 2012, for an overview). Although issues of statistical power, sample characteristics, and choice of measurements have been proffered as potential explanations for inconsistent support for GXE (e.g.., McGuffin, Alsabban, & Uher, 2011), the current findings highlight a host of potential factors that can complicate conducting and interpreting replication studies. Further, despite a proliferation of meta-

analytic studies, there is no currently accepted standard to precisely define the number of similarities a study should possess (e.g., in terms of sample characteristics, measures, statistical power, statistical/methodological approach, coding of variables, examination of outliers, etc.) compared to a seminal study in order to be considered a *true* replication effort of the original study. These findings suggest numerous issues need to be considered when designing replication attempts of existing scientific findings or when determining inclusion criteria (or potential moderating factors) in meta-analytic efforts.

Given the issues noted above it is somewhat difficult what to interpret the current findings. On one hand, there was essentially no evidence that extant GXE involving approach-related personality traits (where 2r/5r are compared to other allele carriers) are reliable; results supporting that 7r differentially respond to environmental influences on personality in AHB was limited and mostly failed to replicate within MOAFTS data. These findings suggest that DRD4 status has little impact on moderating the impact of environment on personality development. On the other hand, the general form of the GXE (i.e., stronger environmental influence for 7r on personality outcomes) was remarkably consistent across approach and personality outcome when using the AHB data and somewhat consistent in analyses conducted on MOAFTS dataset. From this perspective the current results are generally supportive of the notion that 7r are impacted more by environmental influences (e.g., Bakermans-Kranenburg & van Ijzendoorn, 2011; Creswell et al., 2012). Further, this relation did not appear to be moderated by age or explain much overlap between personality and alcohol involvement. In my opinion, the clearest conclusion are that findings reported in the extant GXE are most likely not reliable or robust. Considering no evidence of significant GXE impacting coping

motives and that the overlap between novelty seeking and alcohol dependence was virtually unchanged in models accounting for GXE, the current results did not suggest the interaction between DRD4 status and history of childhood adversity is a common predictor of personality, motives, and alcohol outcomes.

There are several limitations to this study to consider. The current study focused mostly on childhood adversity/history of abuse whereas previous research examining GXE on novelty seeking has used different measures and methods to capture environmental factors (e.g., mother-reported history of harsh parenting; Keltikangas-Järvinen et al., 2004). Thus, though this study had identical measures of DRD4 and very similar measures of personality compared to previous studies the environmental measures were far from isomorphic. The lack of perfect overlap among measures between AHB and MOAFTS data also presents some limitations, as do the differing characteristics of the samples. Notably, this study did not explore a host of potential alternative genetic variants or environments but rather focused on the interaction of DRD4 and childhood adversity to influence levels of impulsivity and coping motives. This decision was based on several considerations, a) DRD4 is the genetic variant that has been most studied in GXE involving approach-related personality traits; to my knowledge DRD4 is the only G in GXE studies involving approach-related traits, b) though not identical to other studies, a history of abuse is a more similar "E" compared to existing studies involving GXE with personality than other potential environments/moderators (e.g., marital status), and c) there is evidence that suggests DRD4 moderates environmental influences on alcohol involvement (e.g., Creswell et al., 2012; and to a lesser extent when considering 7r, Park et al., 2011) and a larger literature suggests DRD4 7rs are more susceptible to

environmental influences in general (see Bakermans-Kranenburg & van Ijzendoorn, 2011). Nevertheless, it is possible that other combinations of GXE that were not explored here (e.g., non- dopaminergic genes, adult roles) relate meaningfully to personality traits related to alcohol involvement. As noted by Carpenter, Tomko, Trull, and Boomsma (2013), this study contained several design features that may impact GXE analyses, including retrospective assessments of environment and small sample sizes for research involving measured genotypes. However, this study represents the largest known study to examine specific GXE on approach-related personality traits and was strengthened by repeated measures of these traits in AHB. Further, though these results are generally consistent with the idea that DRD4 may be a "plasticity" gene rather than a "vulnerability" gene (see Belsky, Jonassaint, Pluess, Stanton, Brummett, & Williams, 2009), it should be noted that there are several methodological issues to be considered when making substantive conclusions from disordinal interactions (Sher et al., in progress).

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Table 1. Standardized factor loadings for respective novelty seeking, impulsivity, and coping motives factors.

	Novelty Seeking	Impulsivity	Coping Motives		
			Trait	Emerging Adulthood	Young Adulthood
Age 18	0.56	0.49	0.68	0.73	-
Age 19			0.74	0.14	-
Age 20			0.70	0.11	-
Age 21			0.76	-0.03	-
Age 25	0.81	0.79	0.68	-	0.34
Age 29	0.85	0.84	0.58	-	0.67
Age 35	0.75	0.73	0.50	-	0.46

Note. All loadings > .15 are significant at $p < .05$.

Table 2. Unstandardized (standardized) coefficients for gene by environment interactions.

	AHB				MOAFTS		
Removing Minorities	Novelty Seeking	Impulsivity	Coping Motives		Novelty Seeking	Control	Coping Motives
7r*Broad Adversity	.57 (.20)+	.46 (.21)+	.04 (.01)	7r*Physical Abuse	2.15*, 68, -.78	-.01	-.15
7r*Physical/Sexual Abuse	.45 (.15)	.15 (.07)	-.20 (-.06)	7r* Physical/Sexual Abuse	.35+	.04	.02
2r/5r*Broad Adversity	-1.19 (-.34)*	-1.06 (-.43)*	-	2r/5r*Physical Abuse	-.58	.03	-
2r/5r* Physical/Sexual Abuse	-.79 (-.23)*	-.76 (-.29)*	-	2r/5r* Physical/Sexual Abuse	-.15	-.02	-
Adjusting for Ethnic/Racial Status							
7r*Broad Adversity	.62 (.21)+	.40 (.18)	-.12 (-.04)	7r*Physical Abuse	.46	.07	-.15
7r*Physical/Sexual Abuse	.30 (.10)	.05 (.02)	-.22 (-.07)	7r* Physical/Sexual Abuse	.30	.04	.02
2r/5r*Broad Adversity	-1.20 (-.38)*	-1.04 (-.43)*	-	2r/5r*Physical Abuse	-.85	-.02	-
2r/5r* Physical/Sexual Abuse	-.74 (-.23)*	-.74 (-.29)*	-	2r/5r* Physical/Sexual Abuse	-.16	-.01	-

Note. * $p<.05$, + $p<.10$. 7r = DRD4 7-repeat carriers vs. non-7-repeat carriers. 2r/5r= DRD 2 or 5-repeat carriers vs. non-2 or 5-repeat carriers. AHB = Alcohol, Health, and Behavior study. MOAFTS = Missouri Adolescent Female Twin Study. Estimate for 7r*Physical Abuse predicting novelty in model removing minorities shows GXE for age one standard deviation below mean age, mean age, and one standard deviation above the mean, suggesting significant GXE in younger participants. Results predicting the overall coping motives trait in AHB is shown. Only unstandardized estimates are shown for MOAFTS data given standardized estimates are not available in SAS PROC MIXED. In MOAFTS, removing thirty-three observations with Cook's D values greater than 4/n changes the estimate and p-value for 7r* Physical/Sexual Abuse predicting novelty seeking from .35 and $p = .09$ to .17 and $p = .40$.

Figure 1. Trait novelty seeking (with standard errors) by DRD4 status (2- and 5-repeats vs. all others) and childhood adversity.

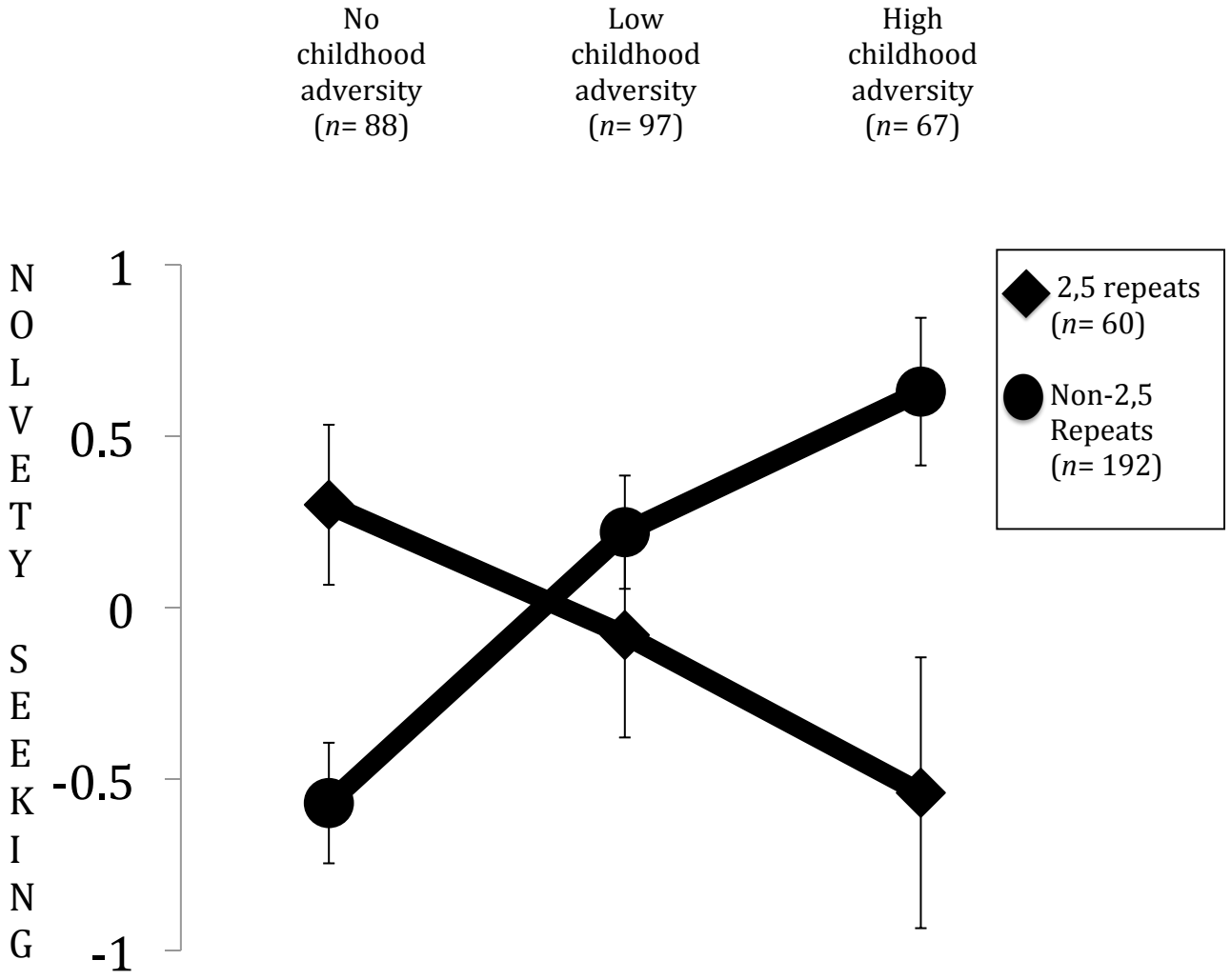


Figure 2. Trait novelty seeking (with standard errors) by DRD4 status (7-repeats vs. all others) and childhood adversity.

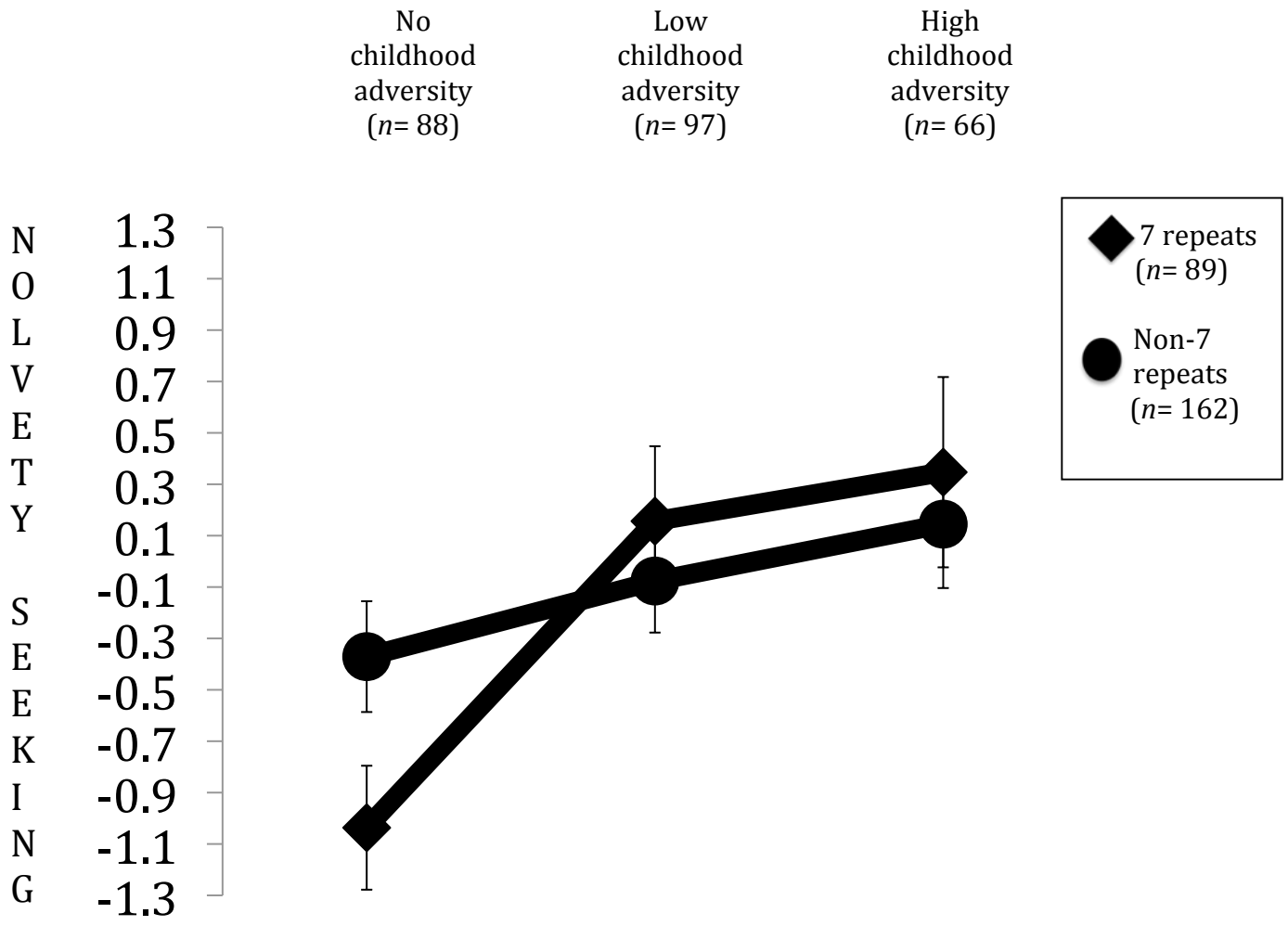
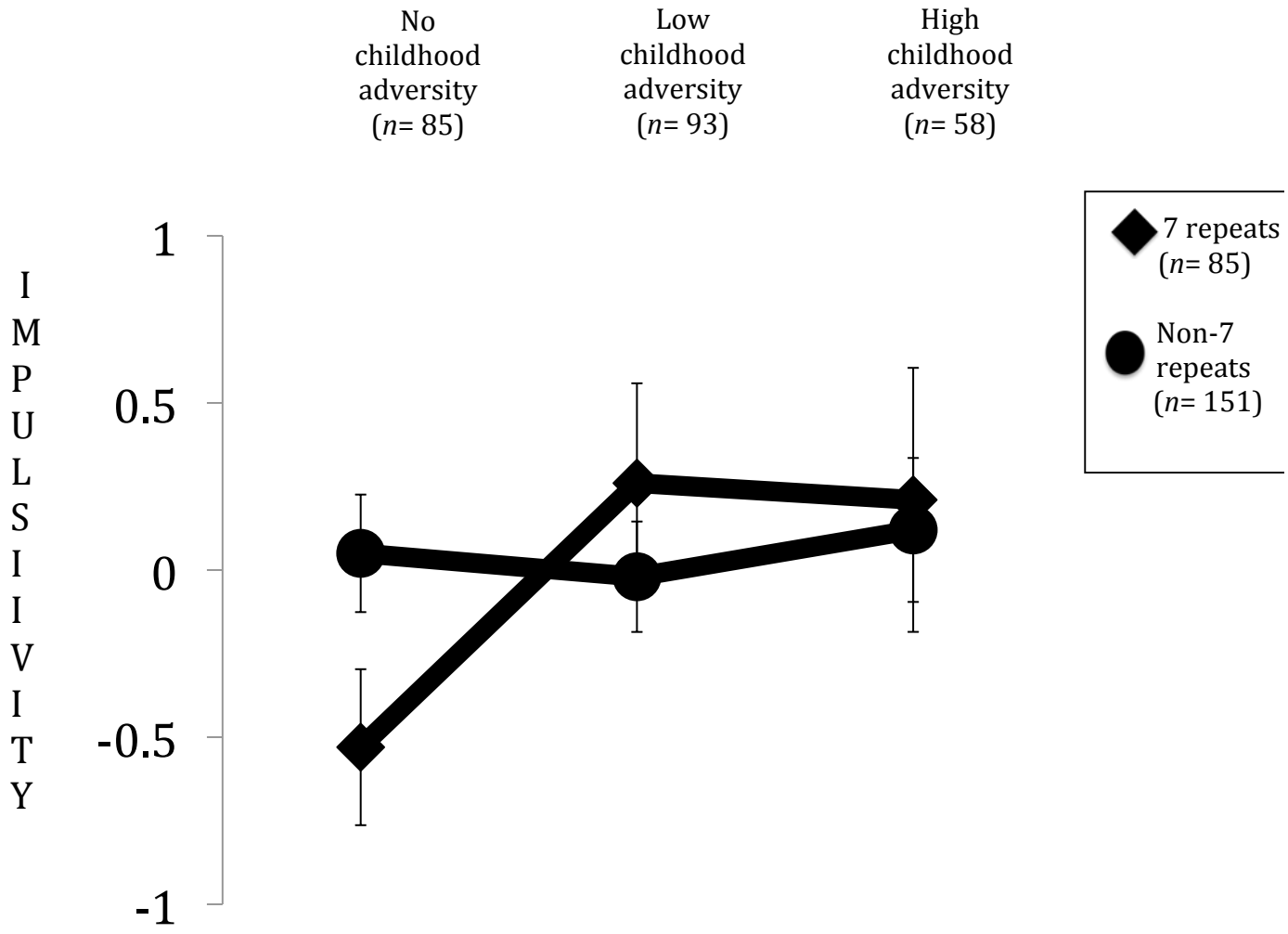


Figure 3. Trait impulsivity (with standard errors) by DRD4 status (7-repeats vs. all others) and childhood adversity.



VITA

Andrew K. Littlefield was born and raised in southwest Missouri. He has obtained two Bachelor's degrees, a Master's degree, and a PhD from the University of Missouri. His research interests are broad and primarily focus on the development and maintenance of substance use disorders. In his spare time Andrew enjoys having fun.