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Intergenerational Continuity in Parents' and Adolescents' Externalizing Problems: The Role of Life Events and their Interaction with *GABRA2*

Jessica E. Salvatore,
Department of Psychiatry, Virginia Commonwealth University

Jacquelyn L. Meyers,
Department of Psychiatry, Virginia Commonwealth University

Jia Yan,
Department of Psychiatry, Virginia Commonwealth University

Fazil Aliev,
Department of Psychiatry, Virginia Commonwealth University and Department of Actuarial and Risk Management, Karabuk University

Jennifer E. Lansford,
Center for Child and Family Policy, Duke University

Gregory S. Pettit,
Department of Human Development and Family Studies, Auburn University

John E. Bates,
Department of Psychological and Brain Sciences, Indiana University

Kenneth A. Dodge,
Center for Child and Family Policy, Duke University

Richard J. Rose,
Department of Psychological and Brain Sciences, Indiana University

Lea Pulkkinen,
Department of Psychology, University of Jyvaskyla

Jaakko Kaprio, and
Department of Public Health and Institute for Molecular Medicine, University of Helsinki and Department of Mental Health and Substance Abuse Services, National Institute for Health and Welfare, University of Helsinki

Danielle M. Dick

Correspondence concerning this article should be addressed to: Jessica E. Salvatore, Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, 800 E. Leigh Street, Room 1-126, PO Box 980126, Richmond, VA 23298-0126, phone: (804) 828-8132, jesalvatore@vcu.edu.
Jacquelyn L. Meyers is now at Columbia University. Jia Yan is now at Virginia Commonwealth University and the National Institute on Alcohol Abuse and Alcoholism.

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Department of Psychiatry, Virginia Commonwealth University

Abstract

We examine whether parental externalizing behavior has an indirect effect on adolescent externalizing behavior via elevations in life events, and whether this indirect effect is further qualified by an interaction between life events and adolescents' *GABRA2* genotype (rs279871). We use data from two samples: the Child Development Project [CDP] (n = 324) and FinnTwin12 (n = 802). In CDP, repeated measures of life events, mother-reported adolescent externalizing, and teacher-reported adolescent externalizing were used. In FinnTwin12, life events and externalizing were assessed at age 14. Parental externalizing was indexed by measures of antisocial behavior and alcohol problems or alcohol dependence symptoms in both samples. In CDP, parental externalizing was associated with more life events, and the association between life events and subsequent adolescent externalizing varied as a function of *GABRA2* genotype ($p \leq 0.05$). The association between life events and subsequent adolescent externalizing was stronger for adolescents with 0 copies of the G minor allele (MA) compared to those with 1 or 2 copies of the MA. Parallel moderation trends were observed in FinnTwin12 ($p \leq 0.11$). The discussion focuses on how the strength of intergenerational pathways for externalizing psychopathology may differ as a function of adolescent-level individual differences.

Keywords

externalizing; *GABRA2*; gene-environment interaction; life events; intergenerational continuity

Factors underlying intergenerational continuity in psychopathology are central to understanding the onset and course of behavioral and affective disorders (Chassin, Pillow, Curran, Molina, & Barrera, 1993; Hicks, Krueger, Iacono, McGue, & Patrick, 2004). Externalizing behavior, which encompasses a broad class of behaviors related to conduct and substance use behaviors (e.g., conduct disorder, ADHD, substance use, abuse, and dependence, and impulsivity) (Krueger et al., 2002), shows evidence for intergenerational continuity (Hussong, Huang, Curran, Chassin, & Zucker, 2010; Hussong et al., 2007; Malone, McGue, & Iacono, 2010; Torvik, Rognmo, Ask, Roysamb, & Tambs, 2011; Verlaan & Schwartzman, 2002). It is important to identify the environmental mechanisms that contribute to this intergenerational transmission as well as factors that may disrupt these pathways (Thornberry, Freeman-Gallant, Lizotte, Krohn, & Smith, 2003; Tremblay, 2010; Wills & Yaeger, 2003). The present paper builds on a small literature examining whether parental externalizing behavior has an indirect effect on adolescent externalizing behavior via elevations in life events (Chassin, Curran, Hussong, & Colder, 1996; Chassin et al., 1993; Hoffmann & Su, 1998e), and extends it to consider whether this indirect effect is further qualified by an interaction between life events and adolescent-level genotypic differences *GABRA2*, a gene previously implicated in adolescent externalizing behavior and sensitivity to one's environment (Dick et al., 2009).

We focus here on life events as an intervening process that may link parent and adolescent externalizing behavior (Chassin et al., 1996; Chassin et al., 1993; Hoffmann & Su, 1998a). Studies document associations between parental externalizing behavior and negative life

events and stressors. For example, a retrospective study of young adult children of alcoholics found that they experienced higher rates of a variety of stressors in childhood and adolescence compared to those without a family history of alcoholism (Sher, Gershuny, Peterson, & Raskin, 1997). Similarly, both cross-sectional and longitudinal studies find that parental substance use and problems predict elevated levels of adolescent-reported life events (Hoffmann & Su, 1998a; Wills, Sandy, Yaeger, & Shinar, 2001). Furthermore, it is well established that negative life events are, in turn, associated with greater adolescent externalizing-spectrum behavior (Blomeyer et al., 2008; Frojd, Kaltiala-Heino, Pelkonen, Von der Pahlen, & Marttunen, 2009; Kim, Conger, Elder, & Lorenz, 2003; Laucht, Treutlein, Schmid, et al., 2009; Windle & Windle, 1996).

To our knowledge, only a few studies have examined the indirect pathway from parental externalizing → life events → adolescent externalizing. Chassin et al. (1993) found that adolescents' exposure to life events mediates, in part, the link between parental alcoholism and adolescent substance use. Retrospective work with a college age sample similarly indicated that childhood stressors mediated the link between paternal alcohol dependence and young adult alcohol use disorders (Sher et al., 1997). Although others have reported null results for this indirect pathway (e.g., Hoffman & Su, 1998), evidence from these two independent samples suggests that the offspring of parents with externalizing problems are exposed to more stressful or chaotic environments, which is subsequently associated with their own externalizing behavior.

Not all adolescents whose parents suffer from an externalizing problem or who experience a large number of life events go on to exhibit externalizing behavior themselves (Thornberry et al., 2003). Continuity and discontinuity in this intergenerational pathway may reflect, in part, an interaction between life events and individual differences, such as genetic predispositions. To date, studies examining interactions between life events, measured genetic predispositions, and externalizing behavior in adolescence have focused narrowly on genes implicated in the stress response (e.g., *5-HTTLPR* and *CRHR1*; Blomeyer et al., 2008; Covault et al., 2007; Laucht, Treutlein, Blomeyer, et al., 2009; Schmid et al., 2010). In contrast, there has been relatively little attention paid to how life events interact with measured genetic predispositions for externalizing behaviors themselves (Kendler et al., 2012). This represents an important gap in the literature, particularly in view of evidence that latent genetic variance for externalizing behaviors increases under conditions of more life events (Hicks, South, DiRago, Iacono, & McGue, 2009). Although the Hicks et al. study of gene-environment interaction only looked at changes in latent genetic variance (i.e., heritability) as a function of life events, the findings suggest that life events and specific genes that are known to predispose individuals to externalizing behavior may interact.

Our goal in this study was to integrate across the intergenerational continuity and latent gene-environment interaction literatures to examine whether the intergenerational pathway from parental externalizing → life events → adolescent externalizing is qualified by an interaction between life events and variation in a gene that predisposes adolescents to externalizing behaviors. Selecting the relevant gene or genetic variant for any study of gene-environment interaction is likely to be somewhat controversial (Dick et al., 2015). In keeping with our primary goals for the present study, we used the empirical literature to

select *GABRA2*, which has been previously associated with adolescent externalizing behaviors (Dick, Bierut, et al., 2006; Dick et al., 2009), and whose genotypic effects change as a function of the environment (Dick et al., 2009; Perry et al., 2013; Villafuerte, Trucco, Heitzeg, Burmeister, & Zucker, 2014).

GABRA2 codes for the receptor for the central nervous system inhibitory neurotransmitter $GABA_A$ alpha-2 subunit. $GABA_A$ receptors are involved in the mesolimbic dopamine system (Enoch, 2008), suggesting that *GABRA2* is likely involved in a range of reward-related disinhibited behaviors that broadly reflect the inability to control one's impulses. *GABRA2* was initially associated with adult alcohol dependence in multiple independent samples (Covault, Gelernter, Hesselbrock, Nellissery, & Kranzler, 2004; Edenberg et al., 2004; Enoch et al., 2009; Zintzaras, 2012). Subsequent studies have demonstrated that variation in *GABRA2* is associated with a range of externalizing disorders, including drug dependence (Agrawal et al., 2006), childhood conduct disorder symptoms (Dick, Bierut, et al., 2006) and increased risk (odds ratios ranging from 2.1 to 2.7) of exhibiting an elevated persistent trajectory of externalizing behavior across adolescence and early adulthood (Dick et al., 2009). Further evidence that *GABRA2* variation poses non-specific risk towards externalizing behaviors comes from studies of its association with specific patterns of neurological function (e.g., differences in EEG power in the beta frequency and insula activation) that are linked to cognitive functioning, information processing, and sensitivity to reward and loss (Edenberg et al., 2004; Porjesz et al., 2002; Villafuerte et al., 2012).

Above and beyond these main effects, environmental factors interact with variation in *GABRA2* to predict externalizing behavior. The pattern of findings emerging from these analyses is largely consistent with the idea that genotypic differences become more pronounced in environments characterized by greater social opportunity and less social control (Shanahan & Hofer, 2005), such as affiliations with deviant peers or less parental monitoring (Dick et al., 2009; Villafuerte et al., 2014). For example, adolescents with more copies of the major allele for SNPs in the risk-increasing *GABRA2* haplotype block were more likely to exhibit an elevated persistent trajectory of externalizing behavior if they also experienced less parental monitoring (Dick et al., 2009). Likewise, *GABRA2* genotypic differences become minimized in less adverse environments. Perry et al. (2013) found that positive life events (i.e., the degree to which one's work, finances, spouse, and children were uplifting or pleasurable) interacted with *GABRA2* genotype to predict men's alcohol dependence. Men with the risk-increasing *GABRA2* haplotype (operationalized as having two copies of the major A allele at rs279871) were less likely to have alcohol dependence if they reported recently experiencing more positive life events. Taken as a whole, these findings suggest that specific characteristics of the environment may interact with *GABRA2* variation to predict externalizing, making this a good candidate for the present study.

We first examine whether there is an indirect pathway between parental externalizing behavior and adolescent externalizing behavior that is marked by elevations in life events. We then test whether life events and adolescent-level genotypic differences in *GABRA2* interact to qualify this intergenerational pathway. We do this in two independent samples. Our discovery sample is a community-based American sample for which there are six repeated measures of life events and adolescent externalizing, two repeated measures of

teacher-reported adolescent externalizing, and adolescent *GABRA2* genotype and parental externalizing information (as indexed by measures of antisocial behavior and alcohol problems). To test for the replicability of any effects that emerged from our densely and longitudinally assessed discovery sample, we use data from a population-based Finnish twin sample for which there are similar life events and adolescent externalizing data, in addition to adolescent *GABRA2* genotype and parental externalizing measures.

Method

Discovery Sample: Child Development Project

Participants in the present study are the European-American subsample (n = 324) of the Child Development Project (CDP) for whom parental externalizing, life events, adolescent externalizing, and *GABRA2* genotype information were available. The original CDP sample included 585 children who were recruited from public schools in Nashville and Knoxville, Tennessee and Bloomington, Indiana. Since enrolling in the study, participants have been contacted annually for follow-up assessments of their social development and emotional and behavioral adjustment. As described in greater detail in Dick et al. (2009), DNA data were collected in the context of an annual follow-up visit in early adulthood. Analyses were limited to the European-American participants (n = 477 from the full sample) for whom relevant phenotypic data were also available (n = 324; 50% male) because allele frequencies and linkage disequilibrium structures often differ across populations.

Parental Antisocial Behavior and Alcohol Problems—Mothers and fathers (if available) reported on their own lifetime antisocial behavior and alcohol problems on separate scales at the target child's age 16 assessment. It would have been ideal to use a measure of parental antisocial behavior that was collected prior to adolescents' externalizing outcome data, but these data were not available in the CDP sample. Accordingly, we used the following lifetime antisocial behavior and alcohol problems measures as global indices of parental externalizing problems, and assume, based on high levels of continuity of externalizing problems from childhood to adulthood (Odgers et al., 2008; Petersen, Bates, Dodge, Lansford, & Pettit, in press; Pitkanen, Kokko, Lyyra, & Pulkkinen, 2008) that parents' antisocial behavior and alcohol problems antedated life events and adolescents' externalizing.

The antisocial behavior scale was adapted from Frick and Hare (2001), and each parent reported how well a series of seventeen statements indicative of antisocial behavior (e.g., acting without thinking of consequences, irritability, engagement in risky activities) describe himself or herself on a three-point scale anchored 0 (*not at all true*) to 2 (*definitely true*). Reliabilities (alpha) were 0.55 and .71 for mothers and fathers, respectively. Maternal scores ranged from 0–15 (M = 4.42), and paternal scores ranged from 0–19 (M = 4.81). Forty-one percent of the sample only had mother data, 5% only had father data, and <1% were missing data on both parents. When both mother and father data were available (52% of sample), the maximum score was used in the analysis. For 53% of these participants, the maximum antisocial behavior score was from the father, for 37% the maximum antisocial behavior score was from the mother, and for 10% the mother and the father had the same score.

Mother and father scores were positively related, although the effect was not significant, $\tau = .05$, $p = 0.35$.

Alcohol problems were assessed using twelve items from the Short Michigan Alcohol Screening Test (Selzer, Vinokur, & van Rooijen, 1975). Parents indicated whether a series of questions indicative of problem drinking applied to them on a two-point scale, 0 (*no*) or 1 (*yes*). Reliabilities (alpha) were 0.67 and .81 for mothers and fathers, respectively. Sum scores were calculated for use in the present analyses. Maternal MAST scores ranged from 0–7 (M = 0.55), and paternal MAST scores ranged from 0–12 (M = 0.98). Forty-six percent of sample only had mother data, 4% only had father data, and <1% were missing data on both parents. When both mother and father data were available (50% of sample), the maximum score was used in analysis. For 32% of these participants, the maximum alcohol problems score was from the father, for 14% the maximum alcohol problems score was from the mother, and for 54% the mother and the father had the same score. Mother and father scores were positively related, although the effect was not significant, $\tau = .11$, $p = 0.12$. Twenty-six mothers and twenty-six fathers had scores ≥ 3, indicating a probable alcohol problem.

Life events—At each annual assessment between ages 11–16, life events experienced by the child and his/her family were assessed using the Family Changes and Adjustments Questionnaire (Dodge, Pettit, & Bates, 1994). This questionnaire asked mothers whether 18 life events (listed in Table 1) happened in the past year. Events were coded 0 (*did not happen in past year*) or 1 (*did happen in the past year*). No measure of internal consistency (e.g., alpha) is calculated for this scale because events appearing on the checklist can and do occur independently. For each age, separate life events sum scores of the items were calculated. Life events data were available for 80–93% (M = 86%) of the sample at each time point.

Externalizing behavior [mother (CBCL) and teacher (TRF) reports]—At each annual assessment at ages 12–17 mother-reported externalizing behavior was assessed using the Achenbach Child Behavior Checklist (CBCL; Achenbach, 1991c). Mothers were asked whether a series of 33 items on the Externalizing Behavior subscale (e.g., gets in many fights, destroys things belonging to others) described their children in the past six months on a three-point scale anchored 0 (*not true*) to 2 (*very true or often true*). At ages 12 and 13, teacher-reported externalizing behavior was assessed using the Achenbach Teacher Report Form (TRF; Achenbach, 1991a). Classroom teachers who knew the target child best were asked how well a series of 34 items on the Externalizing Behavior subscale described target children using the same three-point scale as listed above. The Achenbach manual reports excellent psychometric properties for the CBCL and TRF externalizing scales, including high test-retest reliability, and convergent and divergent validity (Achenbach, 1991a, 1991c). Separate mother and teacher externalizing symptom sum scores for each age were used in longitudinal linear mixed modeling analyses (described below). Alphas across years ranged from .88 to .92 for mother reports and .95 to .96 for teacher reports[1]. CBCL data were available for 85–95% (M = 89%) of the sample at each time point, and 34, 39, 25, 32, 34, and 23 of the participants' scores were in the clinical range at ages 12–17, respectively.

TRF data were available for 85% and 81% of the sample at ages 12 and 13, and 25 and 24 of participants' scores were in the clinical range.

Genotyping—We genotyped 10 single nucleotide polymorphisms (SNPs) in *GABRA2*, which were selected based on previous evidence for an association with alcohol dependence in the Collaborative Study on the Genetics of Alcoholism (see Dick et al., 2009 for a description of selection criteria and further genotyping details including chromosomal position and minor allele frequency). Linkage disequilibrium across these markers was very high, with an r^2 average of 0.91, indicating that the SNPs do not reflect independent tests of association (Dick et al., 2009). As in previous developmental and gene-environment interaction (G × E) studies of *GABRA2* (Dick, Agrawal, et al., 2006; Dick, Bierut, et al., 2006; Perry et al., 2013), we selected the SNP with the single most significant association from the COGA sample (Edenberg et al., 2004), rs279871, to represent the risk-associated haplotype block in the present analyses. Genotypic information for this SNP was available for 97% of the sample. Genotyping was done on the minus strand, and the minor allele frequency (MAF) for the G allele was 0.43.

Covariates—Sex was entered as a covariate in view of previous sex differences for this outcome (Newman et al., 1996). We also included the number of reporters on the parental antisocial behavior and parental alcohol problems measures (i.e., 1 parent or 2 parents) as covariates in the respective models in order to account for the possibility that missing parental data, particularly missing father data, may reflect some degree of risk for externalizing behavior.

Replication Sample: FinnTwin12

FinnTwin12 is a population-based Finnish twin sample of approximately 2,700 twin pairs; of these parental externalizing (measured when the twins were age 12), adolescent life events, adolescent externalizing behavior (both measured at age 14), and genotypic data were available for 802 twins from 478 families (297 monozygotic individuals, 497 dizygotic individuals, and 8 individuals of unknown zygosity; 52% female, 48% male). Further details about the sample and assessments can be found in Kaprio, Pulkkinen, and Rose (2002) and Knaapila et al. (2011).

Parental Antisocial Behavior and Alcohol Dependence Symptoms—Maternal and paternal antisocial behavior was indexed using symptom counts for DSM-3-R (American Psychiatric Association, 1987) Antisocial Personality Disorder as assessed using the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz et al., 1994) when the twins were age 12. Total symptom counts were used in analyses. If only one parent's data were available, his/her score was used (11% of sample only had mother data, 1% only had father data, and <1% were missing data on both parents). When both mother and father data were available (87% of the sample), the maximum score was used in

[1]We examine the full externalizing scale here in view of the theoretical perspective that GABRA2 confers risk for behavioral disinhibition, broadly construed (Dick et al., 2006). An alternative would be to test the impulsivity, inattention, and aggression subfacets separately; however, we did not feel that this was appropriate in the absence of a priori hypotheses and in view of the high inter-item reliability for the overall externalizing scale.

analysis. For 53% of these participants, the maximum score was from the father, for 5% the maximum score was from the mother, and for 42% the mother and the father had the same score. Maternal symptoms ranged from 0–4 (M = 0.24), and paternal symptoms ranged from 0–7 (M = 1.10), and 5 and 51 of mothers and fathers endorsed three or more of the criteria, thus meeting Criterion A for antisocial personality disorder. Mother and father scores were positively correlated, $\tau = .20$, $p < .01$.

Maternal and paternal alcohol dependence symptoms were indexed using lifetime symptom counts for DSM-3-R (American Psychiatric Association, 1987) Alcohol Dependence as assessed using the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz et al., 1994) when the twins were age 12. Total symptom counts, which ranged from 0–9, were used in analyses. If only one parent's data were available, his/her score was used (11% of sample only had mother data, 1% only had father data, and <1% were missing data on both parents). When both mother and father data were available (87% of the sample), the maximum score was used in analysis. For 57% of these participants, the maximum score was from the father, for 10% the maximum score was from the mother, and for 33% the mother and the father had the same score. Maternal symptoms ranged from 0–9 (M = 0.58), and paternal symptoms ranged from 0–9 (M = 2.07), and 33 and 137 of mothers and fathers endorsed three or more criteria and met clinical criteria for alcohol dependence. Mother and father scores were positively correlated, $\tau = .17$, $p < .01$.

Life Events—At age 14, twins reported on their life events using a checklist that asked whether a series of 15 life events items (listed in Table 1) had occurred in the past two years. Each item was coded 0 (*did not happen in past two years*) and 1 (*did happen in the past two years*). Sum scores were used in analyses, and were available for all participants in the subsample.

Externalizing Behavior—At age 14, externalizing behavior was measured using the Behavioral Problems scale from the Teacher Form of the Multidimensional Peer Nomination Inventory (Pulkkinen, Kaprio, & Rose, 1999). This scale tapped behavioral problems related to three factors: hyperactivity-impulsivity (seven items such as "is hyperactive" and "is talkative"); aggression (six items such as "goes around telling people's secrets to others" and "hurts other kids when angry"); and inattention (four items such as "tends to ignore instructions" and "is conscientious with homework"). Teachers were asked how much each statement applied to each twin in their classroom on a four-point scale anchored 0 (*does not apply*) to 3 (*applies in a pronounced way*). Reliability for the scale was high ($\alpha = 0.95$). Items were reverse scored as needed and averaged for the present analyses. Externalizing data were available for all participants in the subsample.

Covariates—As with CDP, we statistically controlled for sex and for the number of parental reports for antisocial behavior and alcohol dependence symptoms.

Genotyping—Genome-wide data were collected using blood samples obtained at the age 22 assessment. Genotyping was performed at the Welcome Trust Sanger Institute (Hinxton, UK) on the Human670-QuadCustom Illumina BeadChip (Illumina, Inc., San Diego, CA, USA), as previously described in Broms et al. (2012). The data were checked for MAF >1%,

genotyping success rate per SNP and per individual (> 95%; >99% for SNPs with MAF<5%), Hardy-Weinberg Equilibrium (HWE $p > 1 \times 10^{-6}$), sex, and heterozygosity. In addition, to check whether any individuals were unexpectedly related to each other, a multidimensional scaling plot (using a pairwise-IBS matrix) with only one member of each known family was created. After the pedigree was checked for accuracy, the basic filters (MAF, genotyping success, HWE) were reapplied to the data. The *GABRA2* SNP rs279871 was not initially genotyped on this array, and was imputed using ShapeIT (Delaneau, Marchini, & Zagury, 2012) in pre-phasing and IMPUTE2 (Howie, Donnelly, & Marchini, 2009) for genotype imputation. The posterior probability threshold for "best-guess" imputed genotype was 0.9. Genotypic information for this SNP was available for 100% of the sample[2]. Imputation was done on the plus strand, and the MAF for the C allele (which corresponds to the G allele in CDP, due to strand differences in genotyping and imputation) was 0.41.

Analytic Plan

CDP—Six time points of repeated-measures data were available for both life events and CBCL externalizing. Two time points of repeated-measures data were available for TRF externalizing. Accordingly, we adopted a linear mixed modeling (LMM) approach to test for an indirect effect of parental externalizing problems (antisocial behavior and alcohol problems) on subsequent adolescents' externalizing that is transmitted through life events, and to test whether life events and adolescents' *GABRA2* genotype interacted to qualify this indirect effect. Linear mixed modeling allows for the incorporation of missing data and models the covariance structure with fewer parameters relative to a repeated-measures ANOVA. We used restricted maximum likelihood estimation, a continuous autoregressive correlation structure, and random intercepts and slopes. Parental antisocial behavior and alcohol problems were run in separate models, as were CBCL and TRF externalizing outcomes.

Per the recommendations of MacKinnon et al. (2002), we tested for the indirect effect of parental externalizing problems on adolescents' externalizing using tests of the joint significance of two pathways: parental externalizing problems predicting life events and life events predicting subsequent adolescent externalizing while simultaneously controlling for parental externalizing problems[3]. The generic LMM model used to test each of these pathways (expressed in hierarchical linear model [HLM] form) was:

Parental Externalizing Predicting Life Events

[2]Imputation is a common practice in genetics now. The imputation procedure uses known linkage disequilibrium information (indicating how correlated nearby genetic variants are) from a large scale genetic sequencing study (the 1000 Genomes Phase I integrated variant set release (v3) reference panel) to infer with a high degree of accuracy an individual's genotype at loci that are not directly measured (Marchini & Howie, 2010). Because SNPs can be inferred with such a high degree of accuracy using linkage disequilibrium, the number of SNPs actually genotyped in genetic studies has been reduced dramatically, and simulation studies demonstrate that SNP imputation makes lower coverage genome-wide genotyping platforms (e.g., those with ~600,000 genotyped markers) as powerful as high coverage platforms (e.g., those with 1 million genotyped markers) (Spencer, Su, Donnelly, & Marchini, 2009).

[3]Tests for indirect effects are related to, but distinct from, tests for mediation. The key difference is that tests for mediation require a main effect for the predictor (e.g., parental antisocial behavior or alcohol problems) on the outcome, while the joint effects strategy recommended by MacKinnon et al. (2002) does not.

Level 1: Life Events$_{ij}$ = β_{1i} + $\beta_{2i}t_{ij}$ + e_{ij}

Level 2: β_{1i} = β_1 + β_3Sex$_i$ + β_4Parent Externalizing$_i$ + β_5Number of Parent Externalizing Reporters$_i$ + b_{1i}

Level 2: β_{2i} = β_2 + b_{2i}

where β_1 is the intercept, β_2 is the slope for the linear time term (t), β_3 is effect of sex on the intercept, and β_4 is the effect of parental externalizing problems on life events, β_5 is the effect of number of parental externalizing reporters on life events, b_1 is the random intercept allowing for individual variation around the mean (β_1), b_2 is the random intercept allowing for individual variation around the slope (β_2), and β_{1i} and β_{2i} denote the participant-specific intercepts and slopes.

Life Events Predicting Adolescent Externalizing

Level 1: Adol Externalizing$_{ij}$ = β_{1i} + $\beta_{2i}t_{ij}$ + β_{3i}Life Events$_{i(j-1)}$ + e_{ij}

Level 2: β_{1i} = β_1 + β_4Sex$_i$ + β_5Parent Externalizing$_i$ + β_6Number of Parent Externalizing Reporters$_i$ + b_{1i}

Level 2: β_{2i} = β_2 + b_{2i}

Level 2: β_{3i} = β_3

where β_1 is the intercept, β_2 is the slope for the linear time term, β_3 is the effect of life events at the prior assessment (at time *j*-1) on subsequent adolescent externalizing (at time *j*), β_4 is the effect of sex on externalizing, β_5 is the effect of parental externalizing problems on adolescent externalizing, β_6 is the effect of number of parental externalizing reporters on adolescent externalizing, b_1 is the random intercept allowing for individual variation around the mean (β_1), b_2 is the random intercept allowing for individual variation around the slope (β_2), and β_{1i} and β_{2i} denote the participant-specific intercepts and slopes. We note that we used parental externalizing to predict intercepts but not slopes of adolescent externalizing because we anticipated that parental externalizing would predict initial levels of adolescent externalizing, but not necessarily changes in externalizing behavior across time. This was confirmed in preliminary analyses.

We then tested whether life events interacted with adolescent *GABRA2* genotype to predict adolescent externalizing while controlling for parental externalizing. Following the recommendations of Muller et al. (2005), we included an interaction term between life events and *GABRA2* to predict adolescent externalizing. The Level 1 and Level 2 equations were as follows:

Level 1: Adol Externalizing$_{ij}$ = β_{1i} + $\beta_{2i}t_{ij}$ + β_{3i}Life Events$_{i(j-1)}$ + β_{4i}(Life Events$_{i(j-1)}$ × *GABRA2*$_i$) + e_{ij}

Level 2: β_{1i} = β_1 + β_5Sex$_i$ + β_6Parent Externalizing$_i$ + β_7*GABRA2*$_i$ + β_8Number of Parent Externalizing Reporters$_i$ + b_{1i}

Level 2: β_{2i} = β_2 + b_{2i}

Level 2: β_{3i} = β_3

Level 2: $\beta_{4i} = \beta_4$

Where β_1 is the intercept, β_2 is the slope for the linear time term, β_3 is the effect of life events at the prior assessment (at time *j*-1) on subsequent adolescent externalizing (at time *j*), β_4 is the effect of the interaction of between life events at the prior assessment and *GABRA2* on subsequent adolescent externalizing, β_5 is the effect of sex on adolescent externalizing, β_6 is the effect of parent externalizing on adolescent externalizing, β_7 is the effect of *GABRA2* on adolescent externalizing, β_8 is the effect of number of parental externalizing reporters on adolescent externalizing, b_1 is the random intercept allowing for individual variation around the mean (β_1), b_2 is the random intercept allowing for individual variation around the slope (β_2), β_{1i} and β_{2i} denote the participant-specific intercepts and slopes, and β_{3i} and β_{4i} denote the participant-specific longitudinal effects of life events at the prior assessment on subsequent adolescent externalizing and of the interaction of life events at the prior assessment and *GABRA2* on subsequent adolescent externalizing, respectively.

We ran the analyses in the nlme package version 3.1–117 (Pinheiro et al., 2014) in R version 3.0.3 (R Development Core Team, 2014). In order to account for autoregressive effects in our models, we specified a "corCAR1" correlation structure (i.e., an autocorrelation structure of order 1, with a continuous time covariate). Preliminary analyses examining the shape of the CBCL externalizing trajectory across time indicated a decreasing linear trajectory; accordingly, a linear time term was included in the model. A linear time term was also included in the TRF externalizing models in view of preliminary analyses that indicated an increasing level of externalizing behavior between ages 12–13. Time was centered at age 12 in all models to aid in the interpretation of the intercepts. *GABRA2* genotype was coded 0, 1, or 2, representing the number of copies of the minor allele. The life events, parental antisocial behavior, and parental alcohol problems independent variables were standardized. Effect size was calculated as the percent of the variance (R^2) accounted for by a parameter of interest above and beyond the covariates and main effects (for interactions) using the residual variance procedure described by Selya et al. (2012).

To test the robustness of our effects against potential confounders, we performed supplementary analyses that included all covariate x environment and covariate x genotype interaction terms in addition to the G × E interaction, per the recommendations of Keller (2014). Finally, in view of Perry et al.'s (2013) recent findings that the interaction between positive life events and *GABRA2* in predicting alcohol dependence is more pronounced in males compared to females, we also examined whether the anticipated G × E effect was further modified by sex.

FinnTwin12—Analyses were run in the same statistical software program for the CDP sample to account for the nesting of twins within dyads. We specified a "corCompSymm" (compound symmetry) correlation structure. An autoregressive correlation structure was not necessary for FinnTwin12 because only one time point of data were available for the sample.

Results

CDP Representativeness Analyses, Descriptive Statistics, and Zero-Order Correlations

A series of dropout-control comparisons indicated that the subsample examined here did not significantly differ (i.e., $p > 0.05$) from those not in the subsample in terms of sex, parental antisocial behavior or alcohol problems, or the number of life events experienced between ages 12–16. However, the subsample did experience fewer life events at age 11 (Cohen's $d = -0.05$, indicating a small effect) and had lower scores on the Achenbach Child Behavior Checklist (ages 12, 14, 16, and 17; Cohen's d ranged from −0.20 to −0.26, indicating small effects) and on the Teacher Report Form (ages 12 and 13; Cohen's d ranged from −0.53 to −0.54, indicating medium effects) externalizing measures compared to those not in the subsample.

Descriptive statistics and zero-order correlations among the parental externalizing problems, life events, and adolescent externalizing measures are shown in Table 2. The six CBCL externalizing measures were highly intercorrelated, rs 0.63 – 0.82 ($M = 0.74$), and the six life events measures were modestly intercorrelated, rs 0.32 – 0.59 ($M = 0.43$). The two TRF externalizing measures were moderately intercorrelated, $r = .44$. There were positive associations between life events and cross-lagged CBCL externalizing, rs 0.23 – 0.39 ($M = 0.30$). Life events and cross-lagged TRF externalizing were positively correlated at age 12 ($r = 0.16$) but not at age 13 ($r = .05$). Parental antisocial behavior and alcohol problems were positively related, although this effect was modest, $r = .15$.

On a zero-order level, parental antisocial behavior was, in general, positively related to life events rs 0.02 – 0.20 ($M = 0.12$). Parental alcohol problems were, in general, not significantly related to life events, rs 0.02 – 0.13 ($M = 0.06$) on a zero-order level. Parental antisocial behavior was positively correlated with CBCL externalizing at all ages, rs 0.22–0.31 ($M = 0.28$), and with TRF externalizing, rs 0.16–0.24 ($M = 0.20$). Parental alcohol problems were positively and significantly correlated with CBCL externalizing at age 15 only, $r = 0.18$, and with TRF externalizing at ages 12 and 13, rs 0.19–0.30 ($M = 0.24$).

Testing For Indirect Effects in CDP

Higher parental antisocial behavior ($B = 2.23$, $t(318) = 6.63$, $p < .01$, $R^2 = 9.92\%$) and alcohol problems ($B = 0.69$, $t(318) = 2.01$, $p = .05$, $R^2 = 1.30\%$) predicted higher CBCL adolescent externalizing. Higher parental antisocial behavior ($B = 1.61$, $t(289) = 4.00$, $p < .01$, $R^2 = 4.93\%$) and alcohol problems ($B = 2.14$, $t(290) = 5.49$, $p < .01$, $R^2 = 6.57\%$) also predicted higher TRF externalizing. Higher parental antisocial behavior ($B = 0.36$, $t(316) = 3.94$, $p < .01$, $R^2 = 2.32\%$) and alcohol problems ($B = 0.21$, $t(316) = 2.35$, $p = .02$, $R^2 = 0.68\%$)[4] also predicted a greater number of life events. We note that due to convergence problems, the random effects for slope were dropped from these particular analyses.

[4]The positive and significant association between parental alcohol problems and life events that emerges in the linear mixed model analyses may appear to contradict the non-significant zero-order correlations among these variables. However, this is possible because a linear mixed model analysis has more power to detect effects owing to the repeated measures data.

Life events did not predict cross-lagged CBCL externalizing (B = 0.16, t(1230) = 1.23, p < .21, R^2 = 1.58%) after controlling for the main effect of parental antisocial behavior (B = 2.21, t(309) = 6.53, p = .01). Furthermore, life events did not predict cross-lagged CBCL externalizing (B = 0.21, t (1227) = 1.61, p = 0.11, R^2 = 2.17%) after controlling for the main effect of parental alcohol problems (B = 0.69, t(309)= 1.98, p = 0.05). Likewise, life events did not predict cross-lagged TRF externalizing (B = 0.59, t(216) = 1.64, p = .0.10, R^2 = 2.70%) after controlling for the main effect of parental antisocial behavior (B = 1.38, t(280) = 3.41, p < .01). And life events did not predict cross-lagged TRF externalizing (B = 0.56, t(216) = 1.64, p = .10, R^2 = 4.15%) after controlling for the main effect of parental alcohol problems (B = 2.27, t(281)= 5.92, p < .01). Taken as a set, the results of the analyses suggest that parental antisocial behavior and alcohol problems predict a greater number of life events. However, we did not find evidence for an indirect effect whereby life events in turn predicts cross-lagged adolescent externalizing behavior as reported by either mothers or teachers.

Testing for Moderated Indirect Effects in CDP

We tested whether life events interacted with *GABRA2* genotype to predict cross-lagged CBCL externalizing while simultaneously controlling for parental externalizing. The results are shown as a series of models in Tables 3 and 4. Model 1 includes the main effects of all variables. Model 2 includes the main effects and the interaction of life events × *GABRA2*. Model 3 includes the main effects, the life events × *GABRA2* interaction effect, and additional statistical controls for all covariate × genotype and covariate × environment interactions. In terms of main effects, CBCL externalizing decreased over time. Adolescents who were missing a parental antisocial behavior report, or whose parents had higher parental antisocial behavior and alcohol problems had higher CBCL externalizing (see Model 1 in Tables 3 and 4). Sex, missing a parental alcohol problem report, life events, and *GABRA2* genotype were not significantly associated with CBCL externalizing.

Above and beyond these main effects, the life events × *GABRA2* interaction effects reached statistical significance for the parental antisocial behavior and alcohol problems models (see Model 2 in Tables 3 and 4). The interactions accounted for 0.47% and 0.46% percent of the variance in the respective models. Figure 1 depicts the mean levels of CBCL externalizing as a function of life events and *GABRA2* genotype for the model that included parental antisocial behavior. A consistent pattern of effects was found for the model that included parental alcohol problems (available upon request from the first author). Figure 2 illustrates how the association (depicted as standardized betas and their 95% confidence intervals (CI)) between life events and subsequent CBCL externalizing varied as a function of genotype. In the model that included parental antisocial behavior (Panel A, left) life events predicted subsequent CBCL externalizing for those with no copies of the minor allele (β = 0.06, 95% CI [0.001, 0.12]), but not for those with one or two copies of the minor allele (MA) (β_{1MA} = 0.01, 95% CI [−0.05, 0.06]); β_{2MA} = −0.04, 95% CI [−0.13, 0.04]). Similarly, in the model that included parental alcohol problems (Panel B, left), life events predicted subsequent CBCL externalizing for those with no copies of the MA (β = 0.06, 95% CI [0.001, 0.12]), but not for those with one or two copies of the MA (β_{1MA} = 0.02, 95% CI [−0.04, 0.07]); β_{2MA} = −0.05, 95% CI [−0.13, 0.04]). In supplementary analyses that included all covariate

× environment and covariate × genotype interaction terms, the interaction between life events and *GABRA2* was attenuated, which is to be expected given the additional parameters in the model and corresponding loss of degrees of freedom, but did not entirely disappear (*p* values = 0.06 and 0.07). These results are summarized as Model 3 in Tables 3 and 4.

The TRF externalizing results were similar to the CBCL externalizing results. In terms of main effects, adolescents who were male, who were missing a parental alcohol problem report, and whose parents had higher antisocial behavior and alcohol problems had higher TRF externalizing (see Model 1 in Tables 5 and 6). Missing a parental antisocial behavior report, life events, and *GABRA2* genotype were not significantly associated with TRF externalizing. As shown in Model 2 of Tables 5 and 6, the interaction between cross-lagged life events and *GABRA2* was significant in the parental antisocial behavior and alcohol problems models. The interaction effects accounted for 1.54% and 1.48% of the variance in the respective models. Figure 3 depicts the mean levels of TRF externalizing as a function of life events and *GABRA2* genotype for the model that included parental antisocial behavior. A consistent pattern of effects was found for the model that included parental alcohol problems (available upon request from the first author).

Figure 2 illustrates how the strength of the association (depicted as standardized betas) between life events and TRF externalizing varied as a function of genotype. In the model that included parental antisocial behavior (Panel A, right) life events predicted subsequent TRF externalizing for those with no copies of the MA (β_{0MA} = 0.19, 95% CI [0.03, 0.35]), but not for those with one or two copies of the minor allele (β_{1MA} = 0.07, 95% CI [−0.05, 0.20]); β_{2MA} = −0.16, 95% CI [−0.39, 0.06]). Similarly, in the model that included parental alcohol problems (Panel B, right), life events predicted subsequent TRF externalizing for those with no copies of the MA (β_{0MA} = 0.17, 95% CI [0.03, 0.32]), but not for those with one or two copies of the MA (β_{1MA} = 0.08, 95% CI [−0.05, 0.21]); β_{2MA} = −0.17, 95% CI [−0.38, 0.05]). In supplementary analyses that included all covariate × environment and covariate × genotype interaction terms, the interaction between life events and *GABRA2* continued to be significant (*p* values ≤ 0.02). These results are summarized as Model 3 in Tables 5 and 6.

In a series of exploratory analyses we examined whether sex further modified the interaction between life events and *GABRA2*. There was no evidence for a three-way interaction between sex, life events, and *GABRA2* in the CBCL models (*p* values for the three-way interaction effect were 0.32 and 0.26 for the models that included parental antisocial behavior and parental alcohol problems, respectively) or in the TRF models (*p* values for the three-way interaction effect were 0.14 and 0.08 for the models that included parental antisocial behavior and parental alcohol problems, respectively)

FinnTwin12 Analyses

FinnTwin12 Representativeness Analyses, Descriptive Statistics, and Zero-Order Correlations—A series of dropout-control comparisons indicated that the FinnTwin12 subsample examined here did not significantly differ from those not in the subsample in terms of sex, parental antisocial behavior, parental alcohol dependence symptoms, or adolescent externalizing. However, those in the subsample experienced more

life events on average compared to those not in the subsample (Cohen's $d = 0.09$, which corresponds to a small effect size). Descriptive statistics and zero-order correlations for the focal variables are presented in Table 7. Life events, parental antisocial behavior, and parental alcohol dependence symptoms were positive and significant predictors of adolescent externalizing. Both measures of parental externalizing behaviors were positively intercorrelated, and were positively correlated with adolescent externalizing.

Testing For Indirect Effects in FinnTwin12—Parental antisocial behavior ($B = 0.06$, $t(480) = 2.64$, $p < .01$, $R^2 = 1.26\%$), but not alcohol dependence symptoms ($B = 0.03$, $t(479) = 1.53$, $p = 0.13$, $R^2 = 0.53\%$) [5], predicted higher levels of adolescent externalizing. Consistent with the pattern observed in the zero-order correlations, LMM tests indicated that parental antisocial behavior ($B = .27$, $t(475) = 3.54$, $p < .01$, $R^2 = 2.63\%$) and alcohol dependence symptoms ($B = .24$, $t(474) = 3.15$, $p < .01$, $R^2 = 1.60\%$) predicted a greater number of life events.

The associations between life events and adolescent externalizing were also significant after controlling for both measures of parental externalizing behavior. Life events ($B = 0.05$, $t(322) = 2.93$, $p < .01$, $R^2 = 1.47\%$) were associated with higher adolescent externalizing after controlling for the main effect of parental antisocial behavior ($B = 0.05$, $t(475) = 2.25$, $p < .05$). Life events were also a significant predictor of adolescent externalizing ($B = 0.06$, $t(321) = 3.09$, $p < .01$, $R^2 = 1.66\%$) in the model that controlled for parental alcohol dependence symptoms ($B = 0.03$, $t(474) = 1.20$, $p = .23$). Thus, the results of this two-step analysis in the FinnTwin12 sample provide evidence for indirect effects whereby parental antisocial behavior and alcohol dependence symptoms predict a greater number of life events, which in turn predicts higher adolescent externalizing.

Testing for Moderated Indirect Effects in FinnTwin12—We tested whether life events and *GABRA2* interacted to predict adolescent externalizing while simultaneously controlling for parental externalizing behavior. The results from these analyses are shown as a series of models in Tables 8 and 9. In terms of main effects, adolescents who were male, whose parents had higher parental antisocial behavior, and who experienced more life events had higher teacher-reported externalizing (see Model 1 in Tables 8 and 9). Missing a parental antisocial behavior or alcohol dependence symptom report, parental alcohol dependence symptoms, and *GABRA2* genotype were not significantly associated with teacher-reported externalizing. As shown in Model 2 of Tables 8 and 9, the life events × *GABRA2* interaction effects did not reach strict ($p < 0.05$) statistical significance in either the parental antisocial behavior or alcohol dependence symptoms models (the p values for the interaction effects ranged were 0.09 and 0.11, respectively). Figure 4 depicts adolescent externalizing as a function of life events and *GABRA2* genotype for the model that included parental antisocial behavior. A consistent pattern of effects was found for the model that included parental alcohol dependence symptoms (available upon request from the first author). And, as shown in Figure 5, the direction of these effects mirrored the results from

[5]The null association between parental alcohol dependence symptoms and adolescent externalizing in the linear mixed model may appear to contradict the significant zero-order correlations among these variables. However, this is possible because the standard errors are adjusted in the linear mixed model to account for the dyadic nature of the data.

the CDP sample. In the model that included parental antisocial behavior (Panel A) life events predicted subsequent teacher-reported externalizing for those with no copies of the minor allele (β = 0.18, 95% CI [0.06, 0.30]), but not for those with one or two copies of the minor allele (β_{1MA} = 0.08, 95% CI [−0.02, 0.17]); β_{2MA} = 0.03, 95% CI [−0.14, 0.21]). Similarly, in the model that included parental alcohol dependence symptoms (Panel B), life events predicted subsequent teacher-reported externalizing for those with no copies of the minor allele (β = 0.11, 95% CI [0.04, 0.17]), but not for those with one or two copies of the minor allele (β_{1MA} = 0.04, 95% CI [−0.01, 0.09]); β_{2MA} = 0.02, 95% CI [−0.08, 0.12]).

In supplementary analyses that included all covariate × environment and covariate × genotype interaction terms, the interaction between life events and *GABRA2* was attenuated in the parental antisocial behavior model (p = 0.13), but not in the parental alcohol dependence symptoms model (p = .10). These results are summarized as Model 3 in Tables 8 and 9. In a series of exploratory analyses we examined whether sex further modified the interaction between life events and *GABRA2*. There was no evidence for a three-way interaction among sex, life events, and *GABRA2* (p values for the three-way interaction effect were 0.96 and 0.90 in models controlling for parental antisocial behavior and parental alcohol dependence symptoms, respectively).

Discussion

The present study brings together the literatures on mechanisms of intergenerational continuity in externalizing disorders (Chassin et al., 1993; Sher et al., 1997; Thornberry et al., 2003) and gene-environment interplay (Dick, 2011; Feder, Nestler, & Charney, 2009), and offers a new perspective on central questions regarding the factors that promote intergenerational continuity versus discontinuity in externalizing psychopathology. Using longitudinal data from the CDP sample, we found evidence for an indirect effect whereby parental externalizing behavior (as indexed by measures of antisocial behavior and alcohol dependence symptoms) predicts a greater number of life events, which in turn predict higher adolescent externalizing behavior for those with a specific *GABRA2* genotype. The association between life events and subsequent externalizing behavior was stronger for adolescents who were homozygous for the major allele compared to those who were heterozygous or homozygous for the minor allele. A similar interaction was found in the FinnTwin12 sample, although the effects did not replicate at a statistically significant level of $p < .05$.

Our results expand on previous studies of the disruptive effect of parental externalizing psychopathology on family life (Hoffmann & Su, 1998a; Sher et al., 1997; Wills et al., 2001), the increases in adolescent externalizing behavior associated with life events (Kim et al., 2003; Timmermans, van Lier, & Koot, 2010; Windle, 1992), and the role of life events in mediating parental and adolescent externalizing-spectrum problems (Chassin et al., 1993; Pillow, Barrero, & Chassin, 1998; Sher et al., 1997). Most notably, our analyses in the CDP sample highlight the interaction between life events and adolescent-level genotypic factors in *GABRA2* in promoting continuity and discontinuity in this intergenerational pathway. We found that parental antisocial behavior and alcohol problems were associated with a greater number of life events, and that the association between life events and externalizing

behavior was stronger for adolescents who are homozygous for the major allele compared to those heterozygous or homozygous for the minor allele.

We found that these life events × *GABRA2* interaction effects accounted for more variance in teacher reports of adolescent externalizing compared to the mother reports. Although this difference in magnitude was not initially hypothesized, our findings suggest that adolescents may act out at school in response to family-related changes and stressors to a greater degree than they act out at home, and that this varies as a function of genotype. It is also possible that teacher reports are more sensitive to variation in externalizing behavior because teachers have more expertise about the range of adolescents' behavior or because the school situation elicits a wider range of externalizing behavior. We note that the G × E effects observed in CDP did not replicate at a statistically significant level in the FinnTwin12 sample; however, the pattern of the genotypic effects was in the same direction. There was reduced power to find effects in FinnTwin12 because there were a fewer number of total observations relative to CDP owing to the CDP's longitudinal repeated measures design. As expected given the reduced degrees of freedom, our G × E effects were attenuated to some degree in the analyses that included all covariate × environment and covariate × genotype interaction effects. However, the effects were not removed, which adds confidence that these effects are not due to these potential statistical confounds.

A few findings emerged from our analyses that are inconsistent with prior studies. First, we note that the correlations between parental antisocial behavior and alcohol problems measures were unexpectedly low in the CDP sample ($r = 0.15$). This association not as strong as other reports in the literature (e.g., Krueger et al., 2002). We speculate that the low correlation may be attributable to restriction of range in the CDP parental antisocial behavior and alcohol problems measures, which can attenuate correlations. Second, we did not find evidence for main effects of *GABRA2* on adolescent externalizing in either the CDP or FinnTwin12 samples. This could be attributable to a couple of factors. Genetic associations for *GABRA2* tend to be more robust in clinically-ascertained samples compared to community-based samples (Irons et al., 2014). Previous work in the CDP sample has found evidence for association between *GABRA2* and an elevated persistent trajectory of externalizing behavior across adolescence and emerging adulthood (Dick et al., 2009). However, that study used a latent class approach to test for genetic association with a relatively extreme phenotype; in contrast, we used dimensional measures of externalizing. The fact that we did not find main effects for *GABRA2* in CDP or FinnTwin12 samples may be attributable to differences in ascertainment and measurement strategies.

Third, in contrast to previous studies, we did not find evidence for an indirect effect from parental externalizing→life events→adolescent externalizing at the population level in the community-based CDP sample. Rather, this indirect effect was only observed for adolescents who were homozygous for the major allele at rs279871. Although analyses in Chassin's sample of children of alcoholics and a demographically matched comparison group (Chassin et al., 1993) and in the population-based FinnTwin12 sample (reported here) find evidence for this indirect effect, others have reported null results (Hoffmann & Su, 1998a). We believe that the mixed findings for this effect underscore the need to test

hypotheses regarding the individual difference factors (genetic or otherwise) that alter the strength of this intergenerational pathway.

As these factors begin to be identified, this opens up avenues for future research into the mechanisms driving their effects. Previous research on aggression suggests that proximal psychological mechanisms, such as emotion dysregulation (Herts, McLaughlin, & Hatzenbuehler, 2012), might contribute to the indirect effects from parental externalizing→life events→adolescent externalizing. Although we were unable to test this possibility directly in the present study, it may be the case that adjustment to numerous life events taxes adolescents' burgeoning ability to effectively modulate their emotions, giving rise to externalizing behavior. However, it could also reflect the likelihood that parents in families that experience many life events are also more likely to foster the development of coercive behavior in their children and to fail to prevent externalizing behavior (Conger, Patterson, & Ge, 1995; Patterson, 1982).

Interpreting G × E effects as part of an intergenerational pathway is more complex than in the typical G × E study. This is because parental genetic predispositions for externalizing behavior contribute to the externalizing behavior of the adolescent through genetically- and environmentally-mediated processes (Hicks et al., 2004). Although the focus of the present intergenerational study was on the interaction of life events and adolescent *GABRA2* genotype to predict externalizing, it is possible that life events and parental *GABRA2* genotype may interact to predict the types of sub-optimal parenting practices (e.g., participating in coercive interactions) that in turn contribute to adolescents' externalizing. Although we are unable to examine this possibility in the present study, we believe that these types of process-oriented hypotheses are important for understanding the intergenerational transmission of externalizing behavior, and the interaction of environmental and genetic factors (both parental and offspring) (Klahr & Burt, 2014).

Our gene-environment interaction results conceptually map onto findings for a positive association between childhood trauma and cocaine addiction for those homozygous or heterozygous for the G (minor) allele at *GABRA2* SNP rs11503014 (Enoch et al., 2010) in a clinically-ascertained African-American sample. However, in our Caucasian samples, the effects were with respect to the opposite allele (i.e., the association between life events and externalizing was more positive for those homozygous for the major allele at *GABRA2* SNP rs279871 compared to those heterozygous or homozygous for the minor allele). We note that the effects in the present study are for the same genotype previously associated with alcohol dependence (Edenberg et al., 2004), conduct disorder (Dick, Bierut, et al., 2006), and, as previously found in the CDP sample, a greater likelihood of displaying an elevated-persistent trajectory of externalizing behavior in the context of low parental monitoring (Dick et al., 2009). Other studies report that the minor allele is the risk-increasing allele (Fehr et al., 2006); however, we note that inconsistency in the identity of the risk-increasing allele for *GABRA2* may be attributable to high heterozygosity, genotyping methods adopted across different labs (e.g., genomic strand differences), and variation in allele frequency across populations. For example, previous reports have found differential allelic effects for *GABRA2* and nicotine dependence across racial/ethnic groups (Beuten et al., 2005),

underscoring the importance of attending to the direction of genetic effects across diverse samples.

Although we initially selected *GABRA2* for the present analyses in view of its previous associations with externalizing behavior and externalizing disorders (Dick, Bierut, et al., 2006; Edenberg et al., 2004), more recent findings from the model organism (mouse) literature indicate that *GABRA2* is also involved in a network of genes that regulate the stress response (Dai et al., 2009). This regulation of the biological cascade associated with stress may explain why the parental externalizing → life events → adolescent externalizing pathway is more robust for those with certain *GABRA2* genotypes compared to others.

Strengths of the present study include data from multiple reporters (parents, teachers, and adolescents) across two samples, as well as genotypic information on *GABRA2* in order to examine whether parental externalizing behavior exerts an indirect effect on adolescent externalizing behavior via elevations in life events, and whether life events interact with adolescents' *GABRA2* genotype such that this pathway is stronger for some genotypes compared to others. Despite these strengths, the results of the present study should be interpreted in the context of several limitations. First, analyses were limited to Caucasians. Doing so reduces the risk of false positives due to population stratification; however, generalizability to other racial groups is limited as a consequence. Previous work from the Collaborative Study on the Genetics of Alcoholism suggests that self-reports of race/ethnicity are highly correlated with ancestry informative markers (unpublished data), which reduces concerns that population stratification may be driving the significant G × E effects observed in CDP. In FinnTwin12, principal components analyses of the population structure performed in Eigenstrat indicated a single dimension of ancestry. Second, although we are able to bring two datasets together to examine the role of life events and genotypic differences in intergenerational continuity in externalizing problems, there is imperfect correspondence in the measures, reporters, and study designs. For example, in the CDP sample, mothers reported on life events, and in the FinnTwin12 sample adolescents reported on life events. In the context of these differences, the parallel but non-significant trends observed in our replication sample are encouraging.

A third limitation is that the measures of life events used in both samples tapped events that were in the normative range of the types of changes and transitions that adolescents and their families are likely to face. Whether the same indirect and gene-environment interaction effects would be observed in the context of more extreme stressors (e.g., physical, emotional, or sexual abuse) remains an important direction for future research. Fourth, we are unable to account for parental *GABRA2* genotype in the present samples. Fifth, it would have been ideal to use measures of parental antisocial behavior and alcohol problems in the CDP sample that were obtained prior to mothers' and teachers' first reports of their adolescent's externalizing behavior; however these data were not available. In view of evidence that antisocial behavior and alcohol problems are relatively stable in adulthood (Bennett, McCrady, Johnson, & Pandina, 1999; Neumann, Wampler, Taylor, Blonigen, & Iacono, 2011; Odgers et al., 2008; Petersen et al., in press; Pitkanen et al., 2008), we believe it is appropriate to conceptualize the measures as global indices of parental externalizing behavior. Lastly, paternal antisocial behavior and alcohol problems data were not available

for all participants, which may have resulted in an underestimation of these indices since these behaviors are more prevalent in males than in females. The impact of this underestimation on the association between antisocial behavior and alcohol problems in the parental generation, life events, and adolescent externalizing is unknown.

In summary, we integrated across distinct literatures on intergenerational continuity in externalizing behavior and latent gene-environment interaction to test hypotheses about the role of individual genotypic differences in altering the parental externalizing→life events→adolescent externalizing pathway. We found that the strength of the pathway from life events to adolescent externalizing varies as a function of *GABRA2* genotype. The positive association between life events and externalizing behavior was more robust for those homozygous for the major allele compared to those heterozygous or homozygous for the minor allele, with trends indicating a parallel effect in a second sample. Extending this work to racially/ethnically diverse samples and accounting for intergenerational *GABRA2* genotype represent important avenues for future research in this area.

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References

Achenbach, TM. Manual for Teacher’s Report Form and 1991 profile. Burlington, VT: University of Vermont; 1991a.

Achenbach, TM. Manual for the Child Behavior Checklist and 1991 profile. University of Vermont, Department of Psychiatry; Burlington, VT: 1991c.

Agrawal A, Edenberg HJ, Foroud T, Bierut LJ, Dunne G, Hinrichs AL, Dick DM. Association of GABRA2 with drug dependence in the collaborative study of the genetics of alcoholism sample. Behavior Genetics. 2006; 36(5):640–650.10.1007/s10519-006-9069-4 [PubMed: 16622805]

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition. Washington, D. C: American Psychiatric Association; 1987.

Bennett ME, McCrady BS, Johnson V, Pandina RJ. Problem drinking from young adulthood to adulthood: Patterns, predictors, and outcomes. Journal of Studies on Alcohol. 1999; 60:605–614. [PubMed: 10487729]

Beuten J, ZMJ, Payne TJ, Dupon RT, Crews KM, Somes G, Li MD. Single- and multilocus allelic variants within the GABA(B) receptor subunit 2 (GABAB2) gene are significantly associated with nicotine dependence. American Journal of Human Genetics. 2005; 76:859–864.10.1086/429839 [PubMed: 15759211]

Blomeyer D, Treutlein J, Esser G, Schmidt MH, Schumann G, Laucht M. Interaction between CRHR1 gene and stressful life events predicts adolescent heavy alcohol use. Biological Psychiatry. 2008; 63(2):146–151.10.1016/j.biopsych.2007.04.026 [PubMed: 17597588]

Broms U, Wedenoja J, Largeau MR, Korhonen T, Pitkaniemi J, Keskitalo-Vuokko K, Loukola A. Analysis of detailed phenotype profiles reveals CHRNA5-CHRNA3-CHRNB4 gene cluster association with several nicotine dependence traits. Nicotine & Tobacco Research. 2012; 14(6): 720–733.10.1093/ntr/ntr283 [PubMed: 22241830]

Bucholz KK, Cadoret R, Cloninger CR, Dinwiddie SH, Hesselbrock VM, Nurnberger JL, Schuckit MA. A new, semi-structured psychiatric interview for use in genetic linkage studies: A report on the reliability of the SSAGA. Journal of Studies on Alcohol. 1994; 55(2):149–158. [PubMed: 8189735]

Chassin L, Curran PJ, Hussong AM, Colder CR. The relation of parent alcoholism to adolescent substance use: A longitudinal follow-up study. Journal of Abnormal Psychology. 1996; 105:70–80.10.1037/0021-843X.105.1.70 [PubMed: 8666713]

Chassin L, Pillow DR, Curran PJ, Molina BSG, Barrera M. Relation of parental alcoholism to early adolescent substance use: A test of 3 mediating mechanisms. Journal of Abnormal Psychology. 1993; 102(1):3–19.10.1037//0021-843x.102.1.3 [PubMed: 8436697]

Conger RD, Patterson GR, Ge XJ. It takes 2 to replicate: A mediational model for the impact of parents' stress on adolescent adjustment. Child Development. 1995; 66(1):80–97.10.1111/j.1467-8624.1995.tb00857.x [PubMed: 7497831]

Covault J, Gelernter J, Hesselbrock V, Nellissery M, Kranzler HR. Allelic and haplotypic association of GABRA2 with alcohol dependence. American Journal of Medical Genetics Part B-Neuropsychiatric Genetics. 2004; 129B(1):104–109.10.1002/ajmg.b.30091

Covault J, Tennen H, Armeli S, Conner TS, Herman AI, Cillessen AHN, Kranzler HR. Interactive effects of the serotonin transporter 5-HTTLPR polymorphism and stressful life events on college student drinking and drug use. Biological Psychiatry. 2007; 61(5):609–616.10.1016/j.biopsych.2006.05.018 [PubMed: 16920076]

Dai J, Wang X, Chen Y, Wang X, Zhu J, Lu L. Expression quantitative trait loci and genetic regulatory network analysis reveals that Gabra2 is involved in stress responses in the mouse. Stress and Health. 2009; 12(6):499–506.10.3109/10253890802666112

Delaneau O, Marchini J, Zagury JF. A linear complexity phasing method for thousands of genomes. Nature Methods. 2012; 9(2):179–181.10.1038/nmeth.1785 [PubMed: 22138821]

Dick DM. Gene-environment interaction in psychological traits and disorders. Annu Rev Clin Psychol. 2011; 7:383–409.10.1146/annurev-clinpsy-032210-104518 [PubMed: 21219196]

Dick DM, Agrawal A, Keller MC, Adkins A, Aliev F, Monroe S, Sher KJ. Candidate gene-environment interaction research: Reflections and recommendations. Perspectives on Psychological Science. 2015; 10(1):37–59.10.1177/1745691614556682 [PubMed: 25620996]

Dick DM, Agrawal A, Schuckit MA, Bierut L, Hinrichs A, Fox L, Begleiter H. Marital status, alcohol dependence, and GABRA2: Evidence for gene-environment correlation and interaction. Journal of Studies on Alcohol. 2006; 67:185–194. [PubMed: 16562401]

Dick DM, Bierut L, Hinrichs A, Fox L, Bucholz KK, Kramer J, Foroud T. The role of GABRA2 in risk for conduct disorder and alcohol and drug dependence across developmental stages. Behavior Genetics. 2006; 36(4):577–590.10.1007/s10519-005-9041-8 [PubMed: 16557364]

Dick DM, Latendresse SJ, Lansford JE, Budde JP, Goate A, Dodge KA, Bates JE. Role of GABRA2 in trajectories of externalizing behavior across development and evidence of moderation by parental monitoring. Archives of General Psychiatry. 2009; 66(6):649–657.10.1001/archgenpsychiatry.2009.48 [PubMed: 19487630]

Dodge KA, Pettit GS, Bates JE. Socialization mediators of the relation between socioeconomic status and child conduct problems. Child Development. 1994; 65:649–665.10.1111/j.1467-8624.1994.tb00774.x [PubMed: 8013245]

Edenberg HJ, Dick DM, Xuei X, Tian H, Almasy L, Bauer LO, Begleiter H. Variations in GABRA2, encoding the α2 subunit of the GABA-A receptor are associated with alcohol dependence and with brain oscillations. American Journal of Human Genetics. 2004; 74(4):705–714.10.1086/383283 [PubMed: 15024690]

Enoch MA. The role of GABA(A) receptors in the development of alcoholism. Pharmacology, Biochemistry and Behavior. 2008; 90:95–104.10.1016/j.pbb.2008.03.007

Enoch MA, Hodgkinson CA, Yuan Q, Albaugh B, Virkkunen M, Goldman D. GABRG1 and GABRA2 as independent predictors for alcoholism in two populations. Neuropsychopharmacology. 2009; 34:1245–1254.10.1038/npp.2008.171 [PubMed: 18818659]

Enoch MA, Hodgkinson CA, Yuan Q, Shen PH, Goldman D, Roy A. The influence of GABRA2, childhood trauma, and their interaction on alcohol, heroin, and cocaine dependence. Biological Psychiatry. 2010; 67(1):20–27.10.1016/j.biopsych.2009.08.019 [PubMed: 19833324]

Feder A, Nestler EJ, Charney DS. Psychobiology and molecular genetics of resilience. Nature Reviews Neuroscience. 2009; 10:446–457.10.1038/nrn2649 [PubMed: 19455174]

Fehr C, Sander T, Tadic A, Lenzen KP, Anghelescu I, Klawe C, Szegedi A. Confirmation of association of the GABRA2 gene with alcohol dependence by subtype-specific analysis. Psychiatric Genetics. 2006; 16(1):9–17. [PubMed: 16395124]

Frick, PJ.; Hare, RD. The antisocial process screening device. Toronto: Multi-Health Systems; 2001.

Frojd S, Kaltiala-Heino R, Pelkonen M, Von der Pahlen B, Marttunen M. Significance of family life events in middle adolescence: A survey on Finnish community adolescents. Nordic Journal of Psychiatry. 2009; 63(1):78–86.10.1080/08039480802533754 [PubMed: 19012055]

Herts KL, McLaughlin KA, Hatzenbuehler ML. Emotion dysregulation as a mechanism linking stress exposure to adolescent aggressive behavior. Journal of Abnormal Child Psychology. 2012; 40(7): 1111–1122.10.1007/s10802-012-9629-4 [PubMed: 22466516]

Hicks BM, Krueger RF, Iacono WG, McGue M, Patrick CJ. Family transmission and heritability of externalizing disorders - A twin-family study. Archives of General Psychiatry. 2004; 61(9):922–928.10.1001/archpsyc.61.9.922 [PubMed: 15351771]

Hicks BM, South SC, DiRago AC, Iacono WG, McGue M. Environmental adversity and increasing genetic risk for externalizing disorders. Archives of General Psychiatry. 2009; 66(6):640–648.10.1001/archgenpsychiatry.2008.554 [PubMed: 19487629]

Hoffmann JP, Su SS. Parental substance use disorder, mediating variables and adolescent drug use: a non-recursive model. Addiction. 1998a; 93(9):1351–1364.10.1046/j.1360-0443.1998.93913516.x [PubMed: 9926541]

Hoffmann JP, Su SS. Stressful life events and adolescent substance use and depression: Conditional and gender differentiated effects. Substance Use & Misuse. 1998e; 33(11):2219–2262.10.3109/10826089809056256 [PubMed: 9758012]

Howie BN, Donnelly P, Marchini J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. PLoS Genetics. 2009; 5(6):e1000529.10.1371/journal.pgen.1000529 [PubMed: 19543373]

Hussong AM, Huang WJ, Curran PJ, Chassin L, Zucker RA. Parent Alcoholism Impacts the Severity and Timing of Children's Externalizing Symptoms. Journal of Abnormal Child Psychology. 2010; 38(3):367–380.10.1007/s10802-009-9374-5 [PubMed: 20084453]

Hussong AM, Wirth RJ, Edwards MC, Curran PJ, Chassin LA, Zucker RA. Externalizing symptoms among children of alcoholic parents: Entry points for an antisocial pathway to alcoholism. Journal of Abnormal Psychology. 2007; 116(3):529–542.10.1037/0021-843x.116.3.529 [PubMed: 17696709]

Irons DE, Iacono WG, Oetting WS, Kirkpatrick RM, Vrieze SI, Miller MB, McGue M. Gamma-aminobutyric Acid system genes-no evidence for a role in alcohol use and abuse in a community-based sample. Alcohol Clin Exp Res. 2014; 38(4):938–947.10.1111/acer.12352 [PubMed: 24460875]

Kaprio J, Pulkkinen L, Rose RJ. Genetic and environmental factors in health-related behaviors: Studies on Finnish twins and twin families. Twin Research. 2002; 5(5):366–371.10.1375/twin.5.5.366 [PubMed: 12537860]

Keller MC. Gene x environment interaction studies have not properly controlled for potential confounders: the problem and the (simple) solution. Biological Psychiatry. 2014; 75(1):18–24.10.1016/j.biopsych.2013.09.006 [PubMed: 24135711]

Kendler KS, Chen X, Dick D, Maes H, Gillespie N, Neale MC, Riley B. Recent advances in the genetic epidemiology and molecular genetics of substance use disorders. Nature Neuroscience. 2012; 15(2):181–189.10.1038/nn.3018 [PubMed: 22281715]

Kim KJ, Conger RD, Elder GH, Lorenz FO. Reciprocal influences between stressful life events and adolescent internalizing and externalizing problems. Child Development. 2003; 74(1):127–143.10.1111/1467-8624.00525 [PubMed: 12625440]

Klahr AM, Burt SA. Elucidating the etiology of individual differences in parenting: A meta-analysis of behavioral genetic research. Psychological Bulletin. 2014; 140(2):544–586.10.1037/a0034205 [PubMed: 24016230]

Knaapila A, Silventoinen K, Broms U, Rose RJ, Perola M, Kaprio J, Tuorila HM. Food neophobia in young adults: genetic architecture and relation to personality, pleasantness and use frequency of foods, and body mass index: A twin study. Behavior Genetics. 2011; 41:512–521. [PubMed: 20953688]

Krueger RF, Hicks BM, Patrick CJ, Carlson SR, Iacono WG, McGue M. Etiological connections among substance dependence, antisocial behavior, and personality: Modeling the externalizing spectrum. Journal of Abnormal Psychology. 2002; 111(3):411–424.10.1037//0021-843X.111.3.411 [PubMed: 12150417]

Laucht M, Treutlein J, Blomeyer D, Buchmann AF, Schmid B, Becker K, Banaschewski T. Interaction between the 5-HTTLPR serotonin transporter polymorphism and environmental adversity for mood and anxiety psychopathology: evidence from a high-risk community sample of young adults. International Journal of Neuropsychopharmacology. 2009; 12(6):737–747.10.1017/s1461145708009875 [PubMed: 19154632]

Laucht M, Treutlein J, Schmid B, Blomeyer D, Becker K, Buchmann AF, Banaschewski T. Impact of psychosocial adversity on alcohol intake in young adults: moderation by the LL genotype of the serotonin transporter polymorphism. Biological Psychiatry. 2009; 66(2):102–109.10.1016/j.biopsych.2009.02.010 [PubMed: 19358979]

MacKinnon DP, Lockwood CM, Hoffman JM, West SG, Sheets V. A comparison of methods to test mediation and other intervening variable effects. Psychological Methods. 2002; 7(1):83–104.10.1037/1082-989X.7.1.83 [PubMed: 11928892]

Malone SM, McGue M, Iacono WG. Mothers' maximum drinks ever consumed in 24 hours predicts mental health problems in adolescent offspring. Journal of Child Psychology and Psychiatry. 2010; 51(9):1067–1075.10.1111/j.1469-7610.2010.02219.x [PubMed: 20085606]

Marchini J, Howie B. Genotype imputation for genome-wide association studies. Nature Reviews Genetics. 2010; 11(7):499–511.10.1038/nrg2796

Muller D, Judd CM, Yzerbyt VY. When moderation is mediated and mediation is moderated. Journal of Personality and Social Psychology. 2005; 89(6):852–863.10.1037/0022-3514.89.6.852 [PubMed: 16393020]

Neumann C, Wampler M, Taylor J, Blonigen DM, Iacono WG. Stability and invariance of psychopathic traits from late adolescence to young adulthood. Journal of Research in Personality. 2011; 45:145–152.10.1016/j.jrp.2010.12.003 [PubMed: 21572537]

Newman DL, Moffitt TE, Caspi A, Magdol L, Silva PA, Stanton WR. Psychiatric disorder in a birth cohort of young adults: Prevalence, comobidity, clinical significance, and new case incidence from ages 11–21. Journal of Consulting and Clinical Psychology. 1996; 64:552–562.10.1037/0022-006X.64.3.552 [PubMed: 8698949]

Odgers CL, Moffitt TE, Broadbent JM, Dickson N, Hancox RJ, Harrington H, Caspi A. Female and male antisocial trajectories: From childhood origins to adult outcomes. Development and Psychopathology. 2008; 20(2):673–716.10.1017/s0954579408000333 [PubMed: 18423100]

Patterson, GR. Coercive family process. Eugene, OR: Castalia; 1982.

Perry BL, Pescosolido BA, Bucholz K, Edenberg H, Kramer J, Kuperman S, Nurnberger JI Jr. Gender-specific gene-environment interaction in alcohol dependence: the impact of daily life events and GABRA2. Behavior Genetics. 2013; 43(5):402–414.10.1007/s10519-013-9607-9 [PubMed: 23974430]

Petersen IT, Bates JE, Dodge KA, Lansford JE, Pettit GS. Describing and predicting developmental profiles of externalizing problems from childhood to adulthood. Development & Psychopathology. (in press).

Pillow DR, Barrero M, Chassin L. Using cluster analysis to assess the effects of stressful life events: Probing the impact of parental alcoholism on child stress and substance use. Journal of Community Psychology. 1998; 26(4):361–380.10.1002/(sici)1520-6629(199807)26:4<361::aid-jcop5>3.3.co;2-i

Pinheiro, J.; Bates, D.; DebYor, S.; Sarkar, D. EISPACK authors, & R-core. Linear and nonlinear mixed effects models. 2014.

Pitkanen T, Kokko K, Lyyra AL, Pulkkinen L. A developmental approach to alcohol drinking behaviour in adulthood: a follow-up study from age 8 to age 42. Addiction. 2008; 103:48–68.10.1111/j.1360-0443.2008.02176.x [PubMed: 18426540]

Porjesz B, Almasy L, Edenberg HJ, Wang K, Chorlian DB, Foroud T, Begleiter H. Linkage disequilibrium between the beta frequency of the human EEG and a GABAA receptor gene locus. Proceedings of the National Academy of Sciences. 2002; 99:3729–3733.

Pulkkinen L, Kaprio J, Rose RJ. Peers, teachers and parents as assessors of the behavioural and emotional problems of twins and their adjustment: The Multidimensional Peer Nomination Inventory. Twin Research. 1999; 2(4):274–285.10.1375/136905299320565762 [PubMed: 10723806]

R Development Core Team. R: A language and environment for statistical computing. Vienna, Austria: 2014.

Schmid B, Blomeyer D, Treutlein J, Zimmermann US, Buchmann AF, Schmidt MH, Laucht M. Interacting effects of CRHR1 gene and stressful life events on drinking initiation and progression among 19-year-olds. International Journal of Neuropsychopharmacology. 2010; 13(6):703–714.10.1017/S1461145709990290 [PubMed: 19607758]

Selya AS, Rose JS, Dierker LC, Hedeker D, Mermelstein RJ. A practical guide to calculating Cohen's f(2), a measure of local effect size, from PROC MIXED. Frontiers in Psychology. 2012; 3:111.10.3389/fpsyg.2012.00111 [PubMed: 22529829]

Selzer ML, Vinokur A, van Rooijen L. A self-administered Short Michigan Alcoholism Screening Test (SMAST). Journal of Studies on Alcohol. 1975; 36(1):117–126. [PubMed: 238068]

Shanahan MJ, Hofer SM. Social context in gene-environment interactions: retrospect and prospect. Journals of Gerontology Series B-Psychological Sciences and Social Sciences. 2005; 60B:65–76.10.1093/geronb/60.Special_Issue_1.65

Sher KJ, Gershuny BS, Peterson L, Raskin G. The role of childhood stressors in the intergenerational transmission of alcohol use disorders. Journal of Studies on Alcohol. 1997; 58(4):414–427. [PubMed: 9203123]

Spencer CC, Su Z, Donnelly P, Marchini J. Designing genome-wide association studies: sample size, power, imputation, and the choice of genotyping chip. PLoS Genetics. 2009; 5(5):e1000477.10.1371/journal.pgen.1000477 [PubMed: 19492015]

Thornberry TP, Freeman-Gallant A, Lizotte AJ, Krohn MD, Smith CA. Linked lives: The intergenerational transmission of antisocial behavior. Journal of Abnormal Child Psychology. 2003; 31(2):171–184.10.1023/A:1022574208366 [PubMed: 12735399]

Timmermans M, van Lier PAC, Koot HM. The role of stressful events in the development of behavioural and emotional problems from early childhood to late adolescence. Psychological Medicine. 2010; 40(10):1659–1668.10.1017/s0033291709992091 [PubMed: 20056023]

Torvik FA, Rognmo K, Ask H, Roysamb E, Tambs K. Parental alcohol use and adolescent school adjustment in the general population: Results from the HUNT study. BMC Public Health. 2011; 1110.1186/1471-2458-11-706

Tremblay RE. Developmental origins of disruptive behaviour problems: the 'original sin' hypothesis, epigenetics and their consequences for prevention. Journal of Child Psychology and Psychiatry. 2010; 51(4):341–367.10.1111/j.1469-7610.2010.02211.x [PubMed: 20146751]

Verlaan P, Schwartzman AE. Mother's and father's parental adjustment: Links to externalising behaviour problems in sons and daughters. International Journal of Behavioral Development. 2002; 26(3):214–224.10.1080/01650250042000717

Villafuerte S, Heitzeg MM, Foley S, Yau WY, Majczenko K, Zubieta JK, Burmeister M. Impulsiveness and insula activation during reward anticipation are associated with genetic variants in GABRA2 in a family sample enriched for alcoholism. Molecular Psychiatry. 2012; 17(5):511–519.10.1038/mp.2011.33 [PubMed: 21483437]

Villafuerte S, Trucco EM, Heitzeg MM, Burmeister M, Zucker RA. Genetic variation in moderates peer influence on externalizing behavior in adolescents. Brain Behav. 201410.1002/brb3.291

Wills TA, Sandy JM, Yaeger A, Shinar O. Family risk factors and adolescent substance use: Moderation effects for temperament dimensions. Developmental Psychology. 2001; 37(3):283–297.10.1037/0012-1649.37.3.283 [PubMed: 11370906]

Wills TA, Yaeger AM. Family factors and adolescent substance use: Models and mechanisms. Current Directions in Psychological Science. 2003; 12(6):222–226.10.1046/j.0963-7214.2003.01266.x

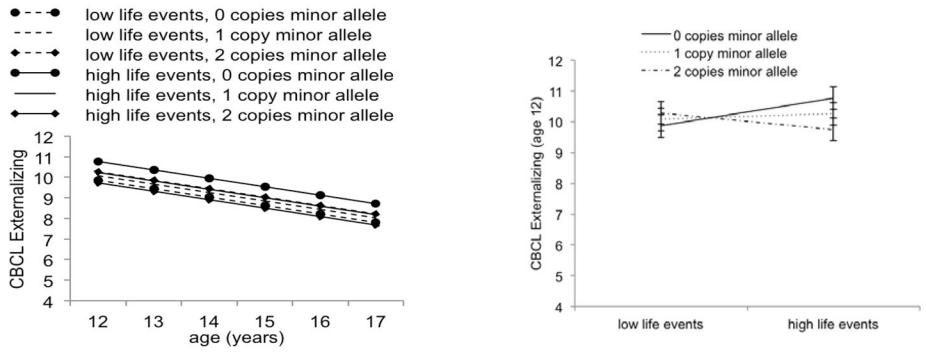
Windle M. A Longitudinal study of stress buffering for adolescent problem behaviors. Developmental Psychology. 1992; 28(3):522–530.10.1037//0012-1649.28.3.522

Windle M, Windle RC. Coping strategies, drinking motives, and stressful life events among middle adolescents: Associations with emotional and behavioral problems and with academic functioning. Journal of Abnormal Psychology. 1996; 105(4):551–560.10.1037//0021-843x.105.4.551 [PubMed: 8952188]

Zintzaras E. Gamma-aminobutyric acid A receptor, alpha-2 (GABRA2) variants as individual markers for alcoholism: a meta-analysis. Psychiatric Genetics. 2012; 22(4):189–196.10.1097/YPG.0b013e328353ae53 [PubMed: 22555154]

Lay summary

Teenagers with a parent who suffers from alcohol problems or antisocial behavior often experience more life events and changes, and exhibit more behavior problems themselves. Our study finds that these intergenerational effects are stronger or weaker depending on the teenager's genetic make-up.



(A) (B)

Figure 1.

Panel A plots Child Behavior Checklist (CBCL) adolescent externalizing as a function of life events (high = +1 SD above the mean, low = −1 SD below the mean) and the number of copies of the minor allele for *GABRA2* SNP rs279871 for the model including parental antisocial behavior in the Child Development Project sample. Panel B further delineates the shape of the interaction for the model including parental antisocial behavior as a function of *GABRA2* SNP rs279871 and high and low life events for an illustrative time point (age 12). Bars represent the standard errors of the estimates.

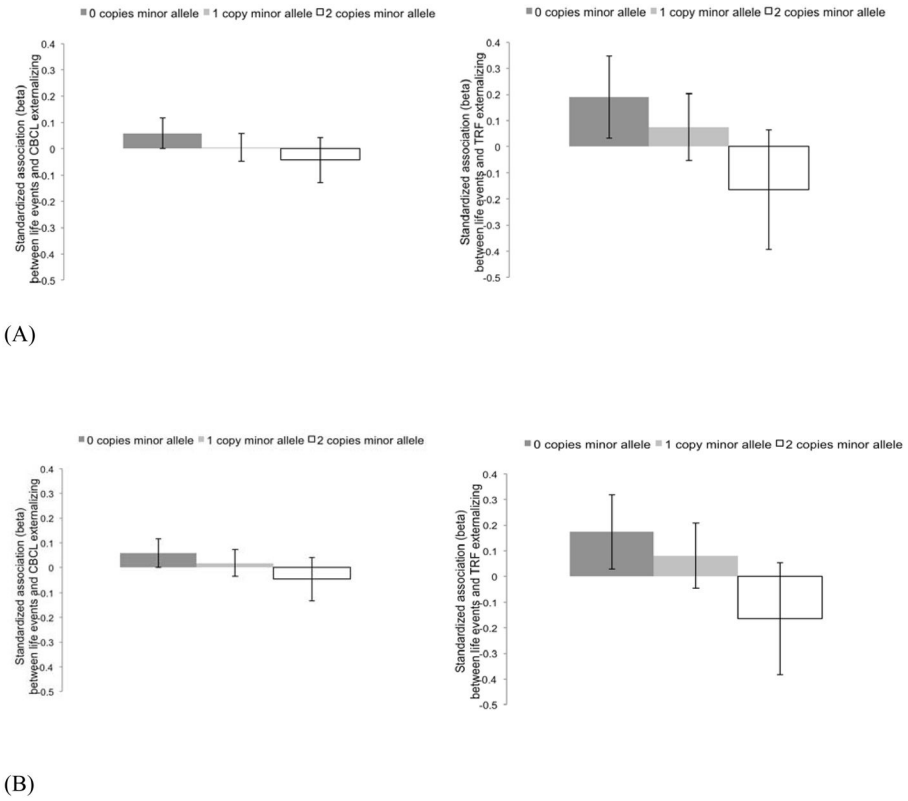


Figure 2.

Strength of the association (depicted as standardized betas) between life events, Child Behavior Checklist (CBCL) externalizing (left), and Teacher Report Form (TRF) externalizing (right) as a function of the number of copies of the minor allele for *GABRA2* SNP rs279871 for the models including parental antisocial behavior (panel A) and parental alcohol problems (panel B) in the Child Development Project sample. Bars represent the 95% confidence intervals for the estimates.

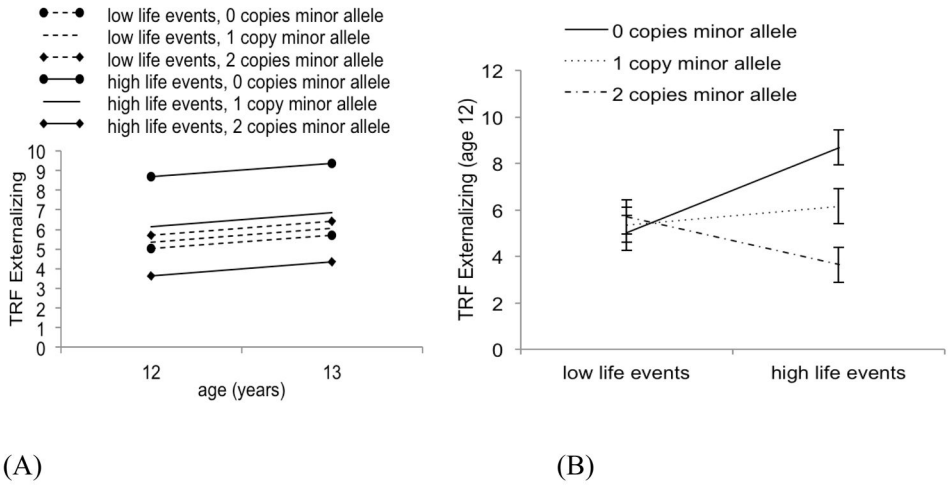


Figure 3.

Teacher Report Form (TRF) externalizing as a function of life events (high = +1 SD above the mean, low = −1 SD below the mean) and the number of copies of the minor allele for *GABRA2* SNP rs279871 for the model including parental antisocial behavior (panel A) in the Child Development Project sample. Panel B further delineates the shape of the interaction for the model including parental antisocial behavior as a function of *GABRA2* SNP rs279871 and high and low life events for an illustrative time point (age 12). Bars represent the standard errors of the estimates.

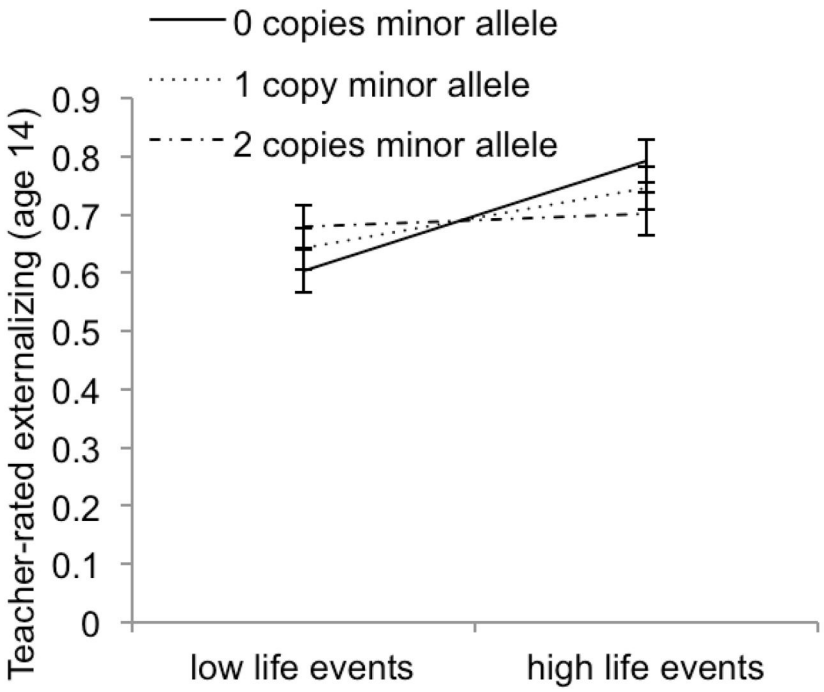
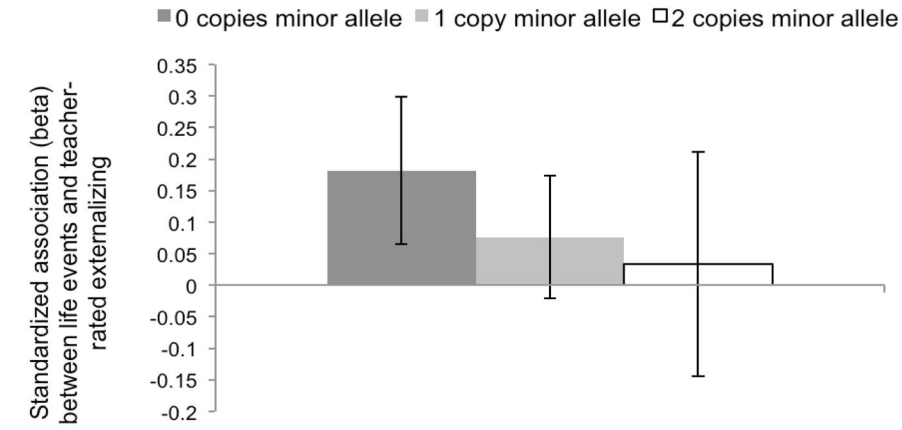
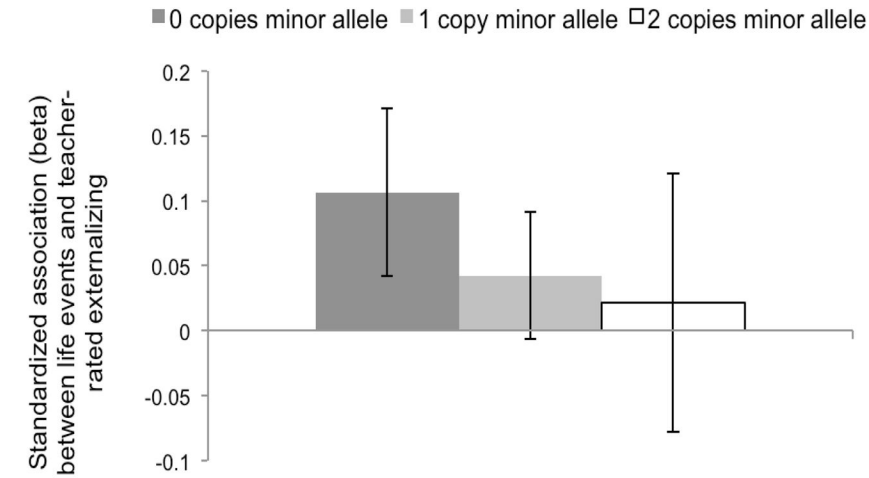


Figure 4.

Teacher-reported adolescent externalizing as a function of life events (high = +1 SD above the mean, low = −1 SD below the mean) and the number of copies of the minor allele for *GABRA2* SNP rs279871 for the model including parental antisocial behavior in the FinnTwin12 sample. Bars represent the standard errors of the estimates.



(A)



(B)

Figure 5.

Strength of the association (depicted as standardized betas) between life events and teacher-reported adolescent externalizing as a function of the number of copies of the minor allele for *GABRA2* SNP rs279871 for the models including parental antisocial behavior (panel A) and parental alcohol dependence symptoms (panel B) in the FinnTwin12 sample. Bars represent the 95% confidence intervals for the estimates.

Table 1

Life events items for the Child Development Project and FinnTwin12 samples

Item
Sample: Child Development Project
Moved
Major repairs/remodeling to home
Severe and/or frequent illness for child
Accidents and/or injuries for child
Other medical problems for child
Medical problems for close family members
Death of close family member
Death of other important person
Divorce and/or separation for you and your husband/wife
Parent and child were separated (due to illness, divorce, work, etc.)
Money problems
Legal problems
Problems and conflicts with relatives
Birth of a baby
Problems at school for child
Problems at work for parents
Loss of a job
Remarriage or marital reconciliation
Sample: FinnTwin12
You moved to a new neighborhood or town with your family
A close friend has moved away
You have changed to another school
You have experienced a serious illness or accident
Someone close to you has been seriously ill.
Your parents or parent and step-parent have had serious conflicts
Mother or father has moved out of home, or they have divorced
A new mate of your mother’s or father’s has moved in
Your sister or brother has moved away from home
A teacher/coach close to your has changed
A close friendship has ended
Mother or father has been unemployed
Mother has started working after being at home for a long time
A new sibling has been born

Table 2

Descriptive statistics and zero-order correlations among Child Development Project parental externalizing, life events, and adolescent externalizing variables

	M	*SD*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Max parental ASB	5.41	3.18															
2. Max parental AP	0.98	1.73	***0.15***														
3. Life Events (Age 11)	2.25	2.18	***0.12***	0.10													
4. Life Events (Age 12)	2.47	2.06	0.09	0.02	***0.59***												
5. Life Events (Age 13)	2.97	2.25	***0.12***	**0.13**	***0.34***	***0.49***											
6. Life Events (Age 14)	2.11	2.10	0.02	0.04	***0.40***	***0.45***	***0.43***										
7. Life Events (Age 15)	2.19	2.34	***0.17***	0.03	***0.39***	***0.32***	***0.34***	***0.59***									
8. Life Events (Age 16)	3.67	2.28	***0.20***	0.06	***0.34***	***0.40***	***0.37***	***0.44***	***0.50***								
9. CBCL Ext (Age 12)	8.57	6.80	***0.29***	0.05	***0.23***	***0.39***	***0.24***	***0.34***	***0.32***	***0.38***							
10. CBCL Ext (Age 13)	8.72	6.89	***0.31***	0.10	***0.14***	***0.27***	***0.26***	***0.30***	***0.25***	***0.29***	***0.80***						
11. CBCL Ext (Age 14)	7.55	7.41	***0.22***	0.10	***0.15***	***0.34***	***0.28***	***0.44***	***0.36***	***0.36***	***0.80***	***0.81***					
12. CBCL Ext (Age 15)	7.62	7.78	***0.30***	***0.18***	***0.20***	***0.27***	***0.22***	***0.39***	***0.39***	***0.37***	***0.71***	***0.73***	***0.80***				
13. CBCL Ext (Age 16)	7.75	7.56	***0.31***	0.08	***0.17***	***0.23***	***0.19***	***0.31***	***0.32***	***0.38***	***0.72***	***0.72***	***0.74***	***0.82***			
14. CBCL Ext (Age 17)	6.46	6.90	***0.25***	0.08	***0.14***	***0.20***	***0.17***	***0.31***	***0.30***	***0.32***	***0.64***	***0.63***	***0.72***	***0.70***	***0.76***		
15. TRF Ext (Age 12)	4.80	7.55	***0.16***	***0.30***	***0.16***	***0.23***	***0.20***	***0.38***	***0.25***	***0.20***	***0.43***	***0.38***	***0.47***	***0.44***	***0.41***	***0.30***	
16. TRF Ext (Age 13)	5.45	8.68	***0.24***	***0.19***	0.03	0.05	0.07	***0.18***	**0.14**	***0.22***	***0.31***	***0.34***	***0.38***	***0.35***	***0.40***	***0.35***	***0.44***

Notes. Bolded and italicized values indicate $p < .01$. Bolded values indicate $p < .05$. Abbreviations: Max = maximum, ASB = antisocial behavior, AP = alcohol problems, CBCL = Child Behavior Checklist, TRF = Teacher Report Form, Ext = externalizing.

Table 3

Child Development Project: Child Behavior Checklist externalizing as a function of parental antisocial behavior, cross-lagged life events, GABRA2 genotype, and cross-lagged life events x GABRA2 genotype interaction

Parameter	*B*	SE (*B*)	*DF*	*t*-value	*p*-value
Model 1					
Intercept	***12.50***	***1.23***	***1198***	***10.20***	***<0.01***
Time	***−0.41***	***0.07***	***1198***	***−5.88***	***<0.01***
Sex	−0.67	0.66	299	−1.02	0.31
Number of parent ASB reports	***−2.16***	***0.68***	***299***	***−3.18***	***<0.01***
Maximum parental ASB	***2.21***	***0.34***	***299***	***6.55***	***<0.01***
Life events$_{j-1}$	0.13	0.13	1198	1.04	0.30
rs279871	−0.13	0.47	299	−0.28	0.78
Model 2					
Intercept	***12.46***	***1.22***	***1197***	***10.19***	***<0.01***
Time	***−0.41***	***0.07***	***1197***	***−5.84***	***<0.01***
Sex	−0.66	0.66	299	−1.00	0.32
Number of parent ASB reports	***−2.14***	***0.68***	***299***	***−3.16***	***<0.01***
Maximum parental ASB	***2.20***	***0.34***	***299***	***6.52***	***<0.01***
Life events$_{j-1}$	**0.45**	**0.21**	**1197**	**2.17**	**0.03**
rs279871	−0.15	0.47	299	−0.33	0.74
Life events$_{j-1}$ × rs279871	**−0.36**	**0.19**	**1197**	**−1.93**	**0.05**
Model 3					
Intercept	***11.98***	***1.81***	***1194***	***6.61***	***<0.01***
Time	***−0.40***	***0.07***	***1194***	***−5.79***	***<0.01***
Sex	−0.22	1.05	296	−0.21	0.84
Number of parent ASB reports	−1.93	1.08	296	−1.79	0.07
Maximum parental ASB	***2.28***	***0.51***	***296***	***4.48***	***<0.01***
Life events$_{j-1}$	0.18	0.48	1194	0.39	0.70
rs279871	0.58	1.70	296	0.34	0.73
Life events$_{j-1}$ × rs279871	−0.36	0.19	1194	−1.92	0.06
rs279871 × sex	−0.54	0.97	296	−0.56	0.58

Parameter	*B*	SE (*B*)	*DF*	*t*-value	*p*-value
rs279871 × number of parent ASB reports	−0.31	0.98	296	−0.31	0.75
rs279871 × maximum parental ASB	−0.05	0.44	296	−0.11	0.91
Life events$_{j-1}$ × sex	0.18	0.26	1194	0.71	0.48
Life events$_{j-1}$ × number of parent ASB reports	0.13	0.27	1194	0.48	0.63
Life events$_{j-1}$ × maximum parental ASB	−0.25	0.14	1194	−1.81	0.07

Notes. Model 1 includes the main effects. Model 2 includes the main effects and the G × E effect. Model 3 includes main effects, the G × E effect, and additional statistical controls for all covariate × genotype and covariate × environment interactions. Bolded and italicized values indicate p ≤ .01. Bolded values indicate p ≤ .05. Abbreviation: ASB = antisocial behavior.

Table 4

Child Development Project: Child Behavior Checklist externalizing as a function of parental alcohol problems, cross-lagged life events, GABRA2 genotype, and cross-lagged life events x GABRA2 genotype interaction

Parameter	*B*	SE (*B*)	*DF*	*t*-value	*p*-value
Model 1					
Intercept	***10.56***	***1.24***	***1195***	***8.50***	***<0.01***
Time	***−0.41***	***0.07***	***1195***	***−5.80***	***<0.01***
Sex	−0.41	0.70	299	−0.59	0.55
Number of parent AP reports	−1.13	0.71	299	−1.60	0.11
Maximum parental AP	**0.75**	**0.35**	**299**	**2.16**	**0.03**
Life events$_{j-1}$	0.19	0.13	1195	1.42	0.16
rs279871	0.02	0.50	299	0.05	0.96
Model 2					
Intercept	***10.54***	***1.24***	***1194***	***8.51***	***<0.01***
Time	***−0.41***	***0.07***	***1194***	***−5.75***	***<0.01***
Sex	−0.40	0.69	299	−0.58	0.56
Number of parent AP reports	−1.12	0.70	299	−1.59	0.11
Maximum parental AP	**0.74**	**0.35**	**299**	**2.11**	**0.04**
Life events$_{j-1}$	**0.50**	**0.21**	**1194**	**2.40**	**0.02**
rs279871	0.01	0.50	299	0.01	0.99
Life events$_{j-1}$ × rs279871	**−0.36**	**0.19**	**1194**	**−1.93**	**0.05**
Model 3					
Intercept	***10.44***	***1.81***	***1191***	***5.76***	***<0.01***
Time	***−0.41***	***0.07***	***1191***	***−5.74***	***<0.01***
Sex	−0.42	1.12	296	−0.37	0.71
Number of parent AP reports	−1.04	1.12	296	−0.93	0.35
Maximum parental AP	**1.10**	**0.49**	**296**	**2.26**	**0.02**
Life events$_{j-1}$	0.47	0.46	1191	1.01	0.31
rs279871	0.10	1.70	296	0.06	0.95
Life events$_{j-1}$ × rs279871	−0.35	0.19	1191	−1.83	0.07
rs279871 × sex	0.10	1.01	296	0.10	0.92

Parameter	*B*	SE (*B*)	*DF*	*t*-value	*p*-value
rs279871 × number of parent AP reports	−0.09	1.01	296	−0.08	0.93
rs279871 × maximum parental AP	−0.51	0.48	296	−1.07	0.28
Life events$_{j-1}$ × sex	0.24	0.26	1191	0.92	0.36
Life events$_{j-1}$ × number of parent AP reports	−0.07	0.27	1191	−0.25	0.80
Life events$_{j-1}$ × maximum parental AP	−0.04	0.12	1191	−0.37	0.71

Notes. Model 1 includes the main effects. Model 2 includes the main effects and the G × E effect. Model 3 includes main effects, the G × E effect, and additional statistical controls for all covariate × genotype and covariate × environment interactions. Bolded and italicized values indicate p ≤ .01. Bolded values indicate p ≤ .05. Abbreviation: AP = alcohol problems.

Table 5

Child Development Project: Teacher Report Form externalizing as a function of parental antisocial behavior, cross-lagged life events, GABRA2 genotype, and cross-lagged life events x GABRA2 genotype interaction

Parameter	*B*	SE (*B*)	*DF*	*t*-value	*p*-value
Model 1					
Intercept	***7.61***	***1.47***	***271***	***5.17***	***<0.01***
Time	0.72	0.57	209	1.27	0.21
Sex	***−2.09***	***0.78***	***271***	***−2.69***	***0.01***
Number of parent ASB reports	−0.72	0.81	271	−0.89	0.37
Maximum parental ASB	***1.43***	***0.40***	***271***	***3.57***	***<0.01***
Life events$_{j-1}$	0.63	0.36	209	1.76	0.08
rs279871	−0.96	0.55	271	−1.73	0.08
Model 2					
Intercept	***7.46***	***1.46***	***271***	***5.11***	***<0.01***
Time	0.71	0.57	208	1.26	0.21
Sex	***−1.97***	***0.77***	***271***	***−2.56***	***0.01***
Number of parent ASB reports	−0.62	0.80	271	−0.78	0.44
Maximum parental ASB	***1.43***	***0.40***	***271***	***3.61***	***<0.01***
Life events$_{j-1}$	***1.83***	***0.58***	***208***	***3.16***	***<0.01***
rs279871	**−1.09**	**0.55**	**271**	**−1.98**	**0.05**
Life events$_{j-1}$ × rs279871	***−1.43***	***0.55***	***208***	***−2.61***	***0.01***
Model 3					
Intercept	***7.48***	***2.15***	***268***	***3.47***	***<0.01***
Time	0.69	0.57	205	1.20	0.23
Sex	**−2.41**	**1.21**	**268**	**−1.99**	**0.05**
Number of parent ASB reports	−0.53	1.27	268	−0.42	0.68
Maximum parental ASB	**1.45**	**0.60**	**268**	**2.43**	**0.02**
Life events$_{j-1}$	2.80	1.30	205	2.15	0.03
rs279871	−1.40	2.00	268	−0.70	0.49
Life events$_{j-1}$ × rs279871	**−1.32**	**0.57**	**205**	**−2.30**	**0.02**
rs279871 × sex	0.56	1.11	268	0.51	0.61

Parameter	*B*	SE (*B*)	*DF*	*t*-value	*p*-value
rs279871 × number of parent ASB reports	0.05	1.14	268	0.04	0.96
rs279871 × maximum parental ASB	−0.09	0.52	268	−0.17	0.87
Life events$_{j-1}$ × sex	−0.97	0.72	205	−1.35	0.18
Life events$_{j-1}$ × number of parent ASB reports	−0.35	0.78	205	−0.44	0.66
Life events$_{j-1}$ × maximum parental ASB	0.22	0.39	205	0.57	0.57

Notes. Model 1 includes the main effects. Model 2 includes the main effects and the G × E effect. Model 3 includes main effects, the G × E effect, and additional statistical controls for all covariate × genotype and covariate × environment interactions. Bolded and italicized values indicate p ≤ .01. Bolded values indicate p ≤ .05. Abbreviation: ASB = antisocial behavior.

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Table 6

Child Development Project: Teacher Report Form externalizing as a function of parental alcohol problems, cross-lagged life events, GABRA2 genotype, and cross-lagged life events x GABRA2 genotype interaction

Parameter	*B*	SE (*B*)	*DF*	*t*-value	*p*-value
Model 1					
Intercept	***8.37***	***1.34***	***272***	***6.26***	***<0.01***
Time	0.68	0.56	209	1.21	0.23
Sex	**−1.65**	**0.74**	**272**	**−2.23**	**0.03**
Number of parent AP reports	**−1.47**	**0.76**	**272**	**−1.94**	**0.05**
Maximum parental AP	***2.33***	***0.38***	***272***	***6.18***	***<0.01***
Life events$_{j-1}$	0.60	0.34	209	1.76	0.08
rs279871	−0.81	0.52	272	−1.55	0.12
Model 2					
Intercept	***8.33***	***1.32***	***272***	***6.29***	***<0.01***
Time	0.67	0.56	208	1.20	0.23
Sex	**−1.53**	**0.73**	**272**	**−2.09**	**0.04**
Number of parent AP reports	−1.43	0.75	272	−1.91	0.06
Maximum parental AP	***2.32***	***0.37***	***272***	***6.20***	***<0.01***
Life events$_{j-1}$	***1.79***	***0.56***	***208***	***3.21***	***<0.01***
rs279871	−0.94	0.52	272	−1.82	0.07
Life events$_{j-1}$ × rs279871	***−1.42***	***0.53***	***208***	***−2.68***	***0.01***
Model 3					
Intercept	***7.92***	***1.91***	***269***	***4.14***	***<0.01***
Time	0.65	0.57	205	1.13	0.26
Sex	−1.89	1.17	269	−1.62	0.11
Number of parent AP reports	−1.04	1.18	269	−0.89	0.37
Maximum parental AP	***2.38***	***0.50***	***269***	***4.77***	***<0.01***
Life events$_{j-1}$	1.65	1.15	205	1.43	0.15
rs279871	−0.68	1.78	269	−0.38	0.70
Life events$_{j-1}$ × rs279871	***−1.36***	***0.54***	***205***	***−2.50***	***0.01***
rs279871 × sex	0.33	1.05	269	0.31	0.75

Parameter	*B*	SE (*B*)	*DF*	*t*-value	*p*-value
rs279871 × number of parent AP reports	−0.24	1.06	269	−0.23	0.82
rs279871 × maximum parental AP	−0.19	0.53	269	−0.35	0.73
Life events$_{j-1}$ × sex	−1.05	0.70	205	−1.49	0.14
Life events$_{j-1}$ × number of parent AP reports	0.45	0.70	205	0.65	0.52
Life events$_{j-1}$ × maximum parental AP	0.18	0.38	205	0.47	0.64

Notes. Model 1 includes the main effects. Model 2 includes the main effects and the G × E effect. Model 3 includes main effects, the G × E effect, and additional statistical controls for all covariate × genotype and covariate × environment interactions. Bolded and italicized values indicate p ≤ .01. Bolded values indicate p ≤ .05. Abbreviation: AP = alcohol problems.

Table 7

Descriptive statistics and zero-order correlations among FinnTwin12 parental externalizing, life events, and adolescent externalizing variables

	M	*SD*	1	2	3
1. Parental antisocial behavior	1.09	1.31			
2. Parental alcohol dependence symptoms	2.13	2.37	***0.43***		
3. Life events (age 14)	2.79	1.75	***0.14***	***0.10***	
4. Teacher-rated externalizing (age 14)	0.47	0.53	***0.10***	**0.08**	***0.13***

Notes. Bolded and italicized values indicate p ≤ .01. Bolded values indicate p ≤ .05.

Table 8

FinnTwin12: Teacher reported externalizing as a function of parental antisocial behavior, life events, GABRA2 genotype, and life events x GABRA2 genotype interaction

Parameter	*B*	SE (*B*)	*DF*	*t*-value	*p*-value
Model 1					
Intercept	***0.84***	***0.13***	***475***	***6.60***	***<0.01***
Sex	***−0.30***	***0.03***	***321***	***−8.54***	***<0.01***
Number of parent ASB reports	−0.11	0.07	475	−1.71	0.09
Maximum parental ASB	**0.05**	**0.02**	**475**	**2.25**	**0.03**
Life events	***0.05***	***0.02***	***321***	***2.92***	***<0.01***
rs279871	0.00	0.03	321	−0.02	0.98
Model 2					
Intercept	***0.83***	***0.13***	***475***	***6.54***	***<0.01***
Sex	***−0.30***	***0.03***	***320***	***−8.55***	***<0.01***
Number of parent ASB reports	−0.11	0.06	475	−1.64	0.10
Maximum parental ASB	**0.05**	**0.02**	**475**	**2.26**	**0.02**
Life events	***0.09***	***0.03***	***320***	***3.17***	***<0.01***
rs279871	0.00	0.03	320	0.01	1.00
Life events × rs279871	−0.04	0.03	320	−1.70	0.09
Model 3					
Intercept	***0.84***	***0.18***	***475***	***4.61***	***<0.01***
Sex	***−0.28***	***0.06***	***314***	***−4.94***	***<0.01***
Number of parent ASB reports	−0.12	0.10	475	−1.24	0.22
Maximum parental ASB	**0.07**	**0.03**	**475**	**2.08**	**0.04**
Life events	0.13	0.11	314	1.14	0.26
rs279871	0.00	0.16	314	−0.02	0.98
Life events × rs279871	−0.04	0.03	314	−1.51	0.13
rs279871 × sex	−0.03	0.05	314	−0.61	0.54
rs279871 × number of parent ASB reports	0.01	0.08	314	0.12	0.90
rs279871 × maximum parental ASB	−0.02	0.03	314	−0.80	0.43
Life events × sex	−0.06	0.04	314	−1.57	0.12

Parameter	*B*	SE (*B*)	*DF*	*t*-value	*p*-value
Life events × number of parent ASB reports	0.00	0.06	314	−0.04	0.97
Life events × maximum parental ASB	0.00	0.02	314	0.03	0.98

Notes. Model 1 includes the main effects. Model 2 includes the main effects and the G × E effect. Model 3 includes main effects, the G × E effect, and additional statistical controls for all covariate × genotype and covariate × environment interactions. Bolded and italicized values indicate p ≤ .01. Bolded values indicate p ≤ .05. Abbreviation: ASB = antisocial behavior.

Table 9

FinnTwin12: Teacher reported externalizing as a function of parental alcohol dependence symptoms, life events, GABRA2 genotype, and life events x GABRA2 genotype interaction

Parameter	*B*	SE (*B*)	*DF*	*t*-value	*p*-value
Model 1					
Intercept	***0.78***	***0.13***	***474***	***6.01***	***<0.01***
Sex	***−0.30***	***0.04***	***320***	***−8.48***	***<0.01***
Number of parent ADSX reports	−0.08	0.07	474	−1.15	0.25
Maximum parental ADSX	0.03	0.02	474	1.20	0.23
Life events	***0.06***	***0.02***	***320***	***3.09***	***<0.01***
rs279871	0.00	0.03	320	−0.14	0.89
Model 2					
Intercept	***0.77***	***0.13***	***474***	***5.94***	***<0.01***
Sex	***−0.30***	***0.04***	***319***	***−8.49***	***<0.01***
Number of parent ADSX reports	−0.07	0.07	474	−1.07	0.29
Maximum parental ADSX	0.02	0.02	474	1.15	0.25
Life events	***0.09***	***0.03***	***319***	***3.21***	***<0.01***
rs279871	<0.01	0.03	319	−0.12	0.91
Life events × rs279871	−0.04	0.03	319	−1.62	0.11
Model 3					
Intercept	***0.76***	***0.19***	***474***	***4.03***	***<0.01***
Sex	***−0.27***	***0.06***	***313***	***−4.89***	***<0.01***
Number of parent ADSX reports	−0.07	0.10	474	−0.70	0.48
Maximum parental ADSX	0.00	0.03	474	0.07	0.94
Life events	0.12	0.11	313	1.06	0.29
rs279871	0.02	0.17	313	0.09	0.93
Life events × rs279871	−0.04	0.03	313	−1.67	0.10
rs279871 × sex	−0.03	0.05	313	−0.58	0.56
rs279871 × number of parent ADSX reports	0.00	0.09	313	−0.03	0.97
rs279871 × maximum parental ADSX	0.03	0.03	313	0.98	0.33
Life events × sex	−0.05	0.04	313	−1.53	0.13

Parameter	*B*	SE (*B*)	*DF*	*t*-value	*p*-value
Life events × number of parent ADSX reports	0.00	0.06	313	0.09	0.93
Life events × maximum parental ADSX	−0.01	0.02	313	−0.39	0.70

Notes. Model 1 includes the main effects. Model 2 includes the main effects and the G × E effect. Model 3 includes main effects, the G × E effect, and additional statistical controls for all covariate × genotype and covariate × environment interactions. Bolded and italicized values indicate p ≤ .01. Bolded values indicate p ≤ .05. Abbreviation: ADSX = alcohol dependence symptoms.