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EMPIRICAL RESEARCH

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Time-varying Effects of GABRG1 and Maladaptive Peer Behavior on Externalizing Behavior from Childhood to Adulthood: Testing Gene × Environment × Development Effects

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Abstract
Engagement in externalizing behavior is problematic. Deviant peer affiliation increases risk for externalizing behavior. Yet, peer effects vary across individuals and may differ across genes. This study determines gene × environment × development interactions as they apply to externalizing behavior from childhood to adulthood. A sample (n = 687; 68% male, 90% White) of youth from the Michigan Longitudinal Study was assessed from ages 10 to 25. Interactions between γ-amino butyric acid type A receptor γ1 subunit (*GABRG1;* rs7683876, rs13120165) and maladaptive peer behavior on externalizing behavior were examined using time-varying effect modeling. The findings indicate a sequential risk gradient in the influence of maladaptive peer behavior on externalizing behavior depending on the number of G alleles during childhood through adulthood. Individuals with the GG genotype are most vulnerable to maladaptive peer influences, which results in greater externalizing behavior during late childhood through early adulthood.

Keywords Genes · TVEM · Externalizing behavior · Peers · *GABRG1*

Introduction

Externalizing behavior, such as rule-breaking and aggression is a pervasive public health concern. Not only is externalizing behavior associated with a host of negative sequelae to the individual (e.g., substance use problems, mental illness; Farmer et al. 2015), but it also has a deleterious impact on society as externalizing behavior early in life conveys risk for adult work incapacity (Narusyte et al. 2017) and later criminal behavior (Harris-McKoy and Cui 2013). Thus, gaining a greater understanding of factors contributing to high-risk trajectories of externalizing behavior can inform preventive interventions. A strong predictor of high-risk externalizing trajectories is affiliation with peers engaging in deviant behavior (Epstein et al. 2017). Prior work indicates that youth affiliating with peers that engage in delinquent behavior (e.g., stealing, truancy) and peers that use substances demonstrate high externalizing behavior compared to youth affiliating with more prosocial youth (e.g., Samek et al. 2016). Yet, individuals vary in their susceptibility to peer influences as a function of differences in genetic susceptibility (Trucco et al. 2017). Moreover, developmental theory posits that the degree of susceptibility to socialization contexts, especially peers, is not static over time (Epstein et al. 2017). Although there is a large literature demonstrating how genetic factors increase susceptibility to environmental factors (i.e., gene × environment [G × E] interactions), few investigations exist examining how G × E interactions change from childhood to adulthood within the same study. In fact, understanding the complex G × E interplay underlying peer relations and social development from a fully developmental perspective is viewed as a challenge hampering continued progress in the field (Trucco et al. 2018). This is due in part to a lack of

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quantitative methods able to model nonlinear change in interactions over time (Epstein et al. 2017). This study employs a state-of-the-art approach, time-varying effect modeling (TVEM), to determine possible gene × environment × development (G × E × D) interactions as they apply to the patterning of externalizing behavior from childhood to adulthood.

Externalizing Behavior Across Development

Externalizing behavior tends to be variable across development. Moreover, trajectories tend to vary somewhat based on the different facets of externalizing behavior. Aggression reflects behavior that is more overt, such as bullying and fighting, whereas rule breaking reflects behavior that is more covert, such as stealing and truancy (Becht et al. 2016). Prior work indicates that aggression is typically characterized by an initial increase from the first year of life to the end of the third year, and by a steady decline thereafter (Broidy et al. 2003). This has led some researchers to conclude that children do not necessarily learn to become physically aggressive; rather, they learn not to be physically aggressive given the combined effects of brain maturation and socialization (Tremblay and Szyf 2010). In contrast, rule breaking behavior tends to be infrequent during childhood, increases over the course of adolescence, and then decreases again during the transition into adulthood (Walton et al. 2017). During childhood, youth are socialized to respect and follow rules set by authority figures (LaFontana and Cillessen 2010). During early adolescence, there is a gradual shift towards engaging in mild forms of rule-breaking behaviors in an effort to explore the boundaries of these rules, followed by an increase over the course of adolescence with externalizing behavior peaking during mid- to late-adolescence (Burt and Neiderhiser 2009). Despite these early developmental differences, in early adulthood, externalizing behaviors tend to decrease or plateau (Walton et al. 2017) as youth obtain roles that are associated with more responsibility, such as entering the workforce (LaFontana and Cillessen 2010). However, prior work indicates that a subset of individuals persist in engaging in externalizing behavior well beyond the transition to adulthood (Shaw et al. 2012). It is these youth who are likely to benefit most from early interventions. Despite these important developmental nuances, by and large prior G × E studies have tended to give minimal consideration to age by either controlling for age (Lu and Menard 2017), examining effects only within a circumscribed age range (Trucco et al. 2017), or collapsing across developmental periods (Simons et al. 2013). There are some notable exceptions. For example, a series of studies recently employed TVEM to examine the longitudinal associations between a preventive intervention and variants in the gene encoding the γ-amino butyric acid α2 receptor subunit (*GABRA2)* on alcohol misuse (Russell et al. 2018) and delinquency (Schlomer et al. 2019) from ages 11 to 19. Although this work has advanced the field, similar examinations focused on socialization factors outside of intervention settings, such as peer delinquency, may help determine who is most likely to benefit from preventive interventions, as well as optimal timing.

Deviant Peers and Externalizing Behavior

As adolescents gain autonomy, there is a shift from spending time with family to spending an increased amount of time with peers, which results in parents having less of an impact on behavior compared to peers (Vitaro et al. 2018). Adolescents also begin to value social belongingness, fear peer rejection, and become more attuned to behaviors that increase peer acceptance (LaFontana and Cillessen 2010). Thus, adolescents are more likely to engage in problem behavior if it is rewarded by peer acceptance. A framework that is helpful in understanding the association between externalizing behavior and deviant peer behavior is social learning theory (Akers 1977). This theory posits that behavior is learned when that behavior is rewarded. For example, if an individual gains popularity from peers for skipping school, they are more likely to continue skipping school. Similarly, the differential association theory posits that an individual's propensity to engage in delinquent behavior is due primarily to affiliation with others, including peers (Sutherland 1947). Prior empirical work indicates that affiliating with peers that engage in various deviant behaviors (Burt et al. 2009), as well as more specific types of deviant behavior, such as substance use (Barnow et al. 2004), increases risk for externalizing behavior during adolescence and early adulthood. Although there is evidence supporting the increasing salience of peer influence on externalizing behavior (Cleveland et al. 2008), several studies support a decrease of peer influence over time (Abadi et al. 2011), as well as curvilinear trends indicating a peak of peer influence during mid- to late-adolescence and then a plateau during adulthood (Cleveland et al. 2012). Thus, quantitative methods that can model nonlinear change in interactions over time can have significant utility for determining possible critical periods during which certain individuals are particularly sensitive to peer effects.

It is important to note that susceptibility to deviant peers is not uniform across individuals. Several factors have been demonstrated to impact susceptibility to peers. These include an individual's dispositional characteristics, such as impulsivity and reward sensitivity (Pfeifer et al. 2011). Developmentally, these dispositional characteristics increase from age 10 to ages 13 to 16 (Steinberg and Monahan 2007), which corresponds to the developmental

period where youth are most sensitive to peers. In addition, genetic studies underscore the possibility that genes impact the degree to which youth are susceptible to peers (Villafuerte et al. 2014b). In fact, the same genetic risk factors demonstrated to increase sensitivity to peers also underlie individual differences in impulsivity and reward sensitivity (Heitzeg et al. 2014; Villafuerte et al. 2014a). Prior work on environmental stressors and the genetics of youth problem behavior indicates that developmental differences in the maturation of brain areas and related behavioral differences in impulsivity and reward sensitivity likely interact in an age-specific way (Zalsman 2010). Thus, it is critical to understand G × E interactions within a developmental framework. The current study focuses on a specific genetic risk factor located in an area of linkage that has received strong empirical support for its role as a predictor of child externalizing behavior (Trucco et al. 2014), impulsivity (Villafuerte et al. 2014a) and reward sensitivity (Heitzeg et al. 2014), as well as its role in impacting the degree of sensitivity to socialization contexts, such as peers (Trucco et al. 2017; Villafuerte et al. 2014b) and parents (Trucco et al. 2016). This investigation leverages cutting-edge methodology, TVEM, to extend prior work by examining G × E effects from childhood to early adulthood.

Gene × Environment Effects

There is strong evidence demonstrating that individuals differ in vulnerability to peers based on their genotype (Kretschmer et al. 2013; Latendresse et al. 2011; Mrug and Windle 2014). Genes involved in the development of neurotransmitter systems, such as gamma-aminobutyric acid receptor genes, have been shown to be correlated with substance use in adults (Enoch et al. 2009), increase risk in externalizing behavior among youth (Dick et al. 2006), and influence vulnerability to social contexts in youth (e.g., Villafuerte et al. 2014b). These include a GABA gene cluster on human chromosome 4, which includes *GABRG1, GABRA2, GABRA4* (Edenberg et al. 2004). Prior work has centered around the *GABRA2* gene. Namely, *GABRA2* has been demonstrated to impact the degree to which youth are susceptible to a variety of socialization contexts that either promote or decrease risk for adolescent externalizing behavior, including parental monitoring (Trucco et al. 2016), deviant peer affiliation (Villafuerte et al. 2014b), prosocial peer affiliation (Trucco et al. 2017), and preventive interventions (Russell et al. 2018). For example, one study demonstrated a *GABRA2* × deviant peer interaction on adolescent externalizing behavior, whereby deviant peer affiliation was a stronger predictor of externalizing behavior for those with the minor (G) allele, compared to those with the major (A) allele (Villafuerte et al. 2014b). Another study supported a *GABRA2* × positive peer involvement interaction on adolescent externalizing behavior, as well as more adaptive contexts. Namely, those homozygous for the minor (G) allele were rated as having fewer adaptive outcomes (e.g., high externalizing behavior, low behavioral and social competence) when exposed to low levels of positive peer involvement, but rated as having greater adaptive outcomes when exposed to high levels of positive peer involvement (Trucco et al. 2017). Taken together, this provides convincing evidence that this GABA gene cluster impacts the degree to which youth are sensitive to environmental exposures, for better or for worse.

Although recent work has focused on *GABRA2*, no functional variant has been found to account for these associations (Ittiwut et al. 2012). Moreover, seminal work indicates that the association between *GABRA2* and problem behavior could be attributable in part to an adjacent gene in strong linkage disequilibrium (LD), *GABRG1*, which has demonstrated stronger associations with later problem behavior (Enoch et al. 2009). Thus, the current study focuses on variants of *GABRG1*. Although biological processes underlying these associations are still unclear, possible mechanisms by which GABA genes impact sensitivity to socialization contexts are emerging. *GABRG1* is expressed primarily in the amygdala and areas receiving innervation from the striatum, including the substantia nigra (Schwarzer et al. 2001). These are brain regions implicated in reward-related disinhibited behaviors (Steffensen et al. 1998) and addiction (Enoch et al. 2009). Given that *GABRG1* is expressed in the amygdala and the substantia nigra suggests that this gene may impact thresholds for sensitivity to both constructed as well as naturally occurring environments; although the focus has been primarily on constructed contexts (preventative interventions; Brody et al. 2013). Given developmental changes that occur in reward areas of the brain, the shifting importance of peer influence on an individual's behavior, and the continued maturation of the GABA system during adolescence (Kilb 2012), it is likely that these G × E effects are developmentally varying. This study will examine the interplay between *GABRG1* variants and maladaptive peer contexts on externalizing behavior over the developmental interval from childhood to early adulthood.

Time-Varying G × E Effects

Progress in the field of G × E effects has been hampered by difficulties replicating effects. One factor that may impact replication across studies is the age of participants (Costello et al. 2013). For example, a series of studies focused on the brain-derived neurotrophic factor (BDNF) gene on response to environmental stressors across different developmental periods in both human and mouse models demonstrated that

risk variants associated with low BDNF levels were most pronounced during infancy, but not evident during young adulthood (Casey et al. 2009). Similarly, another study demonstrated that the interaction between variants of the dopamine D4 receptor (*DRD4*) and peers' alcohol use on an individual's own substance use was significant during young adulthood, but not significant during adolescence or emerging adulthood (Mrug and Windle 2014). Prior work indicates that non-specific genetic risk factors for externalizing behaviors on maximal alcohol consumption rose rapidly during early to mid-adolescence, peaked at ages 15–17 years of age, then declined slowly thereafter (Kendler et al. 2011). Moreover, environmental moderation of genetic effects, including the role of peer group deviance, was also more pronounced in early to mid-adolescence compared to later in life. Another study, focused on interactions between non-specific genetic risk factors, antisocial peer affiliation, and adolescent externalizing disorders from late adolescence to adulthood (i.e., age 17 to age 29) only supported gene × environment interactions on antisocial behavior at age 17 (Samek et al. 2017). Thus, converging evidence indicates that adolescence is a critical period for increased genetic and environmental risk for engaging in externalizing behavior.

Similarly, prior work focused on a specific genetic risk factor using TVEM indicated that the interaction between *GABRA2* and a preventative intervention on adolescent delinquency (Schlomer et al. 2019) and alcohol misuse (Russell et al. 2018) was most pronounced during the 13 to 16 age period. Although several researchers state that the next generation of G × E research must include developmental considerations given that some of these interactions may be age-specific (Casey et al. 2009; Costello et al. 2013; Lenroot and Giedd 2011), progress has been slow-moving. This is due in part to the high cost of longitudinal studies with large enough sample sizes to examine these interactions across development (Costello et al. 2013). Another factor limiting this type of investigation is that conventional methodological approaches are not equipped to adequately capture the inherent complexity of G × E effects across development (Trucco et al. 2018). It will be important to extend existing TVEM studies to include naturally occurring environments, such as deviant peer exposures, as this may help inform who is most likely to benefit from preventative interventions, as well as the optimal timing of these interventions.

Current Study

The current study attempts to extend the current G × E literature by addressing factors that have hampered progression in the field. First, compared to prior work that has focused primarily on specific developmental periods, G × E associations were examined from childhood to adulthood within a large longitudinal dataset. The Michigan Longitudinal Study (MLS) represents an ideal dataset for this investigation as it is one of the largest and longest-running multi-wave studies that encompasses various methodologies (genotyping, observation, survey) across various domains (e.g., social and behavioral development) from childhood to adulthood (Zucker et al. 1996). Second, in order to capture the complexity of developmentally varying gene × peer delinquency effects, the time-varying effect model (TVEM; Yang et al. 2017a, 2017b; Yang et al. 2017b) was used to allow the effect of interest, such as G × E, to vary as a complex function of age. Notable benefits of TVEM are that it allows for the flexible estimation of regression coefficients as nonparametric functions of time and that analyses are based on person-age observations instead of sample size; thus, the power to detect significant interactions is enhanced, which is a prominent obstacle in G × E studies (Epstein et al. 2017). More specifically, variants of *GABRG1* (rs7683876, rs13120165) were examined as they are not only in high LD with previously examined *GABRA2* variants, but they may represent more direct indicators of problem behavior (Enoch et al. 2009). Consistent with prior work demonstrating that individuals carrying the minor allele of specific genes in the same GABA cluster that are in high LD with *GABRG1* have increased sensitivity to various socialization contexts (i.e., parenting (Trucco et al. 2016); peers (Trucco et al. 2017; Villafuerte et al. 2014b)), it was expected that those carrying the G allele of *GABRG1* (rs7683876, rs13120165) would be most susceptible to peer effects. However, specific critical periods for these effects were not hypothesized.

Methods

Design and Sample

Participants were taken from the MLS, a multi-wave prospective study of families at high risk for substance use disorder from early childhood to adulthood (Zucker et al. 1996). Participants were families ascertained through two interconnected population-based methods. Ascertainment of the highest risk portion of the sample was by way of the father's drunk driving conviction with a sufficiently high blood alcohol concentration (0.15% if a first conviction, 0.12% if multiple convictions). The remaining families were systematically recruited door-to-door in the same neighborhoods as the drunk-driver families. The recruitment protocol also required the father to be living with a 3–5-year-old son (the male target child) and the boy's biological mother. The study families were originally recruited as

triads, but thereafter siblings within 8 years of the initial male target child were also recruited.

Ethical Considerations

Written informed consent and assent was obtained from the parents and adolescents, respectively. All procedures were performed in accordance with the ethical standards of the institutional committee where the study was conducted (Family Study of Risk for Alcoholism over the Life Course, HUM00039806) and with the 1964 Helsinki declaration and its later amendments.

Procedures

The study assessment schedule is presented in Fig. 1. Participating families received extensive in-home assessments at baseline. Assessment waves thereafter took place at 3-year intervals (denoted as T). During the critical period of alcohol use (ages 11–26), annual assessments (denoted as A) were also conducted. In order to maximize all available data, data obtained during both the wave and annual assessments were included in the final analyses. Overall, participant retention for the MLS across the 30 years of the study is 89%. This is comparable to retention rates of other large longitudinal studies focused on at-risk youth (Williams et al. 2013) and non-clinical (Orpinas et al. 2016) adolescent populations. The present study includes 363 families and 687 participants (68% male and 90% White) who provided both genotype and phenotype data, with the median number of two siblings within a family. Further, the median number of time points available for a participant was six. The proportion of racial minorities were: 5% Black/African American, 4% Hispanic/Latino, and 1% biracial.

Measures

Externalizing behavior

Participants rated their own social and emotional functioning on the Youth Self-Report (YSR; Achenbach and Rescorla 2001) during adolescence (T4–T5 & A1–A7), and the Adult Self-Report (ASR; Achenbach and Rescorla 2003) during adulthood (T6–T8 & A8–A16). The total score of the items on the externalizing behavior subscale was standardized according to the national norm specific to the participant's age at the assessment (mean = 50, *SD* = 10). Thus, the standardized scores are comparable developmentally. Both measures have excellent reliability and validity. The internal consistency for the YSR and ASR within this sample was good (Cronbach's α range = 0.84–0.89 across time points).

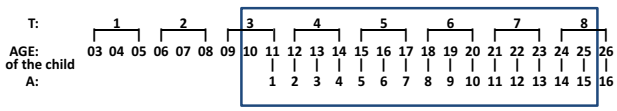

Fig. 1 Michigan Longitudinal Study Assessment Schedule. Note. Assessments were conducted every 3 years beginning when the target child was 3 to 5 years of age. T = 3-year intervals. Annual assessments were also conducted during late childhood. A = annual assessments. The current study focuses on assessments contained within the box

Maladaptive peer behavior

Involvement with delinquent peers was measured as part of the Peer Behavior Profile (Bingham et al. 1995), which asked participants to select how many of their peers (1 = *almost none* to 5 = *almost all*) are involved in specific activities. This instrument was administered during adolescence and adulthood (T4–T8 & A1–A16). Nine items focused on peer delinquency, such as being detained by the police; 14 items pertained to peer substance use (e.g., getting drunk, smoking cigarettes, getting high on drugs). The average score of the items in each subscale was used. The internal consistency across time points for peer delinquency (Cronbach's α range = 0.79–0.89) and peer substance use (Cronbach's α range = 0.88–0.96) within this sample was adequate. Separate models were conducted for peer delinquency and peer substance use to determine whether findings generalize to multiple aspects of maladaptive peer influence.

Genotype Data & Quality Control

Single nucleotide polymorphism (SNP) genotyping data of DNA specimens were obtained using Illumina Human Genotyping Arrays HumanCoreExome-12 v1.0 BeadChip. The HumanCoreExome BeadChip has a highly non-uniform distribution of markers and an emphasis on rare coding variants. It contains more than 240K exonic variants, including nearly 220K non-synonymous coding variants. These data were converted to PLINK format (Purcell et al. 2007) and the quality control (QC) of genotypes was carried out based on established best practices (Anderson et al. 2010). Individuals with elevated missing data rates (the genotype failure rate > 0.05) or large heterozygosity rates (larger than ± *3SD* from the mean) were eliminated. Duplicated samples from the same participant were identified and the one with a smaller rate of missing data was kept. In addition, SNPs with the minor allele frequency being less than 0.01, the rate of missingness per SNP being larger than 0.05, and the *p*-value of the Hardy-Weinberg equilibrium test being less than 0.00001 were filtered out. In total, 280K genotyped autosomal SNPs passed QC. Based on the results of quality control and the focus on exon regions, the SNP rs7683876 and rs13120165 mapping to *GABRG1* was used to represent the $GABA_A$ subunit gene. The genotypes of

both SNPs were coded using the additive model, with GG coded as 0; AG as 1; and AA as 2.

Statistical Analysis

This study applied TVEM developed in prior work (Yang et al. 2017a, 2017b; Yang et al. 2017b) to characterize the time-varying effects of peer delinquency and peer substance use on externalizing behaviors by *GABRG1* genotypes across two separate models. Let $Y(t_{ij})$ be the j-th observed externalizing score (the outcome variable) from the i-th participant at time t_{ij} and $Z(t_{ij})$ be the corresponding environmental factor (i.e., peer delinquency or peer substance use). Let $k(k = 0, 1, 2)$ be the genotype of participant i with 0 corresponding to the GG group, 1 for the AG group, and 2 for the AA group. Two indicator variables were created to model the differences among the three genotype groups with $I_{\{k=1\}}$ contrasting AG with GG and $I_{\{k=2\}}$ contrasting AA with GG. Further, two important demographic variables were included as covariates: biological sex X_1 (coded as 1 for male and 0 for female) and race X_2 (coded as 1 for White and 0 for non-White). The TVEM is written mathematically as follows:

$$\begin{aligned} E\left[Y\left(t_{ij}\right)|a_i, b_i\right] = {} & \alpha_0\left(t_{ij}\right) + \alpha_1\left(t_{ij}\right)I_{\{k=1\}} + \alpha_2\left(t_{ij}\right)I_{\{k=2\}} \\ & + \beta_0\left(t_{ij}\right)Z\left(t_{ij}\right) + \beta_1\left(t_{ij}\right)Z\left(t_{ij}\right)I_{\{k=1\}} + \beta_2\left(t_{ij}\right)Z\left(t_{ij}\right) \\ & \times I_{\{k=2\}} + \gamma_1 X_1 + \gamma_2 X_2 + a_i + b_i \end{aligned}$$

where $\alpha_0(t_{ij})$, $\alpha_1(t_{ij})$, and $\alpha_2(t_{ij})$ are the intercept terms; $\beta_0(t_{ij})$ is the time-varying effect of $Z(t_{ij})$ for the GG group; $\beta_1(t_{ij})$ is the difference in the time-varying effect between the AG group and the GG group; $\beta_2(t_{ij})$ is the difference between the AA group and the GG group; γ_1 is the effect of biological sex; γ_2 is the effect of race; and a_1, b_1 are the random effects accounting for the dependence within family (i.e., family-level clustering) and within participant, respectively. A major strength of TVEM is that the time-varying effects of $Z(t_{ij})$—$\beta_0(t_{ij})$, $\beta_1(t_{ij})$, and $\beta_2(t_{ij})$—can be estimated through non-parametric regression functions that do not assume fixed shapes like conventional growth curves, and thus can better characterize developmental changes based on empirical data. Previous methodological work (Yang et al. 2017a, 2017b; Yang et al. 2017b) has proposed statistical methods for parameter estimation and hypothesis testing of group differences, which performed well across different practical settings by simulation studies. Confidence intervals were also estimated. Non-overlapping confidence intervals indicate statistically significant differences across genotypes.

Results

Means and standard deviations for adolescent externalizing behavior, peer delinquency, and peer substance use across age are presented in the Appendix. Externalizing behavior among adolescents and their peers tended to increase from childhood to late adolescence, with a peak in early adulthood. Overall, correlations, calculated as Kendall's Tau, indicated that *GABRG1* was not associated with peer delinquency ($r = 0.034$, $p = 0.56$) or peer substance use ($r = 0.049$, $p = 0.41$) across ages 10–25. This is notable as gene-environment correlation represents a nonrandom distribution of environments across genotypes, and may confound G × E associations (Trucco et al. 2017). We fit the TVEM on the genotype and longitudinal phenotype data. Findings focus on *GABRG1* rs7683876 (23.7% = GG; 50.1% = AG, 26.2% = AA) for simplicity and clarity, since a similar pattern of significant effects emerged with *GABRG1* rs13120165.

Effects of Peer Delinquency

Figure 2 shows the time-varying effects of peer delinquency on externalizing behavior by *GABRG1* rs7683876, controlling for the effects of sex and race. The pattern of effects indicates a sequential risk gradient in the influence of delinquent peers on externalizing behavior depending on the number of G alleles. Greater peer delinquency was associated with greater externalizing behavior among participants carrying a G allele. Participants with the GG genotype were especially susceptible to delinquent peers. Moreover, this association was slightly greater in early adulthood compared to late childhood among those with the GG genotype, whereas this association was relatively consistent across development for those with the AG genotype. In contrast, the association between peer delinquency on externalizing behavior across development was negative among those with the AA genotype. Table 1 depicts the estimated time-invariant effects of sex and race in the TVEM. Sex did not have a significant effect on externalizing behavior, whereas White participants had significantly higher levels of externalizing behavior compared to non-White participants.

Effects of Peer Substance Use

Similar models were then tested that examined the effect of peer substance use on externalizing behavior. As presented in Fig. 3, the fitted TVEMs examining the time-varying effects of peer substance use on externalizing behavior by *GABRG1* SNP rs7683876, controlling for the effects of sex and race were similar. Namely, the pattern of effects indicates a sequential risk gradient in the influence of substance using peers on externalizing behavior depending on the number of G alleles. Greater peer substance use was associated with greater externalizing behavior among participants carrying a G allele. Participants with the GG genotype

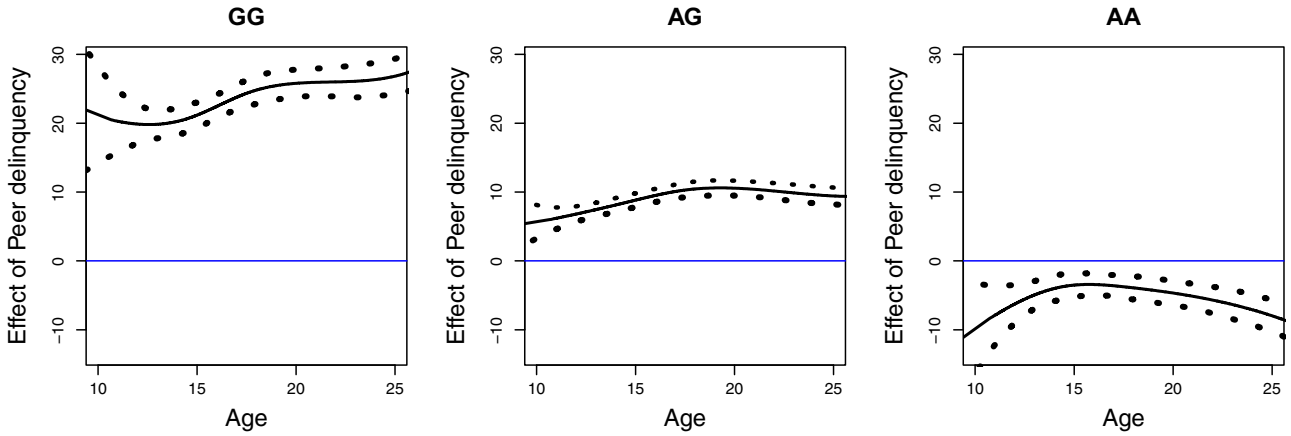

Fig. 2 Time-varying effect model for peer delinquency on externalizing behavior. Note. GABRG1 rs7683876 effects depicted. Solid lines represent trajectories, while the dotted lines represent the 95% confidence intervals. Values above the blue line represent positive associations. Values below the blue line represent negative associations. Confidence intervals that include the blue line are not significant. The y-axes represent estimated effects across time

Table 1 The time-invariant effects of sex and race in the TVEM of peer delinquency × *GABRG1* on externalizing behavior

Parameter	Estimate	Std. error	*p*-value
Male (γ_1)	−0.5251	0.6075	0.3874
White (γ_2)	23.0138	1.1568	<0.0000

were especially susceptible to substance using peers. Moreover, this association was greater in early adulthood compared to late childhood among those with both the GG and the AG genotype. In contrast, the effect of substance using peers on externalizing behavior was not significant in late childhood or early adulthood among those with the AA genotype, and this association was negative from early adolescence to late adolescence. Table 2 depicts the estimated time-invariant effects of sex and race in the TVEM. Sex did not have a significant effect on externalizing behavior, whereas White participants had significantly higher levels of externalizing behavior compared to non-White participants.

Sensitivity Analyses

Additional exploratory analyses were also conducted to examine gene-by-covariate and environment-by-covariate interactions. When examining peer delinquency effects, there was no support for a significant race × peer delinquency interaction. There was evidence of a significant race × genotype interaction indicating that White participants with the AG genotype had a higher level of externalizing behavior (coefficient = 0.30, se = 0.15, $p < 0.05$). In addition, there was evidence for a sex × genotype and a sex × peer delinquency interaction. Among individuals with the AA genotype, males had lower externalizing scores (coefficient = −6.49, se = 0.92, $p < 0.05$), whereas among those with the AG genotype, males tended to have higher externalizing scores (coefficient = 1.91, se = 0.40, $p < 0.05$). Further, the effect of peer delinquency on externalizing behavior was lower among male participants (coefficient = −7.28, se = 0.92, $p < 0.05$). Nevertheless, adding these gene-by-covariate and environment-by-covariate interactions to the model did not change the gene-by-environment pattern observed in Fig. 2.

Gene-by-covariate and environment-by-covariate exploratory interactions were also examined in the context of peer substance use effects. There was no evidence for a significant race × genotype or race × peer substance use interaction. Conversely, sex had significant interactions with both genotype and peer substance use. Among participants with the AA genotype, males had lower externalizing scores (coefficient = −4.73, se = 1.08, $p < 0.05$), whereas among those with the AG genotype, males tended to have higher externalizing scores (coefficient = 1.11, se = 0.48, $p < 0.05$). Further, the effect of peer substance use on externalizing behavior was lower among male participants (coefficient = −6.16, se = 0.95, $p < 0.05$). Nevertheless, adding these gene-by-covariate and environment-by-covariate interactions to the model did not change the gene-by-environment pattern observed in Fig. 3.

Lastly, given that prior work also supported interactions between specific *GABRA2* variants and positive peer affiliation on adolescent externalizing behavior (Trucco et al. 2017), we also conducted exploratory analyses on this environmental context. Positive peer involvement reflected participants' perceptions of their peers' engagement in religious/spiritual activities, scholastic performance, and extracurricular activities as assessed with the Peer Behavior Profile (Bingham et al. 1995). There was no evidence for significant *GABRG1* (rs7683876, rs13120165) × positive peer affiliation interactions across development. The lack of

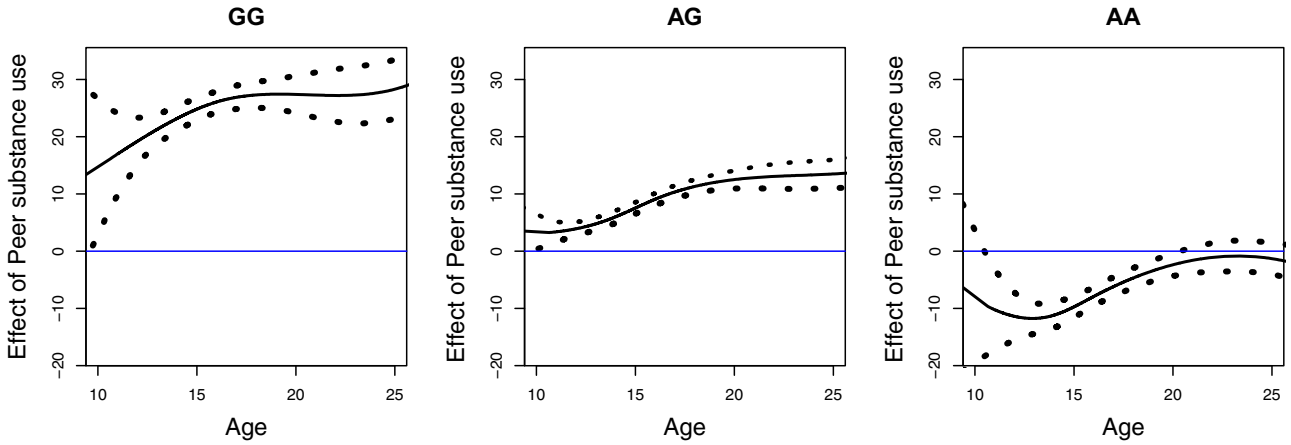

Fig. 3 Time-varying effect model for peer substance use on externalizing behavior. Note. *GABRG1* rs7683876 effects depicted. Solid lines represent trajectories, while the dotted lines represent the 95% confidence intervals. Values above the blue line represent positive associations. Values below the blue line represent negative associations. Confidence intervals that include the blue line are not significant. The y-axes represent estimated effects across time

Table 2 The time-invariant effects of sex and race in the TVEM of peer substance use × *GABRG1* on externalizing behavior

Parameter	Estimate	Std. error	*p*-value
Male (γ_1)	0.1709	0.6821	0.8022
White (γ_2)	18.3603	1.3062	<0.0000

significant interactions could indicate that positive peer involvement benefits most individuals similarly (Pluess and Belsky 2012) or that interactions are specific to *GABRA2* variants (Trucco et al. 2017).

Discussion

Although engagement in externalizing behavior, such as stealing and aggression, during adolescence is relatively normative, involvement in these types of behavior in childhood and early adulthood may be indicative of maladaptive outcomes later in life, including mental health problems and incarceration (Farmer et al. 2015). One of the strongest predictors of engagement in externalizing behavior is involvement with deviant peers (Epstein et al. 2017). Yet, susceptibility to peer influence is not static across development (Epstein et al. 2017). Moreover, certain individuals are likely to be more susceptible to peer influences based on biological characteristics. The current study extends prior work by examining how specific genetic variants in the $GABA_A$ receptor subunit-encoding genes (i.e., *GABRG1* rs7683876, rs13120165) interact with maladaptive peer influence to impact engagement in externalizing behavior from childhood to early adulthood using TVEM. This study addresses a critical gap in the literature; prior work has not used TVEM to examine G × E × D interactions outside of constructed environments (e.g., preventative interventions). Examining how genes may impact susceptibility to naturally occurring environments across development, such as peers, will help inform not only *who* is likely to benefit the most from preventive interventions focused on addressing exposure to deviant peers, but *when* preventive interventions are likely to have the most utility.

As expected, the impact of peer deviancy and peer substance use on externalizing behavior was strongest for those with the GG genotype. This is consistent with prior work indicating that adolescents carrying the G allele across genetic factors that are closely associated with *GABRG1* rs7683876 and rs13120165 (e.g., *GABRA2* rs279858, rs279826, rs279827) were most susceptible to maladaptive environmental exposures, including deviant peer affiliation (Villafuerte et al. 2014b) and poor parenting practices (Trucco et al. 2016). Although biological mechanisms underlying increased sensitivity to environmental exposures remain unclear, there is some evidence indicating that those carrying these specific variants in the $GABA_A$ receptor subunit-encoding genes have greater reward sensitivity and impulsivity (Heitzeg et al. 2014; Villafuerte et al. 2014a) and reduced brain activation to emotionally salient stimuli (Trucco et al. 2018). Thus, those with the GG genotype may not only find social acceptance by peers as particularly rewarding; they may also find it difficult to refrain from imitating externalizing behavior modeled by deviant peers.

Implications

From a developmental perspective, this study provides a novel contribution to the field by demonstrating that increased vulnerability to peer influence by those carrying the *GABRG1* G allele is not confined to the adolescent years. In fact, these results indicate that among those with the GG genotype, the

association between maladaptive peer influences and externalizing behavior is present in late childhood and likely increases throughout adulthood. It is possible that the influence of peer deviance and peer substance use on externalizing behavior increases because of increasing mean levels and variability. This pattern of findings may also be due in part to developmental changes that naturally occur in the social world when transitioning from adolescence to adulthood. During adolescence, parents tend to closely monitor an adolescent's behavior and put limits on whom the child can affiliate. In early adulthood, youth tend to leave the home to attend college, thus gaining more freedom to shape their social worlds. It is likely that this increased autonomy impacts the degree to which genetic vulnerabilities become expressed (Trucco et al. 2018). Accordingly, the larger discrepancies found across genotypes in the association between maladaptive peer exposures and externalizing behavior in adulthood compared to earlier developmental periods found in the current study may be attributable in part to greater expression of individual differences based on fewer social world constraints.

From a clinical perspective, findings offer preliminary evidence that individuals with the GG genotype may benefit the most from interventions focused on how to navigate negative peer influence. Not only are these individuals most vulnerable to maladaptive peer contexts, but prior work indicates that these same individuals may also reap the most benefit from preventative interventions (Russell et al. 2018). This same work indicates that gene by intervention effects on adolescent delinquency (Russell et al. 2018) and alcohol misuse (Schlomer et al. 2019) is most pronounced starting in early adolescence. Similarly, prior work indicates that preventative interventions initiated during the pre- and early adolescent developmental periods may be particularly beneficial in reducing externalizing behavior and substance use (Spoth et al. 2002) compared to early to mid-adulthood when these processes are more developmentally canalized (Kendler et al. 2011). Given that differences across genotypes are present during childhood, there may be particular utility in delivering preventative interventions during pre- and early adolescent developmental periods to disrupt early affiliation with deviant or substance-using peer groups; once youth start forming bonds with deviant peers, it may be more difficult to intervene. Such interventions may target risk factors for exposure to deviant peer processes, such as childhood bullying, peer rejection, and low school connectedness (Van Ryzin et al. 2012).

The current work represents an early stage in a larger body of research that is necessary to gain a greater articulation of the complex mechanisms through which biological differences and environmental exposures interact to impact maladaptive functioning across development. Although the ultimate goal is to develop tailored and time-specific interventions that have the most clinical utility, future work should focus on continued empirical efforts to replicate these findings and to further characterize the inherent complexity of environmental and biological effects on externalizing behavior before specific recommendations can be offered.

Limitations and Future Directions

As large longitudinal datasets that encompass socialization factors and genetic information become available, it will be important to test whether these findings replicate. Until findings are replicated with an independent sample, caution is warranted when drawing inferences. Although this study adopted a hypothesis-driven approach focused on a specific genetic region that has received strong empirical support for its impact on sensitivity to socialization contexts, the focus on single genetic markers provide an incomplete picture regarding the interplay between genetic risk factors and maladaptive peer exposures on externalizing behavior. Complex behavior, such as externalizing behavior, is likely attributable to a number of different genes with small effects as well as a number of different socialization contexts outside of the peer environment (Trucco et al. 2018). Thus, it will be important that future work consider extending this work to include hypothesis-free approaches, such as polygenic methods based on genome-wide association studies, and other socialization contexts, such as neighborhood, school, and family environment. Although racial differences were accounted for in the models, the sample was primarily White. These findings may not generalize to a more diverse sample. The current sample also represents a group of individuals at high-risk for alcoholism; rates of externalizing behavior and exposure to maladaptive peer influences may be greater in this sample compared to a community sample. Lastly, although the MLS represents an ideal data set for this investigation, only perceptions of peer behavior was available. It will be important for future work to include ratings from multiple reporters to account for shared method variance.

Conclusion

Strong theoretical and empirical support exists for the synergistic effect of specific genetics factors and peer environmental contexts (i.e., G × E) on the emergence of externalizing behavior (Trucco et al. 2018). Yet, it is likely that G × E effects may wax and wane across the lifespan. Only a few studies have been able to successfully integrate the complexity of interactions between genetic factors and environmental exposures with the nuances that unfold across development. This study employs time-varying effect modeling (TVEM), to determine possible gene × environment × development (G × E × D) interactions as they

apply to the patterning of externalizing behavior from childhood to adulthood. Study findings support the role of genetic variants in the $GABA_A$ receptor subunit-encoding genes (i.e., *GABRG1* [rs7683876, rs13120165]) as susceptibility factors to peer socialization contexts across a wider developmental period than previously thought. The results indicate that among those with the GG genotype, the association between maladaptive peer influences and externalizing behavior is present in late childhood throughout adulthood. The pattern of findings may be due in part to developmental changes that naturally occur in the social world and with respect to externalizing behavior when transitioning from childhood to adulthood. Preventative interventions targeting childhood and pre-adolescence are likely to have the most impact on peer influences that may exacerbate externalizing behavior. This work provides preliminary evidence for the utility of conducting similar empirical investigations to inform the design, timing, and implementation of preventive interventions for individuals with genetic predispositions for high-risk externalizing trajectories.

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Authors' Contributions EMT conceived of the study, participated in the interpretation of the data, and drafted the manuscript; SY performed the statistical analysis and participated in the interpretation of the data; JJY conceived of the study design, participated in the statistical analysis and the interpretation of the data, and assisted in drafting the manuscript; RAZ participated in the study design and coordination of the study, and helped to draft the manuscript; RL assisted in the statistical analysis and participated in the interpretation of the data; AB assisted in the design of the study, participated in the statistical analysis and the interpretation of the data, and assisted in drafting the manuscript. All authors read and approved the final manuscript.

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Data Sharing and Declaration The datasets generated and/or analyzed during the current study are not yet publicly available but are available from the corresponding author on reasonable request. In addition, these data are currently being prepared for archiving in the publicly available interuniversity consortium for political and social research archiving, and we anticipate the full upload will be available by the end of 2019 (https://www.icpsr.umich.edu).

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures with human participants were in accordance with the ethical standards of the institutional committee where the study was conducted and with the 1964 Helsinki declaration and its later amendments.

Informed Consent Written informed consent and assent was obtained from the parents and adolescents, respectively.

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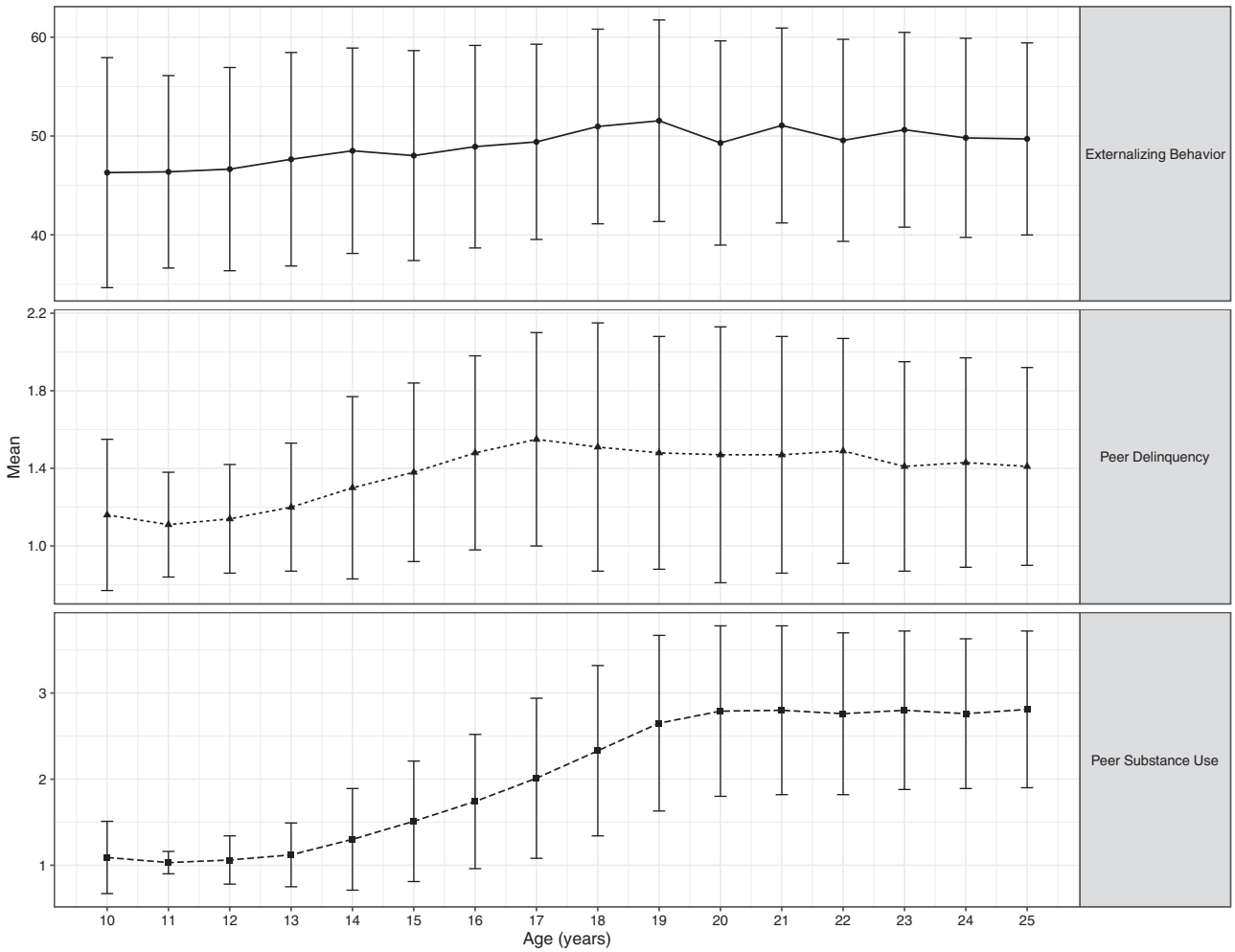
Appendix

Means and Standard Deviations for Study Variables across



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