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Jessica E. Salvatore[1], Fazil Aliev[1], Kathleen Bucholz[2], Arpana Agrawal[2], Victor Hesselbrock[3], Michie Hesselbrock[4], Lance Bauer[3], Samuel Kuperman[5], Marc A. Schuckit[6], John R. Kramer[5], Howard J. Edenberg[7], Tatiana M. Foroud[8], and Danielle M. Dick[1]

[1]Department of Psychiatry, Virginia Commonwealth University; [2]Department of Psychiatry, Washington University; [3]Department of Psychiatry, University of Connecticut; [4]School of Social Work, University of Connecticut; [5]Department of Psychiatry, University of Iowa; [6]Department of Psychiatry, University of California, San Diego; [7]Department of Biochemistry and Molecular Biology, Indiana University; and [8]Department of Medical and Molecular Genetics, Indiana University

Abstract

In this project, we aimed to bring large-scale gene-identification findings into a developmental psychopathology framework. Using a family-based sample, we tested whether polygenic scores for externalizing disorders—based on single nucleotide polymorphism weights derived from genome-wide association study results in adults (n = 1,249)—predicted externalizing disorders, subclinical externalizing behavior, and impulsivity-related traits among adolescents (n = 248) and young adults (n = 207) and whether parenting and peer factors in adolescence moderated polygenic risk to predict externalizing disorders. Polygenic scores predicted externalizing disorders in adolescents and young adults, even after we controlled for parental externalizing-disorder history. Polygenic scores also predicted subclinical externalizing behavior and impulsivity traits in the adolescents and young adults. Adolescent parental monitoring and peer substance use moderated polygenic scores to predict externalizing disorders. This illustrates how state-of-the-science genetics can be integrated with psychological science to identify how genetic risk contributes to the development of psychopathology.

Keywords

externalizing disorders, impulsivity, gene-by-environment, gene-by-development, polygenic, developmental, Collaborative Study on the Genetics of Alcoholism (COGA)

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With widespread recognition of the importance of genetic factors on psychopathology, a growing number of psychological studies are incorporating genetic components. However, there are two critical disconnects between the fields of genetics and psychological science. First, the majority of psychological research on measured gene-by-development effects (i.e., how genetic predispositions unfold across time) as well as gene-by-environment effects (i.e., the role of environmental factors in moderating genetic predispositions) has not kept pace with our understanding of the polygenic basis of complex behavioral outcomes. Despite widespread adoption of

Corresponding Authors:
Jessica E. Salvatore and Danielle M. Dick, Department of Psychiatry, Virginia Commonwealth University, P. O. Box 980126, Richmond, VA 23298-0126
E-mails: jesalvatore@vcu.edu and ddick@vcu.edu

candidate-gene approaches—in which a researcher studies genetic variants in a prespecified gene of interest on the basis of its putative biological function (such as the serotonin-transporter-linked polymorphic region in *SLC6A4*)—very few well-replicated associations have emerged from these hypothesized genes of interest (Bosker et al., 2011; Collins, Kim, Sklar, O'Donovan, & Sullivan, 2012). Exceptions to this include variants in the alcohol dehydrogenase gene cluster and alcohol outcomes (Gelernter et al., 2014; Thomasson et al., 1991) and nicotinic receptor genes for smoking outcomes (Broms et al., 2012; Tobacco and Genetics Consortium, 2010). Candidate-gene approaches are also at odds with our understanding that behavioral outcomes are likely to have a polygenic architecture, which means that they include the effects of many common variants of small magnitude across the genome (Plomin, Haworth, & Davis, 2009). Now that there are relatively inexpensive methods for genotyping hundreds of thousands of genetic variants across the genome, candidate-gene approaches no longer represent the state of the science for examining measured gene-by-development and gene-by-environment effects.

Second, the nature of large-scale gene-identification efforts for many common disorders has created a gap in our understanding of how the emerging findings fit into a developmental psychopathology framework. In one common gene-identification study design, known as a genome-wide association study (GWAS), researchers systematically examine whether genotype frequencies for variants across the genome differ between individuals who are affected and unaffected with a disorder. In the area of externalizing-disorder research, adults are often the focus of these investigations because the average age at onset for these disorders is in late adolescence or early adulthood (Hingson, Heeren, & Winter, 2006; Warner, Kessler, Hughes, Anthony, & Nelson, 1995). This makes it important to use adult samples that have passed through the period of greatest risk for developing the disorder in these gene-identification efforts to increase the probability that individuals who are classified as "unaffected" are truly unaffected. Still, it is widely recognized that externalizing disorders do not typically appear de novo in adulthood; rather, they are often foreshadowed by precursor disorders, personality traits, or patterns of behavior (Cicchetti, 1984), some of which are genetically correlated with the eventual adult disorder (i.e., gene-by-development effects).

For example, twin studies have demonstrated that adolescent conduct disorder (CD) and adult alcohol dependence partly share genetic influences (Slutske et al., 1998), and analyses of a specific gene, *GABRA2*, have provided further evidence that this is the case, thereby yielding association with conduct symptoms in adolescents and alcohol problems in adults (Dick et al., 2006). Likewise, polygenic scores that include the effects of many genes illustrate that genetic influences on smoking behaviors differ as a function of developmental stage (Belsky et al., 2013; Vrieze, McGue, & Iacono, 2012). These latter two examples notwithstanding, there have been limited attempts to bring the results from large-scale gene-identification efforts into a developmental psychopathology framework to examine how these genetic predispositions unfold across time, which makes this an important gap in the literature.

Bridging these disconnects and bringing together the best theories and practices in genetics and clinical psychological science is central for understanding how genetic predispositions for behavioral outcomes manifest across development and interface with environmental factors. In the present study, we address these critical gaps in the area of externalizing-disorder research by taking a polygenic approach. This approach considers the contributions of many common genetic variants of small magnitude across the genome to examine gene-by-development and gene-by-environment effects, and it has demonstrated predictive power in cases in which individual genes do not (International Schizophrenia Consortium, 2009). The approach typically uses results from a GWAS. Selecting a liberal *p*-value threshold, a polygenic score for each individual is calculated by summing over the number of alleles for each single nucleotide polymorphism (SNP)—the most common type of genetic variation that involves a single nucleotide substitution in a DNA sequence, such as an adenine substitution for a guanine base—weighted by the effect size drawn from a GWAS. The score then represents the composite additive effect of these multiple variants. As an example, consider two SNPs with the following alleles: SNP 1 (C/T) and SNP 2 (A/G). If a GWAS indicates that increasing copies of the T and G alleles are associated with a higher level of externalizing disorders (βs = 0.06 and 0.08), then an individual who carries two copies for the T and G alleles will have a polygenic score equivalent to $2 \times 0.06 + 2 \times 0.08 = 0.28$, and an individual who carries one copy for the T and G alleles will have a polygenic score equivalent to $1 \times 0.06 + 1 \times 0.08 = 0.14$. A higher polygenic score indicates a greater genetic predisposition toward that trait.

We first tested whether polygenic risk for adulthood externalizing disorders predicted externalizing disorders in adolescents and young adults and whether any observed polygenic effects were robust after we controlled for parental externalizing-disorder history. These analyses addressed the question of whether polygenic risk for adulthood disorders manifest at a clinical level in adolescents and young adults. We then ran a series of analyses to examine whether polygenic risk for adulthood externalizing disorders predicted subclinical levels of

externalizing behavior as well as impulsivity-related traits in adolescents and young adults. These analyses addressed the possibility that polygenic risk for adulthood externalizing disorders may not be related to clinical-level externalizing disorders in adolescents and young adults but, rather, subclinical levels of externalizing behaviors (measured using the Achenbach Externalizing Scale) and broadband indicators of impulse control. We focused on impulsivity-related traits, given that the inability to control impulses is the defining feature of the highly heritable genetic factor shared across externalizing disorders (Kendler, Prescott, Myers, & Neale, 2003; Krueger et al., 2002; Young, Stallings, Corley, Krauter, & Hewitt, 2000). We hypothesized that adolescents and young adults who are genetically predisposed toward adulthood externalizing disorders would have higher levels of subclinical externalizing behaviors and impulsivity. We used a range of impulsivity measures, including impulsiveness, conscientiousness (i.e., constraint), and sensation seeking, to capture impulsivity's multifaceted nature (Depue & Collins, 1999; Evenden, 1999; Miller, Joseph, & Tudway, 2004; Whiteside & Lynam, 2001).

Finally, we examined whether adolescents' reports of parental monitoring and perceived peer substance use moderated polygenic scores to predict externalizing disorders. Our gene-by-environment hypotheses were informed by twin studies, which have demonstrated that permissive environments may allow for the expression of latent genetic predispositions for externalizing psychopathology that more restrictive environments inhibit (Shanahan & Hofer, 2005). Two of the more robust moderation effects in this area are observed for adolescent parental monitoring (i.e., parents' knowledge of one's plans, whereabouts, and friends) and peer deviance (i.e., friends' engagement in substance use or criminal activity). Previous studies have indicated that genetic influences on externalizing increase under conditions of low parental monitoring or high peer deviance (Button et al., 2007; Harden, Hill, Turkheimer, & Emery, 2008; Hicks, South, DiRago, Iacono, & McGue, 2009). However, this has been demonstrated only in twin data, in which genetic influences are inferred by comparisons of relative types; it has not been explored with respect to measured genome-wide indices of risk. We hypothesized that polygenic predispositions toward externalizing disorders would be more pronounced under conditions of lower parental monitoring and higher peer substance use.

Method

Sample

Participants came from the Collaborative Study on the Genetics of Alcoholism (COGA; Begleiter et al., 1995), whose objective is to identify genes involved in alcohol dependence and related disorders. Probands were identified through alcohol treatment programs at six U.S. sites and were invited to participate if they had a sufficiently large family (usually sibships of more than three with parents available) with two or more members in the COGA catchment area. The institutional review boards at all sites approved this study, and written consent was obtained from all participants. As shown in Figure 1, the present analyses included a subset of 118 European American COGA families densely affected with alcohol dependence (at least 3 or more affected members) and for whom genome-wide association data were available (Kang et al., 2013; J. C. Wang et al., 2013). By design, this sample was limited to European American individuals to avoid false positives in the GWAS driven by population stratification (i.e., differences in allele frequencies between populations; for a review, see Cardon & Palmer, 2003). We focused on the adolescent (ages 12–17) and young adult (ages 18–24) participants in the family-based sample who are also part of the COGA Prospective Study of the developmental antecedents of alcohol dependence (Dick et al., 2013). The adolescent and young adult prospective participants were recruited into the COGA Prospective Study beginning in 2004 and have been followed up biennially ever since.

Data on subclinical externalizing behavior, impulsivity-related traits, parental monitoring, and perceived peer substance use came from prospective participants' first assessment of these constructs (adolescents: n = 248, 54% male, 46% female, mean age = 14.44 years, SD = 1.78, range = 12–17; young adults: n = 207, 47% male, 53% female, mean age = 19.86 years, SD = 1.41, range = 18–24). We note that data on parental monitoring and peer substance use were available for adolescent prospective participants only. Given the longitudinal design of the COGA Prospective Study, prospective participants have completed the externalizing-disorders psychiatric interview multiple times. We used data from the interview in which they endorsed the greatest number of alcohol-dependence criteria to create the externalizing-disorder composite, and we note that the mean ages at which the adolescent and young adult groups completed their psychiatric interviews were 16.74 (SD = 1.87) and 21.63 (SD = 2.95), respectively. Our scientific rationale for using externalizing-disorder data from a single interview (vs. calculating average scores across multiple assessments) was that in a high-risk sample such as COGA, we wanted to measure individuals' greatest expression of their predisposition to the externalizing disorder (i.e., alcohol dependence) on which the sample was originally ascertained.

For the GWAS of adult externalizing disorders, we used the participants who were 29 years of age and older

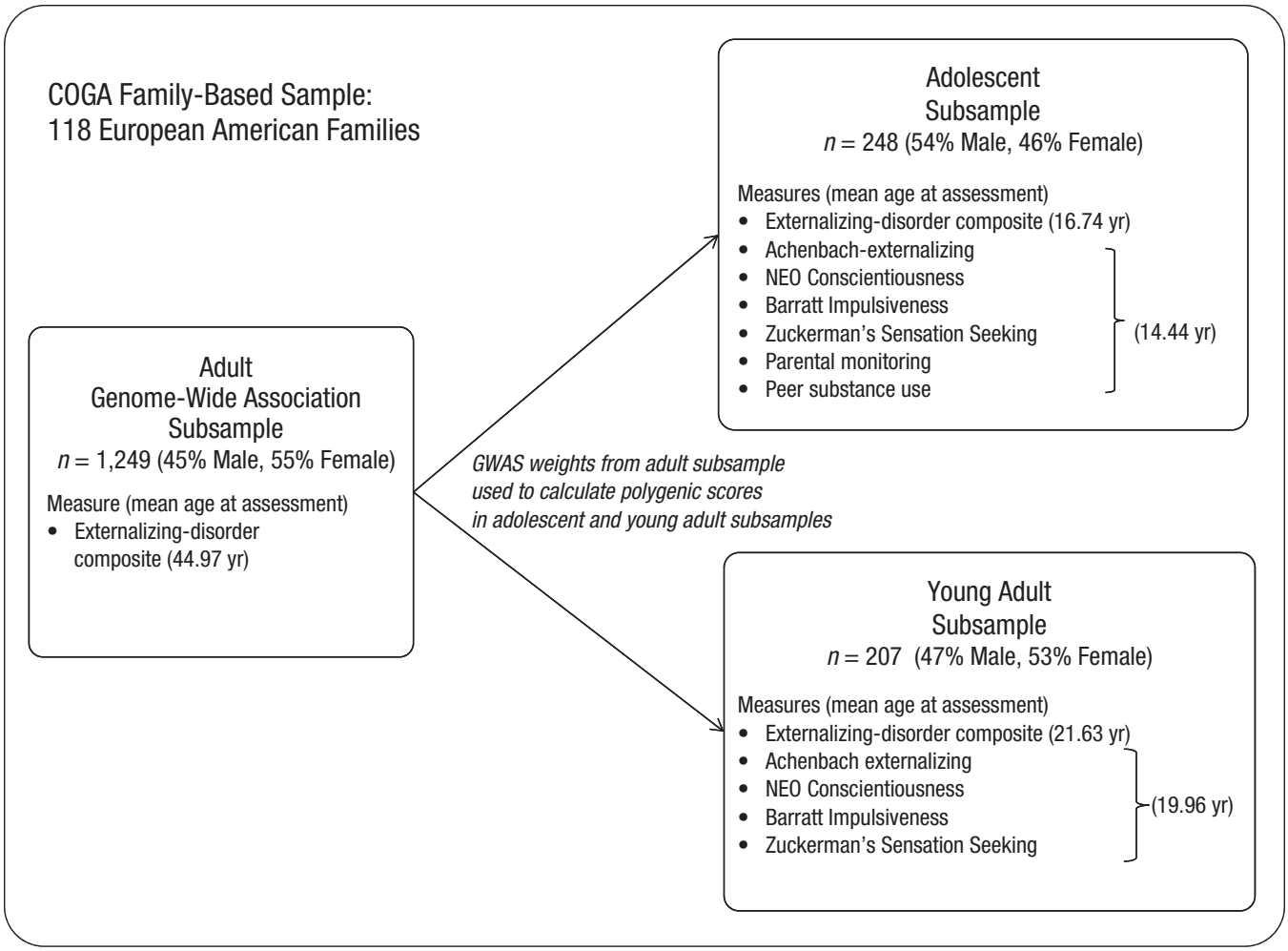

Fig. 1. Schematic of study sample. The adult genome-wide association study (GWAS) subsample included adult participants who were 29 years of age and older at the time of their psychiatric interviews. The GWAS weights from the adult subsample were used to calculate polygenic scores in the subsamples of adolescents and young adults. yr = years.

at the time of their psychiatric interviews (n = 1,249, 45% male, 55% female, mean age = 44.97 years, SD = 12.56, range = 29–88). The age cutoff was selected because the oldest prospective participant's externalizing-disorder data came from a psychiatric interview conducted at age 28. As described in J. C. Wang et al. (2013), the sample was genotyped on the Illumina Human OmniExpress array 12.VI. In total, 587,378 SNPs with minor allele frequency greater than 5% and genotyping success rate per individual greater than 75% were analyzed.

Measures

Externalizing-disorder composite. We created an externalizing-disorder composite based on *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM–IV*; American Psychiatric Association, 1994) alcohol dependence and abuse criteria, *DSM–IV* illicit-drug (cocaine, marijuana, sedatives, stimulants, opiates, and other drugs) dependence and abuse criteria, and antisocial-behavior criteria measured with *DSM–IV* or *DSM–III–R* (3rd ed., rev.; American Psychiatric Association, 1987) antisocial personality disorder (ASPD) or CD criteria, depending on age. Criterion counts were obtained from the reliable (kappas for individual diagnoses range from .70–.90) and valid Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; for those individuals 18 years of age or older) or the adolescent version of the SSAGA (for those individuals 12–17 years of age; Bucholz et al., 1994; Hesselbrock, Easton, Bucholz, Schuckit, & Hesselbrock, 1999). We did not include attention-deficit/hyperactivity disorder, given the mixed literature on the genetic epidemiology of the disorder vis-à-vis other externalizing disorders (Young et al., 2000). Antisocial behavior was measured using either criterion counts for *DSM–IV* ASPD or ASPD *DSM–III–R* criteria modified to

match ASPD *DSM–IV* criteria. Because ASPD is assessed only in those 18 years of age and older, *DSM–III–R* or *DSM–IV* CD criteria were substituted for those younger than 18. Given that ASPD and CD have different numbers of criteria, CD criterion counts were proportionally scored to create a comparable range (0–7) with ASPD scores (e.g., a participant endorsing 7 of 15 CD criteria would receive a proportional score of 3.23/7). Illicit-drug dependence and abuse were measured with separate sum scores of *DSM–IV* cocaine, marijuana, sedatives, stimulants, opiates, and other drugs dependence and abuse criterion counts. For participants with data on the alcohol and illicit-drug dependence and abuse and antisocial-behavior variables—2,148 individuals (93%) in the family-based sample (47% male, 53% female)—we extracted component scores from a principal component analysis. A single component accounted for 68% of the common variance among the externalizing-disorder variables with the following loadings: alcohol dependence, 0.86; alcohol abuse, 0.86; antisocial behavior, 0.80; illicit-drug dependence, 0.82; illicit-drug abuse, 0.79.

Parental externalizing-disorder history. Parental externalizing-disorder data were available for 435 (96%) of the mothers and 326 (72%) of the fathers of prospective participants. We used a three-category measure for parental externalizing-disorder history. Individuals for whom either parent had an externalizing-disorder diagnosis (n = 352, or 77%; of these, 151, or 33%, had two affected parents; 87, or 19%, had only an affected/known to be affected father; and 114, 25%, had only an affected/known to be affected mother) were set as the reference group and were compared with those for whom neither parent had an externalizing-disorder diagnosis (n = 47, 10%) and those for whom there was incomplete parental externalizing-disorder history information (i.e., one parent was unaffected and the other parent was missing externalizing-disorder data; n = 55, 12%).

Achenbach Externalizing Adult Self-Report and Youth Self-Report. Participants were asked how well a series of items described their externalizing behavior in the past 6 months; responses were made on a scale from 0 (*not true*) to 2 (*very true or often true*). Young adult prospective participants were administered the Adult Self-Report (ASR) form (Achenbach & Rescorla, 2001), and their adolescent counterparts were administered the Youth Self-Report (YSR) form (Achenbach, 2003). The YSR and ASR included 32 and 35 items, respectively, tapping rule breaking, aggressive, and intrusive (ASR only) behavior. Sum scores were used.

Barratt Impulsiveness Scale. The Barratt Impulsiveness Scale (Patton, Stanford, & Barratt, 1995) asked participants how well a series of 30 statements related to attentional, motor, and nonplanning impulsiveness described their behavior; responses were made on a scale ranging from 1 (*rarely/never*) to 4 (*usually*). The adolescents completed a modified version so that the questions were more appropriate to adolescents. A sum score was used.

Conscientiousness. Participants responded to the 60-item NEO Five Factor Inventory (Costa & McCrae, 1986) by indicating how well a series of statements described their behavior; responses were made on a 5-point scale with anchors ranging from *strongly disagree* to *strongly agree*. We used sum scores from the Conscientiousness subscale.

Sensation Seeking Scale. The Sensation Seeking Scale (Zuckerman, 1984) presented participants with 40 pairs of items related to differences in stimulation and arousal. A 26-item version was used for adolescents and included modified items on substance use and sexual activity (Russo et al., 1993). Sum scores were used.

Parental monitoring and perceived peer substance use (adolescents only). The measure of parental monitoring asked participants three questions (how much their parent figures know about their plans, their interests, and where and with whom they spend time when not at home) from Chassin, Pillow, Curran, Molina, and Barrera (1993). Responses were made on a 4-point scale from 1 (*always*) to 4 (*rarely*), and the interitem correlations ranged from .45 to .56 (all ps < .0001). The four questions on perceived peer substance use came from FinnTwin12 (Kaprio et al., 2002) and asked participants about how many of their friends smoke, use alcohol, use marijuana, or use other drugs; responses were made on a scale ranging from 1 (*none of them*) to 4 (*all of them*). The interitem correlations for the questions on peer substance use ranged from .45 to .65 (all ps < .0001). Items were summed to create separate composites for parental monitoring and peer substance use. Prior to summing, the items on parental monitoring were reverse-scored so that higher scores indicated more parental monitoring.

Statistical analyses

GWAS and computation of polygenic scores. We ran a family-based GWAS using the GWAF package (Chen & Yang, 2010) on the adult subsample (n = 1,249), which accounts for familial nesting and genetic distance using a kinship matrix. Covariates included gender, age at interview, and cohort. We then used GWAS estimates to calculate polygenic scores for the adolescent and young adult prospective participants using the --score

Table 1. Regressions of the Externalizing-Disorder Composite Onto Polygenic Scores and Covariates in Adolescents and Young Adults

	Adolescent (n = 246, df = 156)				Young adult (n = 190, df = 106)			
	Model 1		Model 2		Model 1		Model 2	
Measure	*b*	*t*	*b*	*t*	*b*	*t*	*b*	*t*
Intercept	***–2.48*** (***0.24***)	***–10.45***	***–2.57*** (***0.24***)	***–10.75***	0.36 (0.49)	0.46	0.54 (0.50)	1.08
Polygenic score	***6.33*** (***1.33***)	***4.74***	***5.85*** (***1.51***)	***3.87***	***12.62*** (***3.00***)	***4.21***	***10.49*** (***3.34***)	***3.14***
Gender	**–0.10** (**0.04**)	**–2.34**	**–0.09** (**0.04**)	**–2.06**	0.00 (0.10)	0.04	0.01 (0.10)	0.06
Age	***0.12*** (***0.01***)	***8.34***	***0.12*** (***0.01***)	***8.61***	–0.02 (0.02)	–1.06	–0.03 (0.22)	–1.25
Parental history								
Either parent ED	—	—	Ref.	Ref.	—	—	Ref.	Ref.
Neither parent ED	—	—	–0.08 (0.05)	–1.68	—	—	–0.18 (0.11)	–1.53
Incomplete parent ED	—	—	**0.12** (**0.06**)	**2.09**	—	—	**–0.30** (**0.11**)	**–2.61**

Note: Standard errors are shown in parentheses. Model 1 includes gender and age as covariates. Model 2 includes gender, age, and parental externalizing-disorder (ED) history as covariates. The "neither parent ED" contrast was not significant in the multivariate model for adolescents or young adults; however, it did have univariate main effects in the respective models—adolescents: $b = –0.25$, $t(156) = –6.68$, $p < .001$; young adults: $b = –0.44$, $t(106) = –3.21$, $p < .001$. Boldface indicates significant statistics ($p < .05$). Italic boldface indicates significant statistics ($p < .01$). Ref. = set as reference. We note that the degrees of freedom reported for these t tests are adjusted to reflect the nested nature of the data (i.e., individuals were nested within families).

procedure in PLINK (Purcell et al., 2007), which computes a linear function of the number of score alleles an individual possesses weighted by the associated GWAS t statistic.

Given that there are no set criteria for establishing a threshold to create maximally informative scores (Evans, Visscher, & Wray, 2009), we conducted preliminary analyses using a series of p-value thresholds ranging from .05 to .50 to evaluate what threshold maximized the variance accounted for (R^2) in the externalizing-disorder composite in the adolescent subsample. We maximized R^2 in this subsample because it was the one in which we subsequently evaluated gene-by-environment effects, and previous work has suggested that SNPs with a nominal main effect may be enriched for gene-by-environment interaction (Thomas, 2010). There was little variability in the percent variance accounted for (range = 5.5–5.9%); a p-value threshold less than .30 (176,562 SNPs) maximized R^2 and was used to create polygenic scores for adolescents and young adults.

Prospective sample polygenic-association and environmental-moderation analyses. Association and moderation analyses for the prospective sample were conducted using the SURVEYREG procedure in SAS, which accounts for the nesting of individuals within families (90 and 84 families were represented in the subsamples of adolescents and young adults, respectively). Covariates included gender and age at assessment. For the association analyses, we examined the variance (R^2) in the externalizing-disorder composite and impulsivity-related traits explained by polygenic scores in the adolescent and young adult prospective subsamples. We examined these associations in adolescents and young adults separately because of measurement differences and in view of the numerous social and legal changes during the transition to adulthood that may change gene-behavior associations. We then tested for gene-environment interaction with parental monitoring and peer substance use in the adolescent subsample (i.e., the subsample for which these environmental measures were available and likely to be developmentally relevant). It has been suggested that variants having a nominal association with an outcome are likely to be enriched for gene-by-environment interaction (Thomas, 2010). Accordingly, we focused our gene-by-environment analyses in adolescents on an externalizing-disorder composite because we constructed our polygenic scores using estimates from a GWAS of an externalizing-disorder composite in adults. We used a p value of less than .05 as suggestive evidence for association and moderation because our tests were not independent (owing to correlated phenotypes) and a Bonferroni correction would be too stringent.

Results

Descriptive statistics, GWAS results, and polygenic-association analyses

The descriptive statistics and correlations across all phenotypes for adolescents and young adults are provided in Tables S1 and S2 in the Supplemental Material available online. The phenotypes were moderately to highly correlated across both age groups, although conscientiousness

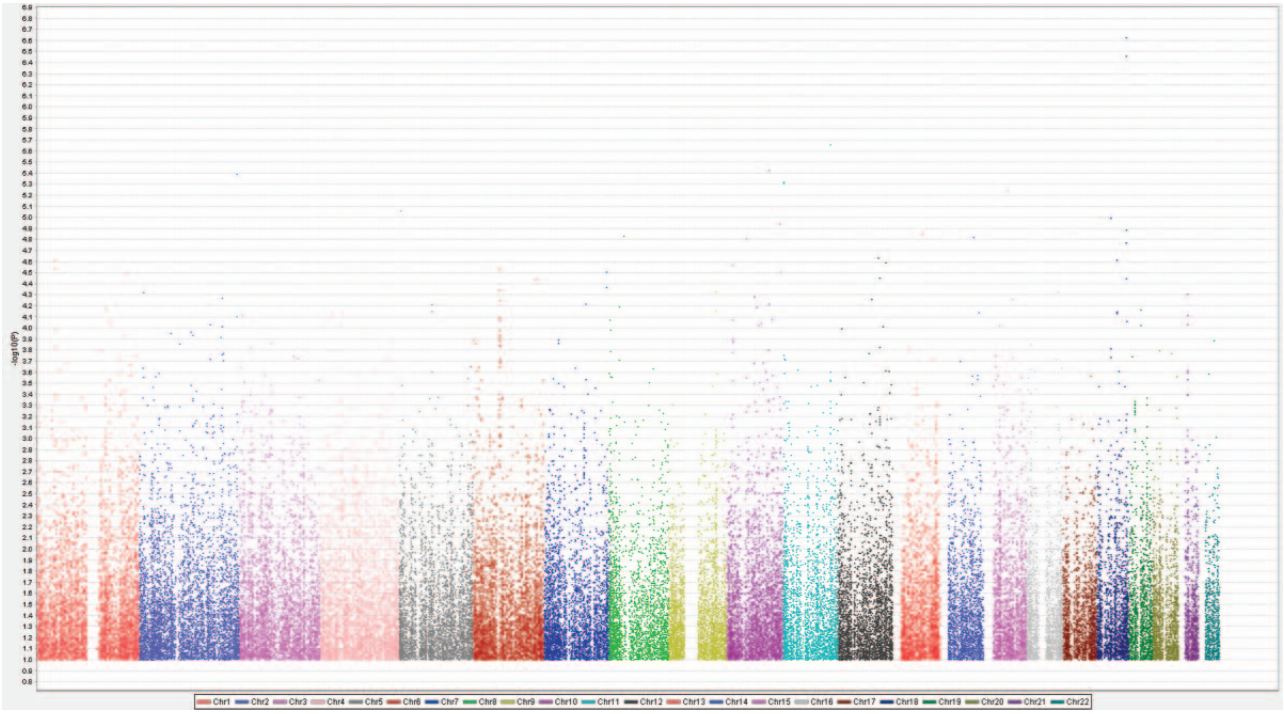

Fig. 2. Association results from the genome-wide association study of the externalizing-disorder composite in the adult sample. On the *x*-axis are chromosomes (Chrs) 1 through 22. On the *y*-axis are inverse logarithms of the *p* values for each single nucleotide polymorphism.

Table 2. Variance Explained (R^2) in Subclinical Externalizing Behavior and Impulsivity-Related Traits as a Function of Polygenic Scores

Measure	Adolescent	Young adult
Achenbach externalizing	***.05***	***.01***
Barratt impulsiveness	***.07***	***.03***
Conscientiousness	***.02***	.00
Sensation seeking	.01	***.02***

Note: Boldface indicates significant values ($p < .05$). Italic boldface indicates significant values ($p \leq .01$).

did not relate to the substance-use and antisocial-behavior variables in young adults. Low parental monitoring and high peer substance use were associated with higher externalizing-disorder composite scores (rs = –.38 and .56, ps < .01).

The GWAS results are summarized in Figure 2 and the quantile-quantile plot is shown in Figure S1 in the Supplemental Material. The genomic-inflation factor, which is mathematically defined as the ratio of the median of the observed distribution of the GWAS test statistic to the expected median (Devlin & Roeder, 1999) was acceptable ($\lambda = 1.01$). Extreme deviations in lambda indicate an excess false-positive rate (i.e., inflation) in a GWAS, which may be attributable to technical problems in the genotyping or uncontrolled population stratification. Thus, in our study, technical issues and population stratification did not appear to inflate the results. The most associated SNP ($p = 2.37 \times 10^{-07}$) was located in zinc finger protein 407 (*ZNF407*) on chromosome 18.

Polygenic scores predicted the externalizing-disorder composite in adolescents and young adults and accounted for 6% of the variance after we controlled for gender and age (see Table 1). Polygenic scores continued to predict the externalizing-disorder composite after we controlled for parental externalizing-disorder history (see Table 1). Table 2 summarizes the variance (R^2) in subclinical externalizing behavior and impulsivity-related traits explained by polygenic scores after we controlled for gender and age. Higher polygenic scores predicted higher Achenbach externalizing and impulsiveness in adolescents and young adults. Higher polygenic scores predicted lower conscientiousness in adolescents but not in young adults. Higher polygenic scores predicted higher sensation seeking in young adults but not in adolescents.

Polygenic Score × Environmental Moderators analyses

Separate moderated multiple regression analyses using the adolescent subsample indicated that parental monitoring and peer substance use moderated polygenic risk to predict the externalizing-disorder composite after we

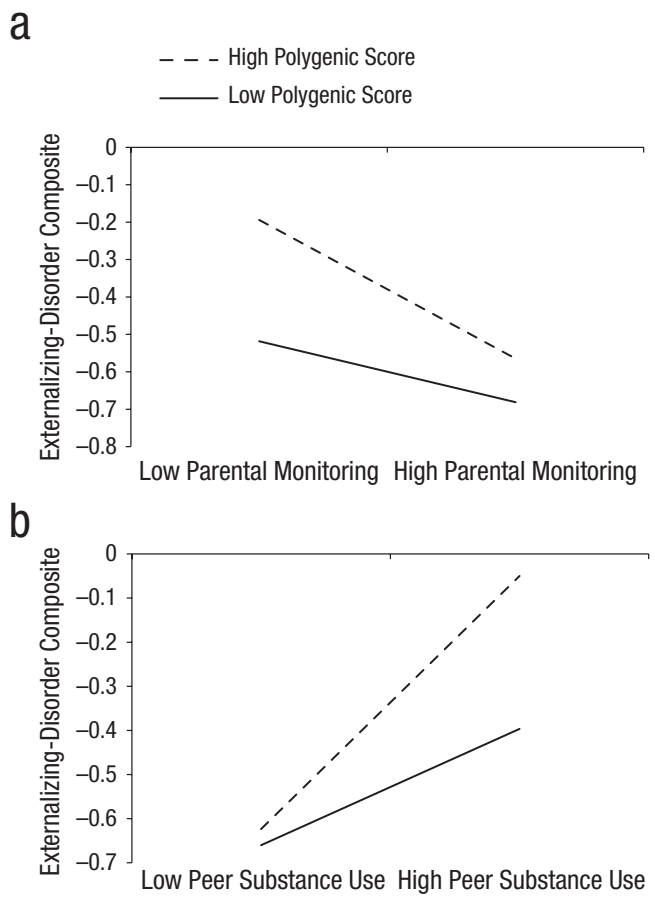

Fig. 3. Polygenic risk to predict the externalizing-disorder composite as a function of adolescent (a) parental monitoring and (b) perceived peer substance use. Interactions are plotted as predicted values. Illustrative low and high values (1 *SD* above and below the mean) for the polygenic scores, parental monitoring, and peer substance use are shown. Values on the *y*-axis are negative because externalizing-disorder composite scores in the adolescent sample were lower, on average, compared with the full sample on which component scores were derived.

controlled for gender, age, and the main effects of the polygenic score and parental monitoring and peer substance use. However, we note that the moderation effect was only marginally significant for parental monitoring—$b_{\text{Parents} \times \text{Polygene}} = -1.30$, $t(154) = -1.88$, $p = .06$, $R^2 = 1\%$; $b_{\text{Peers} \times \text{Polygene}} = 1.81$, $t(155) = 2.68$, $p < .01$, $R^2 = 2\%$. Genetic effects were more pronounced at low levels of parental monitoring and high levels of peer substance use compared with high levels of parental monitoring and low levels of peer substance use (see Fig. 3).

To address concerns that these gene-by-environment effects were due to gene-environment correlation (polygenic scores predicted 1% and 2% of the variance in parental monitoring and peer substance use), we reran our gene-by-environment analyses using residualized variables for polygenic score, parental monitoring, and peer substance use (e.g., by saving the residuals from a regression of polygenic scores onto parental monitoring and vice versa). The use of residualized variables statistically eliminates gene-environment correlation in the model because the genetic and environmental effects have been partialed from one another. The gene-by-environment effects continued to be significant—$b_{\text{Parents} \times \text{Polygene}} = -1.60$, $t(154) = -1.88$, $p = .02$; $b_{\text{Peers} \times \text{Polygene}} = 1.97$, $t(155) = 2.84$, $p < .01$—and again indicated that genetic variance increased at low levels of parental monitoring and high levels of peer substance use.

Discussion

We used genome-wide SNP data to examine how polygenic predispositions for adulthood externalizing disorders manifest in earlier developmental stages and whether key environmental factors moderate genetic influences to predict externalizing disorders. We found a modestly sized effect whereby genetic predispositions toward externalizing disorders in adulthood also manifest as clinical-level problems at younger ages. Identification of whether the small effect size reflects a modest genetic correlation between adolescent and adult externalizing disorders or is attributable to the fact that GWAS-derived polygenic scores account for only common (vs. rare; Gibson, 2012) genetic variation is an important direction for future research. It is especially impressive that polygenic scores predicted adolescents' and young adults' externalizing-disorder composite even after we accounted for parental externalizing-disorder history. We also found that genetic predispositions for adult externalizing disorders predicted subclinical externalizing behavior and multiple facets of impulsivity in adolescents and young adults. This nicely maps onto evidence from twin studies that has shown that a highly heritable behavioral-disinhibition factor broadly predisposes individuals to a range of externalizing disorders (Kendler et al., 2003; Krueger et al., 2002). The differential age associations for conscientiousness and sensation seeking, whereby polygenic scores predicted lower levels of adolescent conscientiousness (i.e., constraint) and higher levels of young adult sensation seeking, but not the reverse, suggest that the genetic influences on distinct impulsivity dimensions may change across development.

Finally, polygenic scores had differential associations with the externalizing-disorder composite in the context of different environments, with stronger effects for peer substance use. Genetic differences were more pronounced under conditions of low parental monitoring or high peer substance versus conditions of high parental monitoring or low peer substance use. This parallels findings from twin studies that have shown that genetic influences for externalizing behavior increase under conditions

of low parental monitoring and high peer deviance (Button et al., 2007; Harden et al., 2008; Hicks et al., 2009). Such moderation effects likely reflect conditions or processes that may limit the expression of an individual's genetic predispositions toward externalizing (Shanahan & Hofer, 2005). We also note that there was evidence for gene-environment correlation, which is common for psychiatric disorders (Kendler & Baker, 2007). Although gene-environment correlations can produce spurious gene-environment interactions, that concern is mitigated by previous twin analyses in this area that yield evidence for gene-environment interaction after accounting for gene-environment correlation (Button et al., 2007; Hicks et al., 2009) and by our supplementary analyses in which we partialed for gene-environment correlation.

As a whole, the present study brings large-scale gene-identification efforts into a developmental psychopathology framework to better understand gene-behavior associations. Applying GWAS results for adult externalizing disorders to younger samples and conducting more fine-grained gene-by-development and gene-by-environment analyses is an important integration of the current best practices in genetics research with the types of research questions that are of key interest to psychologists. It is encouraging to see that measured genotypic results are consistent with gene-by-development and gene-by-environment findings from samples of twins, particularly in view of the criticisms of twin methods (for a review of these critiques, see Tenesa & Haley, 2013). Twin models characterize "genetic influence" latently by inferring genetic influence based on differences between relatives with varying degrees of genetic sharing. Polygenic-risk scores provide a specific measure of genetic risk based on measured genotypes. The fact that divergent methods produce convergent results provides compelling evidence for the developmental and gene-by-environment effects reported here. Furthermore, polygenic approaches have the advantage of providing a more global index of genetic risk that goes beyond widely criticized and only nominally informative candidate-gene studies (Duncan & Keller, 2011). Although polygenic approaches do not—by design—identify specific genes associated with an outcome, complementary methods such as gene-set analyses may identify the potential biological mechanisms underlying their effects (e.g., through examination of whether SNPs included in polygenic scores are located in functionally related genes; L. Wang, Jia, Wolfinger, Chen, & Zhao, 2011). We return to this point shortly.

Despite enthusiasm for using genome-wide information for personalized medicine (Hamburg & Collins, 2010), our results echo the conclusions from previous work (Yan et al., 2013) that it would be premature to use empirically derived polygenic scores to predict an individual's risk for developing externalizing disorders. Rather, our results highlight the potential clinical utility of environmentally focused preventions and interventions for moderating genetic predispositions toward externalizing disorders. Individuals who are genetically predisposed toward externalizing disorders may particularly benefit from such intervention efforts (see Brody, Beach, Philibert, Chen, & Murry, 2009, for an example).

Our study has several limitations. First, our participants included only individuals of European American descent. We selected a homogenous sample to reduce GWAS false positives due to population stratification; however, the GWAS weights we used to calculate the externalizing-disorder polygenic scores in the present study may have limited generalizability as a result. This is because GWAS findings across a number of complex traits from individuals of European ancestry do not replicate in individuals of African ancestry (Marigorta & Navarro, 2013). Relatedly, recent findings from an alcohol-dependence GWAS have implicated the same alcohol-metabolizing pathways and genes in African Americans and European Americans; however, the specific genetic variants differ across populations (Gelernter et al., 2014). Thus, the GWAS weights used to create the polygenic scores in the current study may not be appropriate for constructing externalizing-disorder polygenic scores in samples of diverse ancestry. Second, although we found evidence for our hypothesized main and interactive effects, they account for only a small amount of the variance. Third, we relied on a modest set of self-report measures of the parenting and peer environments, and the incorporation of information from additional reporters or the use of additional methods is important. Finally, our subsamples of adolescents and young adults included broad age ranges, and we were unable to test whether our associations changed as a function of age due to limited sample size.

In summary, we found that polygenic risk for externalizing disorders in adulthood is associated with externalizing disorders, subclinical externalizing behavior, and several impulsivity-related traits in adolescents and young adults and is moderated by adolescent parenting and peer factors. Examination of how polygenic predispositions for externalizing disorders manifest across development and interact with salient environmental moderators is a potentially useful way to characterize pathways toward disorder. These results raise several high-priority directions for future research. Here, we highlight two directions that we believe have the greatest promise for advancing understanding of how genetic predispositions toward adult externalizing disorders manifest earlier in development and interact with environmental factors.

First, development of theory-driven, holistic measures of the environment is central for moving this area of research forward. In the present study, as in many gene-by-environment interaction studies, we considered

parental monitoring and peer substance use in isolation. However, environmental risk factors are often related to one another, and there is no unified framework for measuring or modeling cumulative risk in gene-by-environment interaction studies. A corollary to this point is that to understand gene-by-environment interactions for clinical outcomes across development—an approach that is important for creating effective early preventive-intervention efforts—holistic models of the environment will need to incorporate a developmental perspective. For example, exposure to risk factors later in development may be offset by experiencing protective factors earlier in development (and vice versa; Rönkä, Oravala, & Pulkkinen, 2002; Salvatore, Haydon, Simpson, & Collins, 2013; Sroufe, Egeland, & Kreutzer, 1990). Bronfenbrenner's (1979) classic ecological model, which conceptualizes the environment as a series of transactional, nested environments that both affect and are affected by one another, provides a useful heuristic for what we are suggesting. Translating this conceptual model into an empirical one is critical for moving beyond "candidate environments" and toward an integrative, developmentally sensitive understanding of how multiple, nested environments are likely to interface with genetic predispositions to predict the onset and course of clinical disorders. Psychologists are in a strong position to contribute to these efforts.

Second, as researchers begin to identify the sets of genetic variants contributing to the polygenic architecture of complex behavioral outcomes—efforts that are currently being led through large GWAS collaborations, such as the Psychiatric Genomics Consortium—the next step will be to characterize their underlying biology. Gene-network analyses, which permit examination of whether variants included in polygenic scores are located in functionally related genes (L. Wang et al., 2011), will be critical to these efforts. Relatedly, there are exciting cross-disciplinary opportunities, using data from the ENCODE project (ENCODE Project Consortium, 2004), to identify whether the genetic variants that contribute to polygenic scores are located in regulatory regions of the genome (i.e., regions that include enhancers, promoters, insulators, and silencers). Initial findings from the ENCODE project have indicated that many of the top variants that have emerged from GWASs of complex diseases (e.g., multiple sclerosis and ulcerative colitis) are located in potential regulatory DNA regions (ENCODE Project Consortium, 2012). Whether this is the case for common psychiatric disorders, such as the externalizing disorders examined here, remains to be seen. Moving beyond gene identification to identify how sets of genetic variants are implicated in gene regulation will provide critical insights into the biological processes underlying pathways to complex behavioral outcomes.

In closing, continuing to bridge the gaps between the fields of genetics and psychology is imperative so that genetic-psychological science truly represents the state of the science in each field. The nature of large-scale gene-identification studies conducted in adult samples has historically precluded a more fine-grained, developmentally informed understanding of how genetic risk for externalizing disorders contributes to psychopathology. Our approach represents a substantial departure from candidate-gene studies and illustrates how recent advances in the world of genetics can be successfully integrated into a developmentally sensitive psychological study to enhance our understanding of how genetic risk unfolds across time and interfaces with environmental factors.

Author Contributions

J. E. Salvatore and D. M. Dick conceptualized and designed the study and drafted the manuscript. J. E. Salvatore and F. Aliev conducted the statistical analyses. K. Bucholz, A. Agrawal, V. Hesselbrock, M. Hesselbrock, L. Bauer, S. Kuperman, M. A. Schuckit, J. R. Kramer, H. J. Edenberg, and T. M. Foroud critically revised the manuscript for important intellectual content. All authors critically reviewed the content of the manuscript and approved the final version of the manuscript for publication.

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The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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Supplemental Material

Additional supporting information may be found at http://cpx.sagepub.com/content/by/supplemental-data

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