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Roles of Response Inhibition and Gene-Environment Interplay in Pathways to Adolescents' Externalizing Problems

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Abstract

The current study used two waves of data to investigate pathways through which adolescents' response inhibition related to later externalizing problems. A polygenic risk score indexed genetic risk for poor response inhibition. Adolescents' performance on a response inhibition task mediated the relation between adolescents' polygenic risk scores and mother's inconsistent parenting (i.e., evocative rGE), even after controlling for mothers' genetic risk (i.e., passive rGE). Mothers' inconsistent parenting subsequently prospectively predicted adolescents' externalizing problems. Adolescents' response inhibition also prospectively predicted later externalizing behaviors. These findings were subgroup-specific, with greater risk for non-Hispanic Caucasian boys with substance-disordered parents. Results suggest that poor response inhibition may increase risk for adolescents' externalizing problems both directly and by evoking certain environmental conditions.

Keywords

Evocative gene-environment correlation; passive gene-environment correlation; polygenic risk score; response inhibition; externalizing; parental inconsistency

Executive functions are mental control processes that facilitate goal-directedness and self-control (Pennington & Ozonoff, 1996). One fundamental aspect of executive functioning is response inhibition, which involves the ability to deliberately override a dominant or prepotent response (Miyake & Friedman, 2012). Numerous studies support robust associations between deficits in response inhibition and greater externalizing problems (e.g.,

Brocki, Nyberg, Thorell, & Bohlin, 2007; Kooijmans, Scheres & Oosterlaan, 2000; Nigg, 2003; Young et al., 2009). Generally, these direct associations have been attributed to the role of poor response inhibition as a core cognitive deficit that increases risk for externalizing problems (e.g., Aron & Poldrack, 2005). That is, because individuals with poor response inhibition have difficulty suppressing inappropriate actions, they may display hyperactive, impulsive, or disruptive behaviors at home, school, or with peers. Poor response inhibition may also make it harder to suppress rewarding, but prohibited, behaviors. Although poor response inhibition likely exerts a direct impact on adolescents' externalizing problems, other processes could also explain this association. Moreover, delineating these processes in adolescence is critical. Indeed, adolescence is a period of increased risk taking when processes of self-regulation and response inhibition are not fully mature. Knowledge of risk-related pathways in adolescence could confer important insights toward refining early, developmentally-sensitive interventions.

Evocative and Passive Gene-Environment Correlation

Because response inhibition is heritable (Young et al., 2009), gene-environment interplay could impact the relation between response inhibition and externalizing problems. One form of gene-environment interplay is evocative gene-environment correlation (rGE), which suggests that an individual's genetically influenced behavior may evoke or produce certain environmental conditions (Scarr & McCartney, 1983). For example, children with genetic propensities for response inhibition may be difficult to parent, evoking inconsistent disciplinary strategies and/or parental negativity. In examining evocative rGE, it is important to empirically disentangle the potential confounding influence of passive rGE (e.g., Scarr & McCartney, 1983). That is, adolescents' genetically influenced response inhibition could be spuriously associated with familial or parenting factors, with the true influence being the effect of parents' correlated genetic risk on these contextual factors. For example, parents with particular genotypes may be predisposed to be negative, rejecting, or inconsistent with discipline.

The importance of evocative rGE has been highlighted in several studies (e.g., Avinun & Knafo, 2013; Harold et al., 2013; Jaffee & Price, 2012). One method to test evocative rGE is the adoption-at-birth design which investigates the influence of adoptive children's genetically influenced characteristics on adoptive parents' behaviors (e.g., Elam et al., 2014; Harold et al., 2013). This design minimizes concerns that children's characteristics and postnatal parenting behaviors are simply correlated due to shared genes (i.e., passive rGE) because adoptive children do not share segregating genes with adoptive parents (see Neiderhiser et al., 2004 for more information). Using this methodology, Elam et al., (2014) found that toddlers' genetically influenced low social motivation predicted adoptive mothers' and fathers' hostile behaviors towards the child. Another method to test evocative rGE involves using child- and/or parent-based twin samples to estimate genetic and environmental effects on parenting (see Neiderhiser et al., 2004 for a more detailed review). Such studies have also found that adolescents' externalizing problems evoked maternal negativity and criticism and multiple aspects of fathers' parenting including negativity and lowered levels of monitoring and control (Marceau et al., 2013; Narusyte et al., 2011; Neiderhiser et al., 2007).

Finally, evidence of evocative rGE can be provided using molecular genetic data by showing that children's genotype predicts parenting even after controlling for parents' genotype. This latter control minimizes the possibility that children's genotype is spuriously associated with parenting (i.e., passive rGE). Pender-Tessler et al. (2013) used this approach and found that boys' 5-HTTLPR genotype predicted less positive mothering (operationalized as maternal warmth, autonomy support, low negative affect, and responsiveness) indirectly through boys' lower self-control. This effect also persisted after controlling for mothers' 5-HTTLPR genotype. Although most molecular genetic studies have used a single variant to test evocative and passive rGE, most complex quantitative traits such as response inhibition are influenced by many genetic polymorphisms (i.e., polygenicity; Plomin, Haworth & Davis, 2009). One way to capture polygenicity is to use polygenic risk scores, which aggregate effects of several risk variants (Purcell et al., 2009). The current study used this method to capture genetic risk.

Effects of Poor Response Inhibition on Parents' Inconsistent Discipline

Poor response inhibition might evoke a variety of responses from the environment. One environmental factor that might be particularly susceptible to its effects is parental inconsistent discipline, which is characterized by an inability to consistently enforce rules or enact discipline (Schaefer, 1965). For instance, adolescents with poor response inhibition might be less likely to follow rules set by their parents, especially if it requires the suppression of inappropriate responses and desires. These parents might come to believe that their rule-setting and disciplinary attempts are futile, prompting them to parent more inconsistently (Lengua, 2006). Alternatively, parents may attempt to control their children's dysregulated behavior by setting increasingly more rules, but subsequently have difficulty following through or remembering them. If these sorts of evocative effects are empirically supported, adolescents with poor response inhibition might benefit from interventions that train parents to adapt to the challenge of maintaining consistent discipline. Therefore, the first goal of the current study was to examine whether adolescents' genetic risk for poor response inhibition predicted parents' inconsistent discipline indirectly through adolescents' actual response inhibition (an evocative effect). Because an alternative hypothesis is that evocative effects might be spuriously caused by effects of parents' genes on their own parenting, we also controlled for parents' genetic risk in a separate model in a subsample with both parental and adolescent genetic data (see Figure 1 for the conceptual model).

Pathways to Later Externalizing Problems

Studies show that parents' inconsistent discipline increases risk for adolescents' externalizing problems (Barry, Dunlap, Lochman, & Wells, 2009; Feehan, McGee, Stanton, & Silva, 1991; Lengua, 2006; Patterson, 1995). Indeed, adolescents' disruptive behaviors might be more difficult to extinguish when parents are inconsistent with discipline or rule-setting. Inconsistent discipline might also disrupt adolescents' ability to identify with their parents, thus interfering with the internalization of parental and societal norms and increasing risk for externalizing problems (Deur & Parke, 1970; Hirschi, 1969).

Therefore, one possible pathway to adolescents' externalizing behavior might begin with adolescents' genetically influenced poor response inhibition, which evokes inconsistent parental discipline and subsequently increases risk for externalizing problems. Indeed, previous research supports similar evocative pathways to behavior problems. As noted earlier, Elam et al. (2014) found that toddlers' genetically influenced low social motivation predicted mothers' and fathers' hostility towards the child, which in turn predicted children's greater disruptive behaviors with peers. Similarly, Harold et al. (2013) found that children's genetically influenced impulsivity predicted mothers' hostility towards the child, which subsequently predicted children's attention deficit/hyperactivity disorder symptoms.

Finally, adolescents' poor response inhibition may have direct effects on later externalizing behavior beyond those mediated by parental inconsistent discipline. This seems likely because adolescents with poor response inhibition have difficulty suppressing inappropriate behaviors and because response inhibition and externalizing problems share genetic influences (Young et al., 2009). Testing effects from genetically-influenced poor response inhibition to externalizing problems, both directly and indirectly through parental inconsistency, could greatly clarify pathways to adolescent externalizing problems. For example, although studies have examined whether adolescents' externalizing problems evoked maladaptive parenting behaviors, externalizing problems are heterogeneous (Marceau et al., 2013; Narusyte et al., 2011; Neiderhiser et al., 2007). By examining the evocative effect of response inhibition, the present study can shed light on a specific *adolescent trait* that elicits certain parenting practices and thereby increases subsequent externalizing problems.

Evocative gene-environment effects might also be stronger in adolescence compared to in childhood (i.e., they might increase with age; see Beam & Turkheimer, 2013; Bountress, Chassin, & Lemery-Chalfant, 2016). Indeed, genetic influences on externalizing problems increase during adolescence (e.g., Bergen, Gardner, & Kendler, 2007), likely because adolescents have greater freedom to choose their own environments (e.g., active rGE or niche-picking). Thus, adolescents' genetically-influenced niche-picking could lead to greater behavioral manifestations of genetic predispositions, which could elicit increasingly negative parental reactions and subsequent externalizing behaviors. Thus, our second goal was to test whether adolescents' genetic risk for poor response inhibition prospectively predicted externalizing problems indirectly through parental inconsistency, actual response inhibition, or both (see Figure 1).

The Current Study

Using two waves of data from a high-risk sample of adolescents, this study sought to provide novel insights into the role of response inhibition in externalizing problems during adolescence. We operationalized genetic risk for poor response inhibition by constructing a polygenic risk score reflecting a sum of genetic variants empirically linked to response inhibition (see Methods for more details). The first goal of the study was to test whether this polygenic risk score predicted parental inconsistency and whether this effect was mediated by adolescents' actual response inhibition (evocative rGE). The second goal was to test whether these pathways, in turn, influenced adolescents' externalizing problems. This

included characterizing effects of genetically influenced response inhibition on externalizing problems both directly (two-path mediation from polygenic risk to response inhibition to externalizing) and indirectly through parental inconsistency (three-path mediation from polygenic risk to response inhibition, to parents' inconsistency, to externalizing). When testing evocative effects of adolescents' genetic risk on parental inconsistency (goal 1), we accounted for the possibility that these effects were spuriously caused by effects of parents' genes on their own parenting (passive rGE). Specifically, in a subsample with both parents' and adolescents' genotypes, we controlled for effects of parents' genetic risk scores on their own inconsistency.

Method

Participants

The current study used data from a larger longitudinal investigation of familial alcoholism spanning three generations (referred to here as G1s, G2s, and G3s; Chassin et al., 1992). Participants in the current study were drawn from the G3 sample. The larger study began by recruiting families comprised of G1 parents and their G2 children. These families were interviewed annually for three years and then at five-year intervals for waves 4–6. By waves 5 and 6, the G2 sample's mean ages were 26.0 ($SD=2.2$) and 32.3 years old ($SD=2.4$), respectively, and most had become parents. At these waves, the G2's children (G3s) were added to the study, and the majority of G2s (64.1%) had more than one child participate in the study. Of all the G2 families, 40% had two children, 20.4% had three children, 3.4% had four children, and 0.3% had five children in the study. 18 months after wave 6, only the G3s participated in a follow up assessment. The G3 data used for the current study were drawn from wave 6 (M_{age} of G3s = 12.65; $SD_{age}=1.83$; M_{age} of G2 parents= 35.53; $SD_{age}=4.39$) and the post-wave-6 follow-up (M_{age} = 13.89; SD_{age} = 1.87), hereafter called T1 and T2, respectively.

Adolescent participants from the full G3 sample were included in the study if they were 10–17 years old at T1, 11–18 years old at T2, provided genetic data, lived with their biological mother either full- or part-time (because we tested maternal inconsistent discipline, see measures section), and self-reported their race/ethnicity as non-Hispanic Caucasian or Hispanic (given concerns about ethnicity-related heterogeneity in genetically-informed analyses). This yielded a final $N=393$. The age inclusion criteria were chosen to examine study hypotheses among adolescents who were still living at home, who were more likely to influence and be influenced by their mother's parenting, while retaining as many participants as possible. About 61% of the total possible G3 sample was included in the current study. Compared to excluded G3 participants, included G3s were significantly younger at T2, more likely to have a custodial parent with a substance use disorder, and had marginally significantly greater T2 externalizing problems. Included and excluded participants did not differ significantly on any other study variables. See Table 1 for descriptive data, t-tests, and χ^2 analyses.

Recruitment and Procedure

G1 alcoholic families with G2 adolescent children (COAs) were recruited using court records of DUI arrests, HMO wellness questionnaires, and community telephone screenings. Reverse directories and telephone screening were used to locate G1 non-COA families in the same neighborhoods as G1 COA families. G1 COA and non-COA families were matched in ethnicity, family structure, adolescent age, and socioeconomic status (Chassin et al., 1992). For more details about the recruitment and procedures for the larger study, refer to [Chassin et al., 1992].

Regarding the data used in the current study, G3s were assessed at T1 via interviews conducted at the family's residence or at Arizona State University. G3s were assessed at T2 via telephone interviews. Parents provided informed consent and adolescents provided assent. Genetic data were collected with cheek brushing or saliva samples using Oragene kits. Genotyping was done at the Washington University Genome Sequencing Center. The current study genotyped 1536 selected polymorphisms using the Illumina Golden Gate technology drawing from a previous collaboration illustrated in Hodgkinson et al. (2008) with advances to reflect the literature. The quality control analyses performed included examining cluster plots to rule out ambiguous genotype calls, checking for Mendelian inconsistencies, and flagging SNPs with low call rates ($< 95\%$) and deviations from Hardy-Weinberg equilibrium ($p < 10^{-6}$). 1471 SNPs passed quality control procedures. Participant data were inspected for incorrect gender assignments, sample swaps, and cryptic relatedness. Five adolescents were excluded from the study due to these quality control criteria.

Measures

Demographics—Adolescents self-reported their age, gender, and ethnicity.

Adolescents' IQ—At T1, adolescents completed the Kaufman Brief Intelligence Test, which was a covariate (Kaufman & Kaufman, 1990). This test significantly correlates (r 's from 0.77–0.88) with the Wechsler Adult Intelligence Scale-Revised, suggesting convergent validity (Nagle, Chelune, & Tucker, 1993).

Adolescents' ancestry—Thirty-seven SNPs in our dataset are ancestry informative markers shown to distinguish between non-Hispanic Caucasian and Mexican/Mexican-American ancestry (Tian, Gregersen, & Seldin, 2008). Note that Mexican-American individuals make up the majority of the Hispanic population in the geographic region where data were collected. We performed a principal components analysis on these SNPs. The first component explained 18.99% of the variance (eigenvalue = 7.03), the second explained 3.36% (eigenvalue = 1.24), and the third explained 3.11% (eigenvalue = 1.02). 32 SNPs with loadings greater than 0.30 on the first principal component were used as indicators of a one-factor model using maximum likelihood estimation. The model fit the data well: $\chi^2(464) = 824.99$, $p < 0.001$, RMSEA = 0.03, CFI = 0.94, SRMR = 0.03. Factor scores were saved for use as a covariate. These scores were highly correlated with adolescents' self-reported ethnicity ($r = 0.86$, $p < 0.001$), confirming their validity and demonstrating that ancestry scores are representative of self-reported ethnicity. Higher factor scores indicate higher

levels of non-Hispanic Caucasian versus Mexican/Mexican-American ancestry (hereafter referred to as Mexican-American).

Custodial parent substance use disorder (SUD)—At T1, adolescents' custodial parents were assessed for lifetime alcohol/drug abuse or dependence based on *DSM-IV* criteria using the Computerized Diagnostic Interview Schedule (C-DIS; Robins et al., 2000). For non-interviewed parents, spouses provided this information using Family History Research Diagnostic Criteria (Endicott, Andreasen, & Spitzer, 1975). We classified adolescents as having a parent with an SUD if at least one custodial parent had a lifetime alcohol or drug disorder and this was used as a covariate. We chose custodial-rather than biological-parent SUD because we wanted to ensure that *living* with a parent with an SUD was not a third variable that confounded the relations between maternal inconsistency and adolescent externalizing-related outcomes. Note that biological and custodial SUD were highly correlated ($r = 0.71$, $p < 0.001$). We chose mothers' or fathers' SUD, rather than only mothers' SUD, because both parents' SUDs could impact mothers' inconsistent discipline.

Adolescents' polygenic risk scores for poor response inhibition—Polygenic risk scores are typically computed by summing information on multiple single-nucleotide polymorphisms (SNPs). One method to choose SNPs for a polygenic risk score was to refer to results of an independent genome-wide association study (GWAS; Purcell et al. 2009; Salvatore et al., 2014). Thus, we created a polygenic risk score in our own data based on an independent GWAS of Stroop Colorword task performance conducted in a sample of young adults of European ancestry (18–30 years old; Cirulli et al., 2010; Golden, 1975). The Stroop Colorword task is one of the most widely used measures to examine response inhibition and shows moderate to high reliability and validity (MacLeod, 1991; Schiehser & Bondi, 2009). Because genetic influences on executive functions are largely constant from adolescence to adulthood (Tucker-Drob & Briley, 2014), results from this young adult GWAS should be reflective of genetic risk for response inhibition in our adolescent sample.

We only considered SNPs that were assessed both in our study and the independent GWAS. SNPs were excluded if they had a total sample minor allele frequency (MAF) $< 2\%$ in our data. We reconciled inconsistencies in the strand orientation of SNPs between the GWAS and our data. However, palindromic SNPs (e.g., C/G or A/T) that had a MAF $> 45\%$ were excluded due to increased ambiguity in strand orientation. We pruned SNPs in high linkage disequilibrium to avoid redundancy by using a pairwise $r^2 \geq 0.25$ within a 200 SNP sliding window (Purcell et al., 2009). As in previous studies (e.g., Purcell et al., 2009; Salvatore et al., 2014), preliminary analyses created several polygenic risk scores by using SNPs that met various significance thresholds in the GWAS, weighting each SNP by their t-statistic from the independent GWAS, and averaging them (using --score in PLINK; Purcell et al., 2007). See Supporting Information Table 1 for all SNPs, t-statistics, p-values, and reference alleles used. This resulted in four polygenic risk scores with 3 ($p < 0.01$), 17 ($p < 0.05$), 49 ($p < 0.10$), and 236 ($p < 0.50$) SNPs. This procedure has been used because there are currently no firmly established criteria for choosing the most informative significance threshold (Evans, Visscher & Wray, 2009). Following recommendations by Evans et al. (2013), we chose the score that maximized variance explained in the outcome (our measure of response

inhibition) with the most conservative p -value, which was the score at the $p < 0.01$ threshold ($r^2 = 1.6\%$).

This final polygenic risk score was used in all subsequent analyses and included three SNPs from the dopamine beta-hydroxylase gene (*DBH*; rs2007153), the gamma-aminobutyric acid (GABA) A receptor, beta 1 gene (*GABRB1*; rs6290), and the protein kinase C, epsilon gene (*PRKCE*; rs12471357). Higher levels of the score represent higher polygenic risk for poor response inhibition. Although our lack of genome-wide data resulted in a limited number of SNPs in our score, an advantage of this approach is that it is an empirical method for identifying SNPs that may play a role in response inhibition with an independent replication. Note that we ensured the polygenic risk score did not operate differently for non-Hispanic Caucasian and Mexican-American participants by testing polygenic risk-by-ancestry interactions on all outcomes (see Analyses and Results).

Mothers' polygenic risk scores—A polygenic risk score was created for biological mothers who lived with their adolescent children. The same three SNPs used in creating polygenic risk scores for adolescents (see above) were weighted by corresponding t -statistics and averaged. This score controlled for passive rGE in analyses of a subset of the sample who had both mother and adolescent genetic data (see the “Controlling for passive rGE” section).

Maternal inconsistent discipline—Mothers', as opposed to fathers', inconsistent discipline was chosen in the present study because fewer fathers participated in the study and because more mothers were genotyped (see the Controlling for Passive rGE section below). At T1, adolescents reported perceptions of their mothers' inconsistent discipline and mothers self-reported their inconsistent discipline using the Children's Report of Parental Behavior Inventory (1 = Strongly Agree, 5 = Strongly Disagree; CRPBI; Schafer, 1965). The two subscales are inconsistency of discipline (e.g., “I didn't pay much attention to my child's behavior,” “I let my child get away without doing work they had been given”) and inconsistency of rule enforcement, which is a part of discipline (e.g., “I soon forgot the rules I made,” “I punished my child for doing something one day but ignored it the next day”). Cronbach's alphas were 0.84 and 0.75 for mother-reported rule enforcement and discipline, respectively, and 0.79 and 0.76 for child-reported rule enforcement and discipline, respectively. Correlations between mother- and adolescent-reported inconsistency of rule enforcement and between their reports of inconsistency of discipline were both $r = 0.27$, $p < 0.001$. The correlation between mother-reported inconsistency of discipline and rule-enforcement was $r = 0.76$, $p < 0.001$ and between adolescent-reported inconsistency of discipline and rule-enforcement was $r = 0.75$, $p < 0.001$.

A latent maternal inconsistency factor was estimated using means from these subscales as four observed indicators, with method effects accounted for by allowing residual covariances between (1) mother-reported rule enforcement and discipline and (2) adolescent-reported rule enforcement and discipline. Because this model was just-identified (i.e., $df = 0$), fit indices were unavailable. However, magnitudes of the standardized loadings (0.44–0.52) supported the four subscales as observed indicators of a single maternal inconsistency factor (all p s < 0.001). Factor scores from this model were saved and used to represent maternal

inconsistency in all analyses. Higher factor scores reflect greater maternal inconsistency. Note that our use of both mother and adolescent reports as indicators of a single parenting factor is better supported by the standardized factor loadings from the measurement model, which accounted for method effects, than by their observed correlations, which are attenuated and biased by method effects and error.

Adolescents' response inhibition—At T1, adolescents completed the Immediate Memory Task (Dougherty, Marsh, & Mathias, 2002). Participants saw a five digit number every second and hit a button if the current and prior number matched. There were 200 trials where the current and prior number matched, 200 where they differed by one digit, and 200 where they differed on all digits. Analyses used the number of single-digit commission errors (i.e., hitting the button when the numbers differed by one digit). This measure is interpreted as an indicator of impulsive responding (Dougherty et al., 2002). This task has acceptable internal and test-retest reliability (r 's ranged from .77 to .92; see Mathias, Marsh, & Dougherty, 2002 for greater details).

Adolescents' externalizing problems—Adolescents self-reported (1 = not true, 2 = somewhat true, 3 = very true/often true) their externalizing problems using the DSM-Oriented Attention Deficit/Hyperactivity (ADHD) and Conduct Problems subscales of the Youth Self Report (Achenbach & Rescorla, 2001). Note that the DSM-Oriented Oppositional Defiant Problems subscale was not included in the externalizing measure because prior researchers noted that these symptoms are nearly synonymous with personality dimensions such as negative emotionality and low agreeableness (Moffitt et al., 2008). For theoretical reasons, we wished to only include the more behavioral aspects of externalizing problems (ADHD and conduct problems) due to the focus on prediction by response inhibition.¹ Indeed, our DSM-Oriented measure of oppositional defiant problems included items such as "I have a hot temper" and "I am stubborn."

At T1 and T2, the ADHD and Conduct Problems subscales were summed to form two separate composites of T1 and T2 externalizing problems. Adolescents' self-reports were chosen because only adolescents reported on their externalizing problems at both waves, allowing for prospective prediction. Cronbach's alpha for T1 and T2 externalizing problems were 0.86 and 0.85, respectively. Note that we did not examine separate outcome measures of ADHD and conduct problems due to the lack of parental report at two waves (parents are the best reporters of ADHD symptoms) and due to the low distinctiveness between ADHD and conduct problems in our study ($r = 0.60$, $p < 0.001$).

Analyses

We used Mplus Version 7.11 (Muthén & Muthén, 1998–2013) with maximum likelihood estimation and full information maximum likelihood to include participants with incomplete data (note that we excluded those with missing genetic data). To obtain standard errors and chi-square statistics adjusted for clustering of siblings within families (and robust to non-

¹Note also that a sum score including all three subscales (ADHD, conduct problems, and oppositional defiant problems) was highly and significantly correlated with the sum score including only ADHD and conduct problems ($r = 0.99$, $p < 0.001$). Thus, although the oppositional defiant problems subscale was excluded for theoretical reasons, including the scale likely would not have changed results.

normality), models used a robust sandwich estimator (TYPE=COMPLEX). Response inhibition had a large variance when compared to the other variables in the model so we divided it by 10 for analyses. Covariates and predictors were mean-centered.

Testing the direct effect of adolescents' polygenic risk on maternal

inconsistency (Model 1)—First, we estimated a model in which all covariates and adolescents' polygenic risk score predicted maternal inconsistency. This model assessed whether genetic risk had a direct effect on maternal inconsistent discipline prior to testing response inhibition as a mediator in this relation (i.e., gene-environment correlation; called Model 1). However, we still tested whether response inhibition mediated the relation between polygenic risk and maternal inconsistency as hypothesized even if there was no direct association. This is because, theoretically, the evocative effect could only hold for specific subgroups (see Jaffe & Price, 2012).

Testing the main effects of all paths in the proposed model (Model 2)—In a second main effects model (called Model 2), paths were specified such that adolescents' polygenic risk predicted T1 response inhibition, T1 maternal inconsistency, and T2 externalizing problems. T1 response inhibition predicted T1 maternal inconsistency, and both of these variables predicted T2 externalizing. An autoregressive path was estimated such that T1 externalizing predicted T2 externalizing. Finally, the five covariates (parent SUD, adolescent IQ, gender, ancestry, and age) predicted all other modeled variables. Correlations were estimated among all exogenous variables, between T1 externalizing and response inhibition, and between T1 externalizing and maternal inconsistency. This model is represented by Figure 1, except that mothers' polygenic risk score was not included in this model as is shown in Figure 1.

Final structural equation model: testing and adding potential predictor-by-covariate interactions (Model 3)—It would be erroneous to assume that effects of predictors are constant across differing levels of covariates. Preliminary analyses determined which predictor-by-covariate interactions to include in the final, third, model (called Model 3) by testing the main effects described above along with all possible predictor-by-covariate interactions simultaneously. Because of the large number of tests, we minimized alpha inflation by retaining predictor-by-covariate interactions that survived a false-discovery rate (FDR) corrected *p*-value of 0.05 using the Q-value software (Storey, 2002).

If a *polygenic risk*-by-covariate interaction survived FDR correction, we ensured the interaction was not driven by confounding variables by including all polygenic risk-by-covariate and covariate-by-covariate interaction terms as recommended by Keller (2014). Predictor-by-covariate interactions that did not survive FDR correction were trimmed from the final model unless they were included to control for potential confounding effects for another significant interaction (Keller, 2014). We also ensured that interaction effects were not spurious due scaling by re-testing significant gene-by-environment interactions following monotone transformations of the two interaction variables (Young-Wolff, Enoch, & Prescott, 2011).

Significant moderation effects were probed by calculating simple slopes (Cohen, Cohen, West, & Aiken, 2003) and by calculating regions of significance using the web utility developed by Preacher, Curran & Bauer (2006). We only reported regions of significance that were within the range of our data.

Testing mediation and/or moderated mediation—We used the joint significance test to test mediation based on research suggesting that it is the best approach for balancing Type 1 error and statistical power (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). For the joint significance test, mediation is significant if all paths comprising a potential mediated pathway are significant. If paths of a mediated effect were moderated by other variables, moderated mediation was tested using unstandardized simple slopes.

Results

Zero-Order Correlations

Zero-order correlations are in Table 2. Boys had significantly poorer response inhibition compared to girls. Older adolescents had significantly better response inhibition, more inconsistent mothers, and greater T1 and T2 externalizing problems than did younger adolescents. Note that the correlation between adolescents' older age and maternal inconsistency is not due to older adolescents having mothers who were younger when they had children. Indeed, the age at which mothers had children was not significantly correlated with either maternal inconsistency or adolescents' age. Adolescents with lower IQ scores had poorer response inhibition and greater T1 and T2 externalizing problems. Adolescents' higher polygenic risk was significantly correlated with poorer response inhibition and mothers' polygenic risk scores. Adolescents whose custodial parent(s) had an SUD diagnosis were marginally significantly more likely to have more inconsistent mothers and greater T2 externalizing problems. There was high and significant stability between T1 and T2 externalizing problems.

Structural Equation Modeling

Results from the final model (i.e., model 3) are presented in Table 3 and Figure 2. Model fit was excellent: $\chi^2 = 21.05(20)$, $p = 0.39$, RMSEA = 0.01, CFI = 1.0, SRMR = 0.01. Note that all polygenic risk-by-ancestry interactions were non-significant (even prior to FDR correction) and trimmed from the final model. Thus, population stratification likely did not influence results.

Testing the direct effect of adolescents' polygenic risk on maternal inconsistency (Model 1)—Maternal inconsistency was not predicted by adolescents' polygenic risk in model 1 ($\beta = 0.01$, $p = 0.79$).

Testing the main effects of all paths in the proposed model (Model 2)—Adolescents' poorer response inhibition was predicted by their greater polygenic risk for poor response inhibition ($\beta = 0.19$, $p < 0.001$), male gender ($\beta = 0.22$, $p < 0.001$), younger age ($\beta = -0.30$, $p < 0.001$), and lower IQ ($\beta = -0.18$, $p = 0.02$). No other covariates significantly predicted response inhibition.

Greater maternal inconsistency was predicted by adolescents' poorer response inhibition (marginally; $\beta = 0.12$, $p = 0.09$), older age ($\beta = 0.27$, $p < 0.001$), and custodial parents' SUD (marginally; $\beta = 0.09$, $p = 0.08$). No other covariates significantly predicted maternal inconsistency.

Adolescents' greater T2 externalizing problems were predicted by their poorer response inhibition ($\beta = 0.14$, $p = 0.02$), greater maternal inconsistency ($\beta = 0.10$, $p = 0.03$), greater T1 externalizing ($\beta = 0.57$, $p < 0.001$), female gender ($\beta = -0.08$, $p = 0.03$), and custodial parents' SUD (marginally; $\beta = 0.07$, $p = 0.06$). Polygenic risk for poor response inhibition did not predict T2 externalizing problems ($\beta = -0.05$, $p = 0.25$). No other covariates significantly predicted externalizing problems.

Final structural equation model: testing and adding potential predictor-by-covariate interactions (Model 3)—Response inhibition, maternal inconsistency, and T2 externalizing problems were each predicted by one predictor-by-covariate interaction effect. Because the main effects in this model were very similar to the main effects model (Model 2), they are not described further in this section. For main effects of this final model, see Table 3.

Response inhibition was predicted by the interaction between polygenic risk and custodial parent SUD (even after correcting for alpha inflation, applying monotone transformations, and including polygenic risk-by-covariate and parent SUD-by-covariate interactions; see data analysis section). Probing this interaction showed that greater polygenic risk predicted poorer response inhibition for adolescents with parental SUD ($b = 1.77$, $p = 0.002$), but did not predict for those without parental SUD ($b = 0.16$, *ns*). Regions of significance analyses showed that simple slopes began to significantly differ when polygenic risk was less than -0.38 , or 2.95 *SDs* below the mean (i.e., when polygenic risk was low). In other words, adolescents with parental SUDs had better response inhibition than adolescents without parental SUDs when their polygenic risk was lower. See Table 3 and Figures 2 and 3.

Maternal inconsistency was predicted by the interaction between response inhibition and gender after correcting for alpha inflation. Probing this interaction showed that poorer response inhibition predicted greater maternal inconsistency for boys ($b = 0.06$, $p = 0.01$) but not for girls ($b = -0.02$, *ns*). See Table 3 and Figures 2 and 3. Regions of significance analyses suggested that the simple slopes for boys and girls differed significantly when response inhibition was greater than 3.82 (or 0.73 *SDs* below the mean) and also differed significantly when response inhibition was less than -1.53 (or 1.67 *SDs* below the mean). In other words, boys received less consistent discipline than girls when response inhibition was poorer, but boys received more consistent discipline than girls when response inhibition was relatively better. See Table and Figure 3.

T2 externalizing problems were predicted by the interaction between maternal inconsistency and ancestry. Probing this interaction showed that maternal inconsistency predicted externalizing problems for adolescents with higher ancestry scores (i.e., greater non-Hispanic Caucasian ancestry; $b = 1.42$, $p = 0.004$) but not for those with lower ancestry scores (i.e., greater Mexican/Mexican-American ancestry; $b = 0.16$, *ns*). Regions of

significance analyses showed that the simple slopes began to significantly differ when maternal inconsistency was less than -0.16 , or less than 0.25 *SDs* below the mean (i.e., when maternal inconsistency was low). In other words, adolescents of non-Hispanic Caucasian ancestry had lower externalizing problems than adolescents of Mexican-American ancestry when mothers were more consistent with discipline.

Testing moderated mediation—Given the complex pattern of moderation, we characterized how an overall mediated process was moderated by all relevant covariates. For instance, regarding the two-path mediation, the path from genetic risk to response inhibition was moderated by parent SUD, whereas the path from response inhibition to maternal inconsistency was moderated by gender. Therefore, we probed this moderated mediation by characterizing the entire two-path mediated process at the four possible combinations of parent SUD and gender using the same simple slope method used to probe moderation of individual parameters. This allowed us to clearly demonstrate *for whom* the entire mediated processes operated.

We found that response inhibition mediated the relation between polygenic risk and maternal inconsistency only for boys with parental SUD (i.e., both *a* and *b* paths were significant only for this combination of gender and parent SUD; Table 4). The three-path mediated effect from polygenic risk to response inhibition to maternal inconsistency to externalizing problems was also significant for non-Hispanic Caucasian boys with parental SUD (see Table 4). Finally, only for adolescents with parental SUD, poor response inhibition mediated the relation between polygenic risk and adolescents' T2 externalizing behaviors ($b = 0.48$, $p < 0.001$).

Ruling out a potential alternative mediated process: Because response inhibition and maternal inconsistency were measured at the same wave, we examined whether swapping this mediator and outcome also resulted in significant mediation to evaluate this alternative mediated process. Testing maternal inconsistency as the mediator between polygenic risk and response inhibition showed that maternal inconsistency did not have a main effect on response inhibition ($\beta = 0.06$, *ns*) nor was it moderated by gender to predict response inhibition ($\beta = 0.06$, *ns*). This alternative mediated process is not supported by the data.

Controlling for passive rGE—To ensure that the evocative rGE effect was not solely due to mothers' correlated genetic risk (i.e., passive rGE), we ran separate models in a subset of participants where both adolescents and mothers provided genetic data and controlled for mothers' polygenic risk scores ($N = 190$). All of the mothers were biological and custodial (either full or part time) parents. These separate models were specified identically to the final model mentioned above (i.e., model 3), except we also entered mothers' polygenic risk score as a predictor of T1 poor response inhibition, T1 maternal inconsistency, and T2 externalizing problems. We also entered interaction terms of mothers' polygenic risk-by-custodial parent SUD and adolescents' polygenic risk-by-mother polygenic risk in predicting T1 response inhibition. These terms controlled for the potential confounding influence of mothers' polygenic risk on the interaction between adolescent polygenic risk and parent SUD in predicting T1 response inhibition. None of the paths from adolescents' polygenic risk scores to any of the outcome variables changed substantially after entering

mothers' polygenic risk scores in the model. Thus, there was no evidence that passive rGE processes confounded the evocative rGE effect.

Supplementary analyses—It may be important to establish a direct association between genetic risk and the environment in tests of evocative rGE. Unfortunately, adolescents' polygenic risk did not have a direct effect on, nor did it interact with covariates to predict, maternal inconsistency after correcting for alpha inflation. However, based on our mediational results, it seemed important to examine whether adolescents' polygenic risk had a direct effect on maternal inconsistency for boys and/or adolescents with parental SUD without applying FDR corrections. Thus, we examined whether these two- or three-way interactions significantly predicted maternal inconsistency at an uncorrected $p < 0.05$ level. Neither the three-way interaction among parental SUD, gender, and polygenic risk nor the two-way interaction between polygenic risk and gender significantly predicted maternal inconsistency in the full sample or in a smaller subsample after controlling for mothers' genetic risk. However, adolescents' polygenic risk and parental SUD significantly interacted to predict maternal inconsistency even after controlling for mothers' genetic risk ($b = 0.44$, $p = 0.01$). This interaction was such that adolescents' greater polygenic risk for poor response inhibition significantly predicted greater maternal inconsistency for adolescents with parental SUD ($b = 0.29$, $p = 0.05$), but not without parental SUD ($b = -0.14$, $p = 0.25$). Thus, the association between adolescents' polygenic risk scores and maternal inconsistency may be specific to adolescents with parental SUD.

Summary of key findings—Key findings to note from the analyses include the following. Adolescents' polygenic risk for poor response inhibition indirectly predicted greater maternal inconsistency through poorer response inhibition, but only for boys with parental SUD (evocative rGE). This evocative rGE was not confounded by the potential third variable of mothers' genetic risk. Adolescents' polygenic risk for poor response inhibition also indirectly predicted greater externalizing problems through poor response inhibition, and subsequently, maternal inconsistency (only for non-Hispanic Caucasian boys with parental SUD).

Discussion

The current study aimed to understand the role of response inhibition and maternal inconsistent discipline in externalizing problems in adolescence. We tested whether adolescents' poor response inhibition mediated the relation between their polygenic risk for poor response inhibition and maternal inconsistent discipline (evocative rGE), and whether these pathways then prospectively predicted later externalizing problems. Because we found a complex pattern of moderated mediation, we first discuss findings for each individual moderated path, followed by the full moderated mediation effects.

Polygenic Risk for Poor Response Inhibition in Predicting Poor Response Inhibition

We found that adolescents' polygenic risk scores for poor response inhibition significantly predicted poor response inhibition, but only for adolescents whose custodial parents had SUD diagnoses. In further interpreting this interaction, it is important to consider that

parental SUD could reflect environmental risk (e.g., chaotic or conflictual family lives), inherited genetic risk, or both (Bensley, Spieker, & McMahon, 2006; Sher, 1991). Under the maladaptive environmental and/or biological conditions posed by parental SUD, adolescents' genetic risk for response inhibition, whether low or high, might be unmasked. Conversely, the more favorable environments and less overall genetic risk of adolescents without parental SUDs might dampen the effect of adolescents' genetic predisposition for response inhibition in predicting their actual response inhibition. Indeed, regardless of their genetic risk, this group showed about average levels of actual response inhibition. This parental SUD-by-polygenic risk interaction is consistent with previous studies showing that genetic risk variants predicted children's and adolescents' externalizing problems, but only or more strongly in high risk environments (i.e., high maternal insensitivity or low parental monitoring; Bakermans-Kranenburg & van Ijendoorn, 2006; Dick et al., 2011). It is also consistent with research showing that epistasis, or gene-by-gene interactions, predicted cognitive functioning (Barnett, Xu, Goldman, & Jones, 2011). We further probed this interaction and found that the simple slopes only began to differ at low levels of polygenic risk. Thus, adolescent offspring with low genetic risk, despite having a parent with SUD, might be particularly resilient. However, this effect was unexpected and requires replication.

Poor Response Inhibition in Predicting Maternal Inconsistency

We also found that poorer response inhibition predicted greater maternal inconsistency for boys, but not for girls. Furthermore, when adolescents' response inhibition was poor, boys received significantly less consistent discipline than girls. This finding is in line with previous research suggesting that parents may treat their sons differently than their daughters, with boys receiving less parental involvement, sympathy, and more corporal punishment when compared to girls (Carlo, Raffaelli, Laible, & Meyer, 1999; Lytton & Romney, 1991). Perhaps this gender-dependent parenting is due to differential parental reactions to the characteristics of boys versus girls. Supporting this hypothesis is a study by Pener-Tessler et al., (2013) who similarly found that boys', not girls', lowered self-control predicted less positive mothering. They hypothesized that mothers respond more negatively to undercontrolled boys because boys are at higher risk for severe behavioral outcomes like aggression, social dysfunction, ADHD, and delinquency compared to undercontrolled girls (Breton et al., 1999; DeLisi et al., 2010; Eisenberg et al., 2004). Because poor response inhibition is a prominent feature of low self-control, this explanation might apply to our findings. Alternatively, perhaps inconsistent mothering is only evoked when adolescents' response inhibition is more severely impaired. Indeed, overall, boys had worse response inhibition than did girls in our sample. However, these interpretations do not explain our findings that boys also received *more* consistent discipline than girls when response inhibition was high. Perhaps mothers are simply more responsive, whether positively or negatively, to the behaviors of boys than girls.

Maternal Inconsistency in Prospectively Predicting Adolescent Externalizing Problems

We also found that maternal inconsistent discipline prospectively predicted change in adolescents' externalizing problems 18 months later, but only for non-Hispanic Caucasian adolescents (this effect was not significant for Mexican-American adolescents). This is consistent with previous work showing that inconsistent parenting is an important risk factor

for externalizing problems (Patterson, 1995) and that this effect might vary for different ethnic and/or cultural groups (Roosa, Tein, Groppenbacher, Michaels, & Dumka, 1993). Perhaps inconsistent discipline did not predict externalizing problems for Mexican-American youth because adolescents from these families tend to place greater importance on generational hierarchies, which makes these adolescents less likely to question, notice, and subsequently be affected by their parents' inconsistency (White, Roosa, Weaver, & Nair, 2009).

We further probed this interaction and found that the simple slopes only began to differ at higher levels of consistent discipline. Thus, consistent discipline appears to be more protective against externalizing problems for adolescents of non-Hispanic Caucasian ancestry than for adolescents of Mexican-American ancestry, possibly due to the aforementioned cultural differences. The lack of significant differences at high levels of inconsistency may indicate that Mexican-American ancestry is less important in buffering against externalizing problems when mothers' are highly inconsistent with discipline. Alternatively, our data may have lacked sufficient range at this end of the distribution to detect significance differences.

Evidence for Evocative rGE

In line with hypotheses, we found preliminary evidence for an evocative rGE. Polygenic risk influenced poor response inhibition, which in turn evoked greater maternal inconsistency, but only for boys with parental SUD (even after controlling for passive rGE). Supplemental analyses found that maternal inconsistency did not mediate the relation between polygenic risk and poor response inhibition, suggesting that this alternative mediated process is not supported.

This finding is consistent with previous studies that showed that children's and adolescents' externalizing-related characteristics evoked negative parenting outcomes using a variety of methods and measures (Elam et al., 2014; Harold et al., 2013; Marceau et al., 2013; Narusyte et al., 2011; Neiderhiser et al., 2004, 2007; Pender-Tessler et al., 2013). Results suggest that poor response inhibition is a specific adolescent trait that evokes inconsistent discipline for boys with parental SUD. Because maternal inconsistent discipline has been associated with a host of negative adolescent outcomes (e.g., Patterson, 1995), these results have implications for preventive interventions. Specifically, interventions should educate parents on these evocative processes and teach parents strategies to maintain consistent discipline in the face of adolescents' undercontrolled behaviors. Furthermore, these interventions could be especially useful when implemented for high-risk families with sons.

Pathways to Adolescent Externalizing Problems

It is also important to examine whether evocative rGE processes increase risk for future problem behaviors, creating a "vicious cycle" towards psychopathology (Elam et al., 2014; Harold et al., 2013; Pender-Tessler et al., 2013). Interestingly, we found evidence to support this notion. Specifically, poor response inhibition mediated the effect of polygenic risk for poor response inhibition on maternal inconsistency, and maternal inconsistency subsequently

prospectively predicted change in externalizing problems over an 18-month period, but only for non-Hispanic Caucasian boys with parental SUD.

Taken together, results are consistent with previous research suggesting that boys with parental SUD are a particularly high risk group (Chassin, Curran, Hussong, & Colder, 1996), and provides a framework from which to understand this risk. Results also suggest one pathway through which the intergenerational transmission of substance use and related externalizing disorders might operate. That is, non-Hispanic Caucasian boys with parental SUD have a heritable predisposition for poor response inhibition, which may become unmasked in their rearing environment and evoke inconsistent parental discipline. This evoked maladaptive parenting may then prospectively increase risk for externalizing problems by creating resistance to the extinction of undercontrolled behaviors and/or lowered internalization of parental norms (Deur & Parke, 1970; Hirischi, 1969). Results add to the literature by identifying poor response inhibition as one deficit that evokes negative parental reactions and eventually leads to externalizing problems. Further, interventions to strengthen parental consistency in the face of adolescents' poor response inhibition may curb externalizing problems for this at-risk group.

Direct Role of Response Inhibition in Adolescent Externalizing Problems

We also found that adolescents' poor response inhibition significantly and prospectively predicted change in their externalizing problems over an 18 month period, over and above maternal inconsistent discipline. These findings are consistent with previously established links between poor response inhibition and ADHD symptoms, conduct problems, and broad externalizing problems (Brocki, Nyberg, Thorell, & Bohlin, 2007; Kooijmans et al., 2000; Nigg, 2003; Young et al., 2009). Results reinforce previous findings that response inhibition is an early risk factor that might aid in the identification of high-risk children and might be a good target of prevention programs. Moreover, interventions targeting adolescents' response inhibition might improve later outcomes both directly and indirectly, through more consistent discipline.

Consistent with hypotheses, we found that adolescents' poor response inhibition mediated the effect of polygenic risk for poor response inhibition on externalizing problems. However, this mediational effect only held for adolescents with parental SUD. This finding suggests that the SNPs composing the polygenic risk score might be involved in the common genetic basis of both response inhibition and externalizing problems for adolescents with parental SUD. It also suggests that the SNPs in the polygenic risk score might influence externalizing problems through response inhibition, providing preliminary insights into the mechanisms and functionality of these SNPs. Results also shed light on an additional pathway to externalizing problems for adolescents with parental SUD, which originates directly from their genetically-influenced response inhibition.

In the final model, we also found that female gender predicted greater externalizing problems. However, it is important to note that this represents the effect of gender on externalizing problems after controlling for response inhibition, which was significantly poorer for boys than girls. Post-hoc analyses excluding response inhibition as a predictor of externalizing problems showed that gender no longer significantly predicted externalizing

problems. Furthermore, the zero-order correlation between gender and externalizing problems was non-significant (see Table 2). Thus, this gender effect appears to be due solely to the inclusion of response inhibition as a covariate.

Strengths and Limitations

The study had limitations to consider. First, our polygenic risk score only contained three SNPs due to lack of genome-wide data and, thus, the effect of the score on response inhibition was small in magnitude. Many more polymorphisms are implicated in the development of poor response inhibition, and including these in future polygenic risk scores will enhance understanding of these risk pathways. Moreover, with only a moderate sample size, we might not have detected other true effects of the polygenic risk score, suggesting the need for replication with larger samples. Note that post-hoc power analyses suggested that our sample was adequately powered (80%) to detect an interaction that contributes a small-to-moderate ($f^2 = 0.02$) and statistically significant ($p < 0.05$) increase in explained variance, over and above all other variables (see Faul, Erdfelder, Buchner, & Lang, 2009). Because the joint significance test was utilized to test mediation, the power analyses also apply to our ability to detect mediated effects. This suggests that very small main and interaction effects (e.g., $f^2 < 0.02$), which are common in genetic analyses, might have been difficult to detect. Another limitation of our polygenic risk score was that it could not control adequately for passive rGE in the relation between maternal inconsistency and adolescents' externalizing problems. Although we used a GWAS-approach to create the score, future studies might use biologically-derived polygenic risk scores because they can give insight into biological mechanisms. Note, though, that the current literature on SNP functionality is not entirely conclusive and therefore the biologically-based approach has limitations as well.

Another limitation was that we used a GWAS of a different response inhibition task from an older sample (i.e., Stroop Colorword), and genetic associations and/or heritability may vary depending on the type of measure used and age group assessed (Bergen et al., 2007; Dick et al., 2007). Moreover, few studies to our knowledge have tested whether the Stroop Colorword task taps a similar construct as the Immediate Memory Task in a manner that does not vary over time. Thus, it is difficult to ascertain whether the SNPs selected from the independent GWAS taps response inhibition as measured in our adolescent sample. In addition, we considered only inconsistent discipline and not other types of parenting. Finally, the cross-sectional measurement of response inhibition and maternal inconsistency was a limitation. Future studies should control for prior parenting behaviors to further confirm this evocative effect.

Our study had several strengths. Despite the small number of SNPs in our polygenic risk score and the differences between our sample and measures when compared the Cirulli et al (2010) GWAS, our results nonetheless replicated their findings. This is noteworthy in a field where there has been little replication and provides evidence for the strength of this approach (Ioannidis, Ntzani, Trikalinos, Contopoulos-Ioannidis, 2001). Thus, we extend previous studies that examined gene-environment interplay using single candidate SNPs. In addition, we reduced concerns about passive rGE in the relation between adolescents'

genotypes and maternal inconsistency by using identical polygenic risk scores for adolescents and mothers.

Another strength of our study was the use of adolescents' and mothers' reports of maternal inconsistency and a task measure of response inhibition, thus reducing the likelihood that results were due to reporter-bias. We were also able to test pathways to externalizing problems in a longitudinal sample of adolescents at high risk for externalizing and related disorders. This likely resulted in greater variability in study constructs and facilitated the detection of paths of interest. Finally, this study was able to test multiple types of gene-environment interplay using measured genes in a developmental context, an area that deserves more attention in the literature.

Conclusions

In conclusion, the current study gained a clearer understanding of how poor response inhibition contributes to the risk for externalizing problems. Polygenic risk for poor response inhibition may become unmasked when adolescents have parents with SUDs. Poorer response inhibition may subsequently evoke maternal inconsistency for boys, and this may in turn predict change in later externalizing problems, particularly for non-Hispanic Caucasian adolescents. Thus, there may be a "vicious cycle" of cognitive and parental risk factors that increase the risk for psychopathology, especially for non-Hispanic Caucasian boys with parental SUD. Because this risk pathway to externalizing problems was not found for Mexican-American adolescents, future research should determine the evocative rGE mechanisms that lead to maladaptive outcomes for different ethnic groups. In addition, poor response inhibition had a direct influence on change in later externalizing problems; for adolescents with parental SUD, this process may be initiated by a heritable predisposition for poor response inhibition. Findings provide insights into the processes that make boys and adolescents with parental SUDs particularly vulnerable groups and the specific externalizing-related deficits that might initiate evocative rGE and subsequent externalizing problems.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Conceptual Model with Covariates

Note that mothers' polygenic risk scores were only controlled for in separate analyses with a smaller subset of participants who had both adolescents' and mothers' genetic data. Thus, mothers' polygenic risk score was not included in the final model presented in Figure 2 or in the analyses from Figure 3.

Figure 2. Final Path Model (Model 3)

Standardized coefficients are shown. Solid lines indicate statistically significant paths and dashed lines indicate non-significant paths. Text that is overlaid on arrows designates for whom the path was significant (i.e., moderation) and the corresponding standardized coefficients refer to this simple slope. Main effects of covariates are not shown for ease of presentation. Correlations among exogenous variables, the correlation between T1 externalizing and response inhibition, and the correlation between T1 externalizing and mothers' inconsistency were estimated but not shown for ease of presentation. Model fit was excellent: $\chi^2 = 21.05(20)$, $p = 0.39$, RMSEA = 0.01, CFI = 1.0, SRMR = 0.01.

Figure 3. Interactions from Final Model (Model 3)

Slopes in black are significant and slopes in gray are non-significant. Shapes are predicted values. All variables depicted on X and Y axes are mean-centered (i.e., the mean is zero).

Note that response inhibition was divided by 10.

Table 1
Descriptive Statistics, t-tests, and χ^2 Analyses Comparing Including vs. Excluded Participants

Continuous Variables	N	Included <i>M</i> (<i>SD</i>)	N	Excluded <i>M</i> (<i>SD</i>)	t-test
T1 Age	361	12.65(1.83)	248	12.63(1.99)	-0.13
T2 Age	338	13.89(1.87)	240	14.66(3.16)	3.63**
Intelligence Quotient	260	104.64(10.96)	151	103.10(12.41)	-1.27
Ancestry	342	0.03(0.92)	197	-0.09(0.91)	-1.56
Adolescents' Polygenic Risk for Poor Response Inhibition	361	0.99(0.46)	209	0.96(0.50)	-0.70
Mothers' Polygenic Risk Score	190	0.99(0.53)	88	1.01(0.53)	0.40
T1 Response Inhibition	258	55.99(24.31)	151	59.91(27.42)	1.45
T1 Maternal Inconsistency	361	0.001(0.65)	341	-0.001(0.59)	-0.06
T1 Externalizing Problems	359	6.00(5.54)	246	5.54(5.20)	-1.05
T2 Externalizing Problems	329	5.18(5.14)	233	4.44(4.75)	-1.78
Dichotomous Variables	N	%	N	%	χ^2
Gender	361	47.9% Girls	248	45.6% Girls	0.33
Custodial Parent SUD	361	40.7% Custodial Parents with SUD	441	59.3% Custodial Parents with SUD	16.31**
Ethnicity	361	68.1% non-Hispanic Caucasian 31.9% Hispanic	247	44.5% non-Hispanic Caucasian 27.1% Hispanic 0.4% Asian/Pacific Islander 3.6% American Indian 3.2% African American 21.1% Other	--

Note.

* p 0.05.

** p 0.001.

Polygenic risk, response inhibition, externalizing problems, intelligence quotient, maternal inconsistency, and ancestry are coded such that higher levels indicate greater levels of genetic risk for poor response inhibition, poorer response inhibition, greater externalizing problems, greater intelligence, greater inconsistency, and greater non-Hispanic Caucasian ancestry, respectively. Ancestry and maternal inconsistency are factor scores saved from latent factors; latent factors are scaled such that 0 is the mean. Ethnicity was not a covariate in the study but is shown here for descriptive purposes. '--': t-test was not conducted for this variable.

Table 2

Zero-Order Correlations Among Study Variables

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.
1. Gender	1										
2. Age	-.014 [*]	1									
3. Intelligence Quotient	-.008	-.016 [*]	1								
4. Ancestry	-.005	-.002	0.24 ^{**}	1							
5. Custodial Parent SUD	-.004	0.03	0.01	0.01	1						
6. Adolescents' Polygenic Risk Score for Poor Response Inhibition	-.010	0.07	0.06	-.006	0.04	1					
7. Mothers' Polygenic Risk Score	-.010	-.050	.054	-.084	.072	.474 ^{**}	1				
8. Response Inhibition	0.24 ^{**}	-.032 ^{**}	-.006	0.01	-.004	0.12 [*]	0.12	1			
9. Maternal Inconsistency	-.005	0.24 ^{**}	-.014 [*]	-.010	0.10	0.04	-.002	0.04	1		
10. T1 Externalizing Problems	-.005	0.31 ^{**}	-.014 [*]	-.002	0.05	-.003	0.06	0.02	0.42 ^{**}	1	
11. T2 Externalizing Problems	-.008	0.24 ^{**}	-.014 [*]	-.008	0.10†	-.002	0.08	0.10	0.40 ^{**}	0.65 ^{**}	1

Note.

* $p < 0.05$.

** $p < 0.01$.

$N = 393$. Gender: 0 = Female, 1 = Male. Correlations between mothers' polygenic risk score and other study variables are for a smaller subset of the sample ($N = 190$).

Table 3

Standardized Path Coefficients from the Final Model (i.e., Model 3)

Predictors	Mediators		Outcomes
	T1 Response Inhibition	T1 Maternal Inconsistency	T2 Externalizing Problems
Predictors	β (SE)	β (SE)	β (SE)
Adolescents' Polygenic Risk Score (PRS)	0.15(0.06) *	-0.01(0.05)	-0.05(0.05)
IQ	-0.15(0.08)	-0.05(0.06)	-0.03(0.05)
Ancestry	0.09(0.07)	-0.05(0.06)	-0.08(0.05)
Age	-0.26(0.07) **	0.27(0.05) **	0.06(0.04)
Gender	0.20(0.05) **	-0.02(0.05)	-0.08(0.04) *
Custodial Parent SUD	-0.03(0.06)	0.09(0.05)	0.07(0.04)
PRS-by-Custodial Parent SUD	0.15(0.06) *	--	--
PRS-by-Age	-0.04(0.06)	--	--
PRS-by-Gender	0.01(0.07)	--	--
PRS-by-Ancestry	0.02(0.07)	--	--
PRS-by-IQ	-0.08(0.08)	--	--
Custodial Parent SUD-by-Age	-0.06(0.06)	--	--
Custodial Parent SUD-by-Gender	-0.004(0.06)	--	--
Custodial Parent SUD-by-Ancestry	-0.05(0.06)	--	--
Custodial Parent SUD-by-IQ	0.00(0.07)	--	--
T1 Response Inhibition	--	0.08(0.07)	0.15(0.06) *
T1 Response Inhibition-by-Gender	--	0.14(0.06) *	--
T1 Externalizing Problems	--	--	0.56(0.05) **
T1 Maternal Inconsistency	--	--	0.10(0.05) *
T1 Maternal Inconsistency-by-Ancestry	--	--	0.08(0.04) *

Note.

* $p < 0.05$.** $p < 0.001$.

$N = 393$. IQ: Intelligence Quotient. SUD: Substance Use Disorder. T1: Time 1. T2: Time 2. Higher scores on ancestry indicate higher levels of non-Hispanic Caucasian ancestry. Higher scores on response inhibition indicate poorer response inhibition. Higher scores on all other continuous variables indicate higher levels of that construct. Gender: 0 = Girls, 1 = Boys. Custodial Parent SUD: 0 = no custodial parent with SUD, 1 = custodial parent with SUD. '--': path was not estimated.

Table 4

Moderated Mediation Effects

Combinations of Moderators	Two Path Mediated Effect		
	<i>a</i>	<i>b</i>	
Boys with Parental SUD	2.06(0.61) *	0.08(0.03) *	
Boys without Parental SUD	0.30(0.52)	0.04(0.02)	
Girls with Parental SUD	1.74(0.66) *	0.004(0.04)	
Girls without Parental SUD	−0.01(0.43)	−0.03(0.03)	
Three Path Mediated Effect			
	<i>a</i>	<i>b</i>	<i>c</i>
Non-Hispanic Caucasian boys with Parental SUD	2.07(0.73) *	0.70(0.04) *	1.56(0.69) *
Non-Hispanic Caucasian boys without Parental SUD	0.35(0.65)	0.04(0.03)	1.18(0.75)
Mexican-American boys with Parental SUD	2.03(0.70) *	0.07(0.03) *	0.22(0.61)
Mexican-American boys without Parental SUD	0.27(0.62)	0.03(0.03)	−0.13(0.65)
Non-Hispanic Caucasian girls with Parental SUD	1.78(0.71) *	−0.03(0.05)	1.77(0.66) *
Non-Hispanic Caucasian girls without Parental SUD	0.04(0.50)	−0.08(0.03) *	1.40(0.66) *
Mexican-American girls with Parental SUD	1.77(0.79) *	−0.02(0.05)	0.41(0.66)
Mexican-American girls without Parental SUD	0.01(0.63)	−0.07(0.03) *	0.05(0.62)

Note.

* $p < 0.05$.

Unstandardized coefficients are reported, standard errors are in parentheses. Note that response inhibition had been divided by a factor of 10 for these analyses due to having a large variance when compared with other variables in the model.

a = adolescents' polygenic risk score predicting response inhibition.

b = response inhibition predicting maternal inconsistency.

c = maternal inconsistency predicting externalizing problems. SUD: Substance Use Disorder.