J Youth Adolescence
DOI 10.1007/s10964-014-0198-4

EMPIRICAL RESEARCH

Developmental Differences in Early Adolescent Aggression: A Gene × Environment × Intervention Analysis

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Received: 8 August 2014 / Accepted: 7 October 2014

Abstract Aggression-related problems such as assault and homicide among adolescents and young adults exact considerable social and economic costs. Although progress has been made, additional research is needed to help combat this persistent problem. Several lines of research indicate that parental hostility is an especially potent predictor of adolescent aggression, although most longitudinal research has focused on clarifying the direction of effects. In this study, we used longitudinal data from the PROSPER project ($N = 580$; 54.8 % female), a primarily rural Caucasian preventative intervention sample, to examine developmental change in early- to mid-adolescent aggressive behavior problems (age 11–16 years). In addition, we examined maternal hostility as a predictor of developmental change in aggression and the PROSPER preventative intervention, designed to reduce substance use and aggression, as a potential influence on this association. Lastly, several studies indicate that variation in the *DRD4* 7-repeat gene moderates both parenting and intervention influences on externalizing behavior. Accordingly, we examined the potential moderating role of *DRD4*. As hypothesized, there was a significant maternal hostility by intervention interaction indicating that the intervention reduced the negative impact of maternal hostility on adolescent change in aggressive behavior problems. *DRD4* 7-repeat status (7+ vs. 7−) further conditioned this association whereby control group 7+ adolescents with hostile mothers showed increasing aggressive behavior problems. In contrast, aggression decreased for 7+ adolescents with similarly hostile mothers in the intervention. Implications for prevention are discussed as well as current perspectives in candidate gene-by-environment interaction research.

Keywords Aggression · Adolescence · Growth curve · Parental hostility · Prevention · *DRD4*

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Published online: 16 October 2014

Introduction

Although aggression-related crimes in the United States have steadily declined since the 1990's (Dahlberg and Mercy 2009) they persist at unacceptable rates, particularly among adolescents. Adolescents are disproportionately both victims and perpetrators of violence and in 2011, 700,000 youth age 10–24 were treated in emergency rooms for assault-related injuries (CDC 2012a). Homicide remains a leading cause of death among adolescents and young adults (CDC 2012b). Comorbid with aggressive behavior during adolescence is substantial substance use, which is linked to adolescent dating violence (e.g., Reyes et al. 2012). In addition to the direct impact to those who experience violence, the economic toll of aggression is considerable, costing the U.S. billions of dollars annually (CDC 2014).

Although aggression declines among most adolescents (Bongers et al. 2003), aggression remains high among some and even increases among others (Brame et al. 2001). Importantly, high and increasing aggressive behavior problems during adolescence have been linked to adverse late adolescent and adult outcomes, including poor self-control (Kokko et al. 2009), increased cyber-bullying (Modecki et al. 2013), and intimate partner violence (O'Donnell et al. 2006). Understanding the etiology of persistent adolescent aggression extends beyond adolescence itself into adulthood and beyond aggression to other problem behaviors.

The link between late childhood/early adolescent (approximately ages 7–14) aggressive behavior problems and adult aggression and violence is well established (e.g., Piquero et al. 2012). Early adolescence is a period of substantial change for developmental and social domains generally, as well as aggressive behavior specifically. For example, Cleverley et al. (2012) identified three distinct classes of developmental change in physical aggression from late childhood to mid-adolescence (no aggression, moderate declining, and high increasing) consistent with several prior studies (e.g., Moffitt 1993). Given these distinct changes, early adolescence presents special opportunities for intervention. In addition, research on developmental change in aggressive behavior problems may provide insight into developmental pathways toward adult risk behaviors such as substance use problems, risky sexual behavior (Timmermans et al. 2008), and more serious violence (Schaeffer et al. 2003). Due, in part, to the potential for intervention during early adolescence, correlates of aggressive behavior problems during this period have been a focus of many studies. For example, delinquent peer affiliation (Brechwald and Prinstein 2011), low quality schools (Estévez López et al. 2008), and impoverished neighborhoods (Pabayo et al. 2014) along with family factors such as criminal parents (Nijhof et al. 2009), family instability (VanderValk et al. 2005), and negative parental behaviors (Farrington 2005) are associated with adolescent aggressive behavior problems. In particular, negative parental behaviors, such as child-directed hostility, have been implicated in several lines of research as especially important factors in the development of adolescent aggressive behavior (e.g., Burt et al. 2006; Campbell et al. 2010; see Farrington 2009 for a review). In contrast, less emphasis has been placed on determining the conditions under which parental hostility is related to developmental change in early adolescent aggressive behavior problems.

A handful of studies have addressed family factors other than parental hostility and their association with development of adolescent externalizing behavior problems, which includes aggression but also other components of externalizing such as rule-breaking and delinquency (e.g., Dekovic et al. 2004; Galambos et al. 2003; Leve et al. 2005; Montague et al. 2010). Generally speaking, these studies show that parental negativity results in less reduction, or greater increases, in externalizing behavior problems over time. Inadvertently, these studies have also shown the importance of distinguishing aggression from other types of externalizing behavior problems. Two of the above cited studies found that externalizing behavior problems generally increased during adolescence (Dekovic et al. 2004; Galambos et al. 2003). However, the other two studies found that externalizing behavior problems decreased (Leve et al. 2005; Montague et al. 2010). These different results may stem from examining externalizing behavior problems rather than its components, which have different patterns and etiologies. Specifically, rule-breaking and delinquency tend to increase during adolescence. In contrast, aggression tends to decline (Benson and Beuhler 2012; Bongers et al. 2003, 2004). For example, although Bongers et al. (2003) found adolescent boys' aggressive behavior tends to decline faster than girls', declines were found for both sexes. Results for delinquency were also similar across sexes; however, the growth curves increased. Related to this latter research, few studies have examined gender differences in adolescent externalizing development. A more recent example is a study by Fernandez Castelao and Kröner-Herwig (2014), who found similar patterns of externalizing for both boys and girls. In addition, family factors such as conflict and climate were similarly related to developmental change in externalizing behavior problems for both sexes. This research, however, also does not distinguish between specific components of externalizing behavior, such as aggressive behavior problems.

Aggressive Behavior Problems and Prevention Research

The risk factors for aggressive behavior problems appear to overlap with those of substance use. Universal preventative

interventions targeting these shared risk factors effectively reduce both substance use and behavior problems (Spoth et al. 2000, 2006). Aggressive behavior problem intervention programs focus on emotion regulation and positive peer affiliation strategies and may include components aimed at changing the way youth think and feel about aggression through targeting cognitive and affective processes (see Hahn et al. 2007 for a review). Several substance use interventions incorporate similar self-management and social skills training components (Botvin and Kantor 2000; Ellickson et al. 2003; McNeal et al. 2004). One example is the substance use prevention *Life Skills Training* program (LST), which has been shown to also reduce verbal aggression and forms of physical aggression among adolescents (Botvin et al. 2006). Another example is the *All Stars* program. *All Stars* explicitly targets violence in addition to substance use and includes LST components (McNeal et al. 2004). In the current study, we used data from the PROSPER substance use preventative intervention project, a community-based research project for delivering evidence-based preventive interventions (including LST and *All Stars*) using a university-school-Cooperative Extension collaboration partnership model. Although primarily targeting substance use, a secondary goal of PROSPER interventions was to reduce aggressive behavior problems (see Redmond et al. 2009).

In addition to these studies of intervention on behavior, a growing body of candidate gene-by-environment interaction (cGxE) research has that shown that environmental effects on behavior, including interventions, may differ based on allelic variation (e.g., Beach et al. 2010; Brody et al. 2009). Candidate GxE studies test the hypothesis that environmental effects are conditional on measured genotypes or, equivalently, that genetic effects depend on environmental context. One of the more compelling streams of research involves the dopamine receptor D4 gene (*DRD4*). Studies suggest that genotypes at the Variable Number of Tandem Repeats (VNTR) site in *DRD4* cause differences in biological function of the neural dopamine receptor encoded by this gene. The most common alleles of this VNTR are those with 2, 4, or 7 copies of the repeated DNA (details described in "Methods"). To date, all analyses of function have found the 7-copy allele to function differently than the other two shorter alleles. Three domains of function appear to be altered by genotype status at the VNTR: (1) the receptor's ability to transmit signaling information (Asghari et al. 1995); (2) the level of mRNA transcribed from this gene (Schoots and van Tol 2003); and (3) protein–protein interactions with the DRD2 receptor (Borroto-Escuela et al. 2011). The role of these functional differences in explaining *DRD4*'s association with behavioral traits, including novelty seeking (Kluger et al. 2002) and ADHD (Faraone et al. 2001), is not yet clear. It is possible that one or all of these biological differences affect the brain's ability to respond to dopamine, which plays a role in reward salience and motivated action (Bromberg-Martin et al. 2010). Important for the current inquiry, several studies have demonstrated that the associations between externalizing behavior problems, including aggression, and behavioral interventions and parenting can vary based on *DRD4* genotype. Specifically, youth who carry at least one copy of the 7-repeat allele (7+) compared to youth who do not possess a 7-repeat allele (7−) show greater environmental sensitivity. For example, in a study of infant twins, Bakermans-Kranenberg and van IJzendoorn (2006) randomly selected one twin from each pair (Twin A) and found that *DRD4* status (i.e. 7+ vs. 7−) moderated the effect of observed sensitive mothering (e.g., awareness of the infant, responsiveness) on externalizing behavior; infants with the 7+ allele who had less sensitive mothers showed the highest externalizing behavior. Maternal sensitivity showed no effect for infants 7− infants. These findings were replicated with data from Twin B.

In a follow-up study, Bakermans-Kranenberg et al. (2008a) showed that child *DRD4* status moderated the association between a parenting intervention designed to increase sensitive, responsive parenting, and externalizing behavior problems in children (age 1–3 years). Intervention 7+ children showed the largest decline in externalizing behavior problems following the intervention, particularly aggression, compared to 7− children. Supplemental analysis revealed that this difference was most pronounced among intervention mothers who improved their sensitive parenting. Lastly, in a study of early adolescent substance use progression, Beach et al. (2010) found that *DRD4* genotype moderated a substance use intervention among African American adolescents. The intervention reduced growth in self-reported substance use between the ages of 11 and 14, but only for adolescents with at least one copy of the 7-repeat allele.

Findings from many candidate cGxE studies have often been interpreted as evidence for biologically based differences in environmental sensitivity. Theoretical work from Belsky, Ellis, and others (Belsky and Pluess 2009; Ellis et al. 2011; Ellis and Boyce 2008, 2011) posit that these findings reflect evolutionarily selected adaptive individual differences in susceptibility to the environment (i.e. Differential Susceptibility Theory; DST). Thus, genetic variants, such as *DRD4*, that might otherwise be viewed as "risk genes" or contribute to "genetic risk" for maladjustment—perhaps due to their association with risk-prone phenotypes such as novelty seeking—are viewed in terms of their associated phenotypic flexibility (Ellis et al. 2011). More specifically, DST posits that individuals who are more sensitive to adverse environments, and at higher risk

for negative outcomes in these settings, also could benefit more from exposure to supportive environments. Differential susceptibility theory is often contrasted with diatheses stress and the more recent vantage sensitivity models (see Pluess and Belsky 2013) that posit vulnerability solely to negative and positive environments, respectively. As detailed below, because the measures used in this study do not span the full range of "positive" and "negative" (e.g., participating in the control group does not mean exposure to adversity), our results cannot be interpreted as evidence for (or against) differential susceptibility. However, we do expect *DRD4* 7-repeat genotypes to be associated with differences in environmental sensitivity based on this prior literature.

The Current Study and Hypotheses

This study expands on existing research in several ways. Most developmental studies in this area have focused on change in externalizing behavior as a whole, as opposed to change in its components. In this study, we modeled developmental change specifically in aggressive behavior problems and examine if the well-characterized cross-sectional association between maternal hostility and adolescent aggressive behavior extended to developmental change during adolescence. Accordingly, we hypothesized that maternal hostility will be associated with slower decrease in early-to mid-adolescent aggressive behavior problems. In addition, because the PROSPER preventative intervention targets skills relevant to aggressive behavior problems, we hypothesized that the intervention would be related to greater decline in aggressive behavior problems and reduce any negative effects of maternal hostility. Because prior research and theory suggests both parenting and intervention effects on externalizing are more pronounced among those with the more sensitive *DRD4* genotype, we hypothesized the negative effect of maternal hostility and the positive effect of the intervention on aggressive behavior problems would be greatest among *DRD4* 7+ adolescents. Lastly, because there are few studies that examine gender differences in aggression development during adolescence, we also tested gender differences in our supplemental analyses.

Methods

Participants and Procedure

Data from the PROSPER project were used to model growth curves of aggressive behavior problems from early- to mid-adolescence (age 11–16). The PROSPER project includes 28 school districts in Iowa and Pennsylvania that were randomized into 14 control and 14 intervention communities. All 6th grade students were invited to participate in in-school surveys; approximately 90 % did so at Wave 1. In-school student surveys began when participants were in the first semester of 6th grade; they were repeated late in the second semester of 6th grade, and then continued annually in schools until 12th grade.

The 14 intervention communities utilized the PROSPER partnership model to deliver a sequence of family-focused and school-based preventive programs. From menus of three choices, for each of the two types of programs, community teams selected a universal family-focused program for implementation in 6th grade and a school-based program for implementation in 7th grade (Spoth et al. 2004 for details). All 14 communities chose the *Strengthening Families Program: For Parents and Youth 10–14* (SFP: 10–14) as their family-focused program. The SFP has been shown to reduce adolescent aggressive behavior through skills training such as teaching effective communication and problem solving between parents and children (Spoth et al. 2000). For the 7th grade school-based program *Life Skills Training* (Botvin and Kantor 2000) and *Project Alert* (Ellickson et al. 2003) were each selected by four teams; the *All Stars* curriculum (McNeal et al. 2004) was selected by the other six. All three programs target social norms, personal goal-setting, decision-making, and peer group affiliation. For details on each program see Spoth et al. (2004). Very high levels of implementation quality have been confirmed across intervention models and cohorts (e.g., Spoth et al. 2007).

A random sample of 2,267 families of PROSPER youth were invited to participate in an in-home data collection parallel to the in-school surveys; 979 (43 %) elected to participate. Home-based visits were conducted twice in 6th grade (in the fall and spring, Waves 1 and 2) and annually in the spring thereafter for 3 years (Waves 3, 4 and 5; see Table 1). Some comparisons, such as for differences in perceiving benefits from using substances [$M = 4.71$ vs. $M = 4.77$, $F(1,27) = 12.36$, $p < .01$], indicate that the in-home sample may be at slightly lower risk for problem behavior than the full sample of youth in the PROSPER project responding to school-based assessments. However, in other domains the in-home sample was not different from the total in-school population at Wave 1. For example, the two groups were similar for receipt of school lunch (33.6 vs. 33.0 %) and living with two biological parents, (59.3 vs. 62.5 %; see Lippold et al. 2014). Due to attrition, 740 of the 979 (75.9 %) families took part in the last wave of in-home data collection. Wave 1 comparisons between families with and without Wave 5 data showed families missing data were less likely to be Caucasian [83.4 vs. 90.4 %, $\chi^2(1) = 8.92$, $p < .01$] but did not differ in child

Table 1 Means and standard deviations for aggressive behavior problems, maternal hostility, and adolescent age at each grade and approximate delivery of programming

Grade	Mother report	Father report	Adolescent report	
	Aggression *M* (*SD*)	Aggression *M* (*SD*)	Maternal hostility *M* (*SD*)	Age in years *M* (*SD*)
6th (fall)	.32 (.30)	.32 (.32)	1.36 (1.15)	11.79 (.40)
Family-focused program provided				
6th (spring)	.28 (.29)	.26 (.29)	1.06 (1.03)	12.44 (.39)
School-based program provided				
7th	.29 (.31)	.25 (.26)	1.24 (1.16)	13.43 (.38)
8th	.27 (.28)	.24 (.26)	1.29 (1.16)	14.41 (.39)
9th	.26 (.28)	.24 (.28)	1.40 (1.22)	15.37 (.38)

Mother and father reports of aggressive behavior problems measured with the Child Behavior Checklist (Achenbach 1991). Data collection for 7th, 8th, and 9th grade occurred during the spring

gender, maternal education, or baseline maternal hostility or adolescent aggressive behavior problems.

During Wave 5 of the in-home assessment, parents were also asked to consent to adolescent DNA collection. During a later young adulthood data collection the number of in-home participants who provided DNA was supplemented ($n = 57$). In total, 594 in-home participants provided saliva samples for DNA data collection. Participants received compensation for completing surveys and providing DNA.

Reflecting the community demographics, the sample primarily self-identified as non-Hispanic White (89.5 %) with smaller groups identifying as Hispanic/Latino (4.5 %), African American (1.7 %), Asian (<1.0 %), or other non-Caucasian (2.6 %). Seven participants (1.2 %) did not report their ethnicity; 57.8 % ($N = 318$) were female. Comparisons between the 594 DNA-providing participants and the larger population of PROSPER participants (approximately 11,000) revealed few differences. For example, there were somewhat fewer two-biological parent families among the 594 (55.8 vs. 62.3 %), however, similarities were evident in racial composition (88.3 vs. 84.4 % Caucasian), and free/reduced lunch receipt (32.6 vs. 33.6 %). Effect sizes for these differences were small (r's <.03). Fourteen cases were excluded from the current analyses due to mother absence ($n = 12$) and survey non-response ($n = 2$). All analyses in this study were conducted on the remaining 580 families.

Measures

Aggressive Behavior Problems

Mothers and fathers separately completed the Internalizing and Externalizing components of the Child Behavior Check List (CBCL) at each assessment. The CBCL Aggressive Behavior subscale measures general problems with aggressive behavior (Achenbach 1991; Rapport et al. 2009). Example items include, physically attacks people, destroy things, and tease a lot. These are answered on a 0 = *Never true*, 1 = *Sometimes true*, 2 = *Always true* scale. The CBCL is widely used in child and adolescent psychological research to evaluate, and diagnose, maladaptive behavioral problems including aggressive behavior. Many studies of developmental change in aggression have used the CBCL (e.g., Bongers et al. 2003, 2004; de Haan et al. 2012; Fernandez Castelao and Kröner-Herwig 2014). Alpha reliabilities for the subscale ranged from .88 to .91 across Waves. Mother and father reports, moderately to strongly correlated within Waves ($r = .59$–$.69$), were averaged. At a given assessment, 65–70 % of father reports were available. When father report was unavailable, only mother report was used. Means and standard deviations for each measure at each Wave can be seen in Table 1.

Maternal Hostility

During in-home interviews, adolescents responded to a set of three items designed to measure maternal hostility: How often does your mother "Get angry at you", "Shout, yell, or scream at you", and "Swear or curse at you." Response scales ranged from 1 = *Never* to 7 = *Always* scale. A fourth item, "How often does your mom lose her temper and yell at you when you do something wrong," was added to this scale. Because this item was scored 1 = *Almost Never* to 5 = *Almost Always*, the item was rescaled using the following equation to match the response scale of the other items [1.5*($x - 1$) + 1)] before all four items were averaged ($\alpha = .82$–$.89$ across Waves). Approximately 5 % of adolescents reported on a mother figure who was not their biological mother. Lastly, we took advantage of the longitudinal data and separated the time-varying and time-invariant components of maternal hostility. The time-invariant component is used in the analyses below. This component is equivalent to mean maternal hostility across waves.

Intervention Status

In the current analytic sample of 580 adolescents, 240 (41.4 %) were in the control condition and the remaining 340 (58.6 %) were in the intervention condition. Baseline comparisons showed no differences in maternal hostility [$M = 2.38$ vs. $M = 2.34$; $t(570) = .39$, *ns*] or adolescent aggressive behavior problems [$M = .32$ vs. $M = .31$; $t(578) = .15$, *ns*] between intervention and control groups, respectively.

Genotyping

DNA was collected by buccal swabs and extracted using a modified phenol–chloroform technique (Freeman et al. 2003). A portion of the collected DNA was genotyped for the VNTR polymorphic site in the *DRD4* gene at the Penn State Genomics Core (Anchordoquy et al. 2003) using primer sequences developed by Lichter et al. (1993) with the forward primer fluorescently labeled. Amplification products were analyzed using a 3730XL DNA Analyzer and Genotyper software v4.0 (Applied Biosystems, Foster City, CA, USA). Of the 594 participants who provided DNA, 98.5 % were successfully genotyped for the *DRD4* polymorphism. Genotypes were in Hardy–Weinberg Equilibrium [$\chi^2(1) = .03$, *ns*], further supporting accurate genotyping.

Nine alleles ranging in size from 2 repeats to 10 repeats were detected. Frequencies of the most common repeat alleles (>5 %) were: 2 (9.3 %), 4 (63.9 %), and 7 (19.9 %). The remaining repeat alleles summed to 6.9 %. The 5 most common genotypes from a total of 23 were 7/7 at 3.9 %, 3/4 at 4.1 %, 2/4 at 12.8 %, 4/7 at 27.4 %, and 4/4 at 39.3 %. For the current analyses, *DRD4* was coded for the presence (7+; $N = 209$, 36.0 %) versus absence (7−; $N = 371$, 64.0 %) of at least one copy of the 7-repeat allele. While there is insufficient biological evidence to decide on the proper method of coding alleles at this site, this method of coding implies a dominance of the 7+ allele. This method was chosen based on its function (e.g., Asghari et al. 1995), similar prior research, (Bakermans-Kranenburg and van IJzendoorn 2011) and sample size considerations, given that there are relatively few 7+ heterozygotes. Recent work on interactions of *DRD4* and *DRD2* (Borroto-Escuela et al. 2011) may allow assessment of the true mode of action (dominant, partially dominant, recessive, or additive).

Age Participants were on average 11.79 ($SD = .40$) years of age during the initial assessment in 6th grade and on average 15.37 ($SD = .38$) years of age at the 9th grade follow-up. Adolescent age (centered at 11) was used as the time metric in growth models.

Plan of Analysis

Growth models were conducted using the SAS 9.3 MIXED procedure (SAS Institute 2011). The Aggressive Behavior subscale was grand mean centered prior to analysis. Growth coefficients can be interpreted as change in aggressive behavior problems in sample standard deviation units per 1 year of age during early- to mid-adolescence. Due to nesting within communities, these data may violate the independence assumption (Kenny et al. 2006). However, small intra-class correlations across Waves (.01–.03) indicate that aggressive behavior problems cluster little within communities in this sample. We used adolescent report of maternal hostility and mother/father report of adolescent aggressive behavior problems to help minimize reporter bias and maximize sample size.

A series of models were tested that build in complexity. First, an unconditional growth model was conducted to establish a baseline and to determine if the commonly found decrease in aggressive behavior problems would replicate in these data. Next, main effects were tested by conducting three separate models, each including one of three predictors: (1) Maternal Hostility, (2) Intervention Status, and (3) *DRD4*. Following these analyses we examined potential 2-way interactions between these variables. In the final analysis we tested the full 3-way interaction between Maternal Hostility, Intervention Status, and *DRD4*.

Results

Preliminary Analyses

Time-Variant and Invariant Maternal Hostility

Using methods described by Curran and Bauer (2011), we took advantage of the repeated measures afforded by the PROSPER study to separate the time-variant and invariant components of maternal hostility. First, there was a significant linear increase in maternal hostility across time ($b = .034$, $p < .01$). Case-wise regression models ($N = 580$ regressions with a sample size of $N = 5$ each) were conducted using mean-centered Age as a predictor of Maternal Hostility. The intercepts in the resulting regression models represent mean maternal hostility across the five assessments for each family. The residuals from these regression models represent within-person variability in maternal hostility over time, after removing the person-specific slopes. Individual intercept coefficients and unstandardized residuals were retained from these regression analyses and used as the time-invariant between-person effect and time-varying within-person effect, respectively. Because the main focus of this inquiry was

the individual differences in systematic developmental change in aggressive behavior problems, as opposed to aggression lability, we concentrated primarily on the time-invariant effect of maternal hostility. In all growth models, however, time-varying maternal hostility was included as a random effect covariate to examine the effect of general maternal hostility net of longitudinal lability.

Baseline Analysis of Intervention Effects on Adolescent Aggressive Behavior Problems

To contextualize the growth curve analyses, we first examined mean level differences in aggressive behavior problems at Wave 5 between participants in the intervention and control. An ANCOVA was conducted using intervention as the only predictor and Wave 1 aggressive behavior problems as a covariate. Results showed no effect of the intervention on Wave 5 aggressive behavior problems ($F < 1.0$, *ns*). This lack of association suggests the importance of examining factors that potentiate intervention effectiveness.

Unconditional Growth Model of Early Adolescent Aggressive Behavior Problems

Prior to testing hypotheses, overall change and variance in growth curves were assessed with a growth model including Age as the only predictor. Consistent with prior research, aggressive behavior problems significantly declined during early- to mid-adolescence, ($b = -.057$, $p < .001$). Furthermore, there was significant variance in aggressive behavior growth curves ($\zeta_{1i} = .029$, $p < .001$) suggesting fixed effects can be added to explain this variability.

Primary Analyses

Developmental Differences in Aggressive Behavior Problems for Maternal Hostility, Intervention Status, and DRD4

Fixed effects for Maternal Hostility, Intervention, and *DRD4* were tested in three separate growth models. Note that all analyses that include Maternal Hostility as a fixed effect also include the time-varying Maternal Hostility as a covariate. Results revealed no significant main effects (Maternal Hostility: $b = .011$, *ns*; Intervention: $b = .008$, *ns*; *DRD4*: $b = -.003$, *ns*). Results for Maternal Hostility and *DRD4* were identical when including Intervention Status as a covariate in these models. However, time-varying Maternal Hostility was associated with adolescent aggressive behavior problems ($b = .104$, $p < .001$) and indicates variability in adolescent aggressive behavior problems is paralleled by lability in Maternal Hostility across early- to mid-adolescence.

Two-Way Interactions Between Factors

One possible reason for the above reported null fixed effects may be that the average effects of the predictors on early adolescent aggression growth curves are conditioned by the other variables. To investigate this supposition, three additional analyses were conducted, each adding a different 2-way interaction term. In the first analysis, the product of (or "the interaction between") Maternal Hostility and *DRD4* was included in the model. The second analysis included the interaction between Intervention status and *DRD4*. The third analysis included the interaction between Maternal Hostility and Intervention. Results showed that the *DRD4* genotype did not moderate Maternal Hostility ($b = .008$, *ns*). Further, *DRD4* also failed to moderate Intervention Status on aggression growth curves ($b = -.017$, *ns*). In contrast, the effect of maternal hostility on growth in aggressive behavior problems was significantly moderated by intervention status ($b = -.074$, $p < .001$), consistent with our hypotheses.

Table 2 provides intercept and slope coefficients for follow-up simple effects analyses investigating the Maternal Hostility by Intervention interaction. Among control group adolescents, aggressive behavior problems from early- to mid-adolescence decreased at low (−1 SD; $b = -.116$) and moderate (Mean; $b = -.060$) maternal hostility, but showed no change at high levels of maternal hostility (+1 SD; $b = -.005$; see Fig. 1a). Regions of Significance (RoS; Roisman et al. 2012) tests were conducted and are displayed in Table 3. Results showed that growth in aggressive behavior problems among control adolescents was significant when maternal hostility was below +.49 SD's and above +2.68 SD's. Within the intervention (Fig. 1b), adolescent aggressive behavior problems decreased when maternal hostility was −1 SD and higher (see Table 3); the greatest decline was observed among intervention youth with highly hostile mothers ($b = -.071$) who also differed from adolescents with similarly hostile mothers in the control ($b = -.066$, $p < .05$). Unexpectedly, growth curves differed between intervention and control at low maternal hostility ($b = -.082$, $p < .05$). However, a RoS test indicated that differences between these groups were predicted beyond the range of the current data (i.e. >18 years). Confirming this finding, cross-sectional analysis showed no significant mean differences in aggressive behavior between adolescents in the intervention or control conditions at any assessment wave when at low maternal hostility (all p's > .28). Lastly, adolescents exposed to low maternal hostility were lower in aggressive behavior problems averaged across waves ($M = -.53$, $SD = .51$) compared to adolescents exposed to moderate and high maternal hostility [$M = .09$, $SD = .91$; $t(578) = 6.00$, $p < .05$].

Table 2 Aggressive behavior problems slope and intercept coefficients for the 2- and 3-way interactions

Maternal hostility		2-Way interaction		3-Way interaction			
		Intervention status		*DRD4* 7−		*DRD4* 7+	
		Control	Intervention	Control	Intervention	Control	Intervention
Low	S	−.116***	−.034*	−.087*	−.045*	−.165***	−.017
	(I)	(−.102)	(−.310)***	(−.177)	(−.317)**	(.011)	(.300)*
Moderate	S	−.060***	−.052***	−.061*	−.049**	−.053*	−.061**
	(I)	(.131)*	(.163)**	(.065)	(.152)*	(.244)*	(.187)*
High	S	−.005	−.071***	−.035	−.054*	.059	−.105***
	(I)	(.365)***	(.637)***	(.307)**	(.621)***	(.478)**	(.671)***

2-Way interaction: maternal hostility by intervention status; 3-way interaction: maternal hostility by intervention status by *DRD4* 7-repeat genotype; S = aggressive behavior problems slope, I = aggressive behavior problems intercept

* $p < .05$; ** $p < .01$; *** $p < .001$

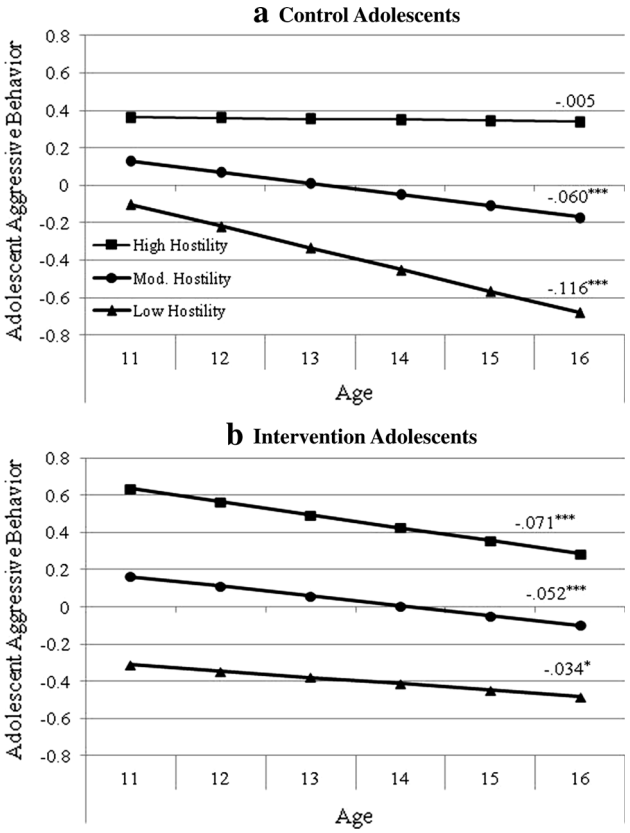

Fig. 1 Effect of maternal hostility and intervention status on adolescent development of aggressive behavior problems. Mod. hostility is mean maternal hostility. *$p < .05$; **$p < .01$; $p < .001$

Table 3 Regions of significance for aggressive behavior problems across levels of maternal hostility

Panel	Maternal hostility boundaries		Region of significance
	Lower	Upper	
Figure 1			
A (control)	.49	2.68	Outside
B (intervention)	−.98	7.37	Inside
Figure 2			
A (control, 7−)	−4.23	.64	Inside
B (control, 7+)	.03	1.20	Outside
C (intervention, 7−)	−1.07	1.48	Inside
D (intervention, 7+)	−24.67	−.39	Outside

Region of significance denotes significant developmental change in aggressive behavior problems across levels of maternal hostility. Slopes for aggressive behavior problems are significant either *outside* or *inside* the upper and lower boundaries. Boundaries are in sample *SD* units of maternal hostility

Three-Way Interaction Between Maternal Hostility, Intervention Status, and DRD4 on Developmental Change in Aggressive Behavior Problems

The above analysis revealed that intervention participation moderated the association between maternal hostility and change in aggressive behavior problems. An additional question, however, is whether this association is further conditioned by variation in the *DRD4* 7-repeat allele. To test this hypothesis, a product term of Maternal Hostility, Intervention Status, and *DRD4* genotype was added to the analysis. This 3-way interaction was statistically significant ($b = -.125$, $p < .01$).

Follow-up analyses for the 3-way interaction are depicted in Fig. 2. For 7− adolescents in the control condition (Fig. 2a), aggressive behavior problems declined significantly at low ($b = -.087$) and moderate ($b = -.061$) maternal hostility, but not at high maternal hostility ($b = -.035$, *ns*; see Table 2 for RoS). Among 7+ adolescents in the control condition (Fig. 2b), aggressive behavior problems significantly declined among adolescents at low ($b = -.165$) and moderate ($b = -.053$) maternal hostility. Although the increasing rate of

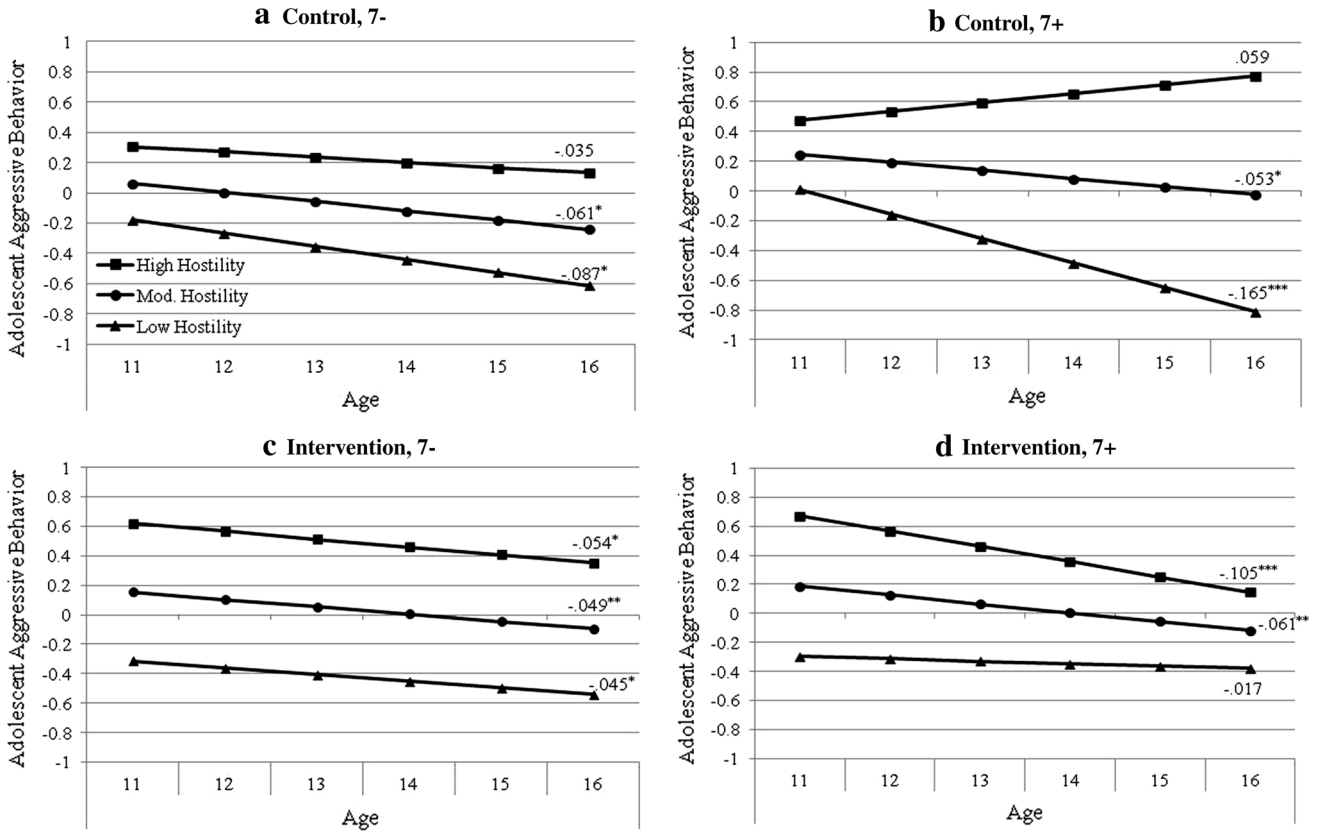

Fig. 2 Effects of maternal hostility, intervention status, and *DRD4* on developmental change in adolescent aggressive behavior problems. *$p < .05$; **$p < .01$; ***$p < .001$. Mod. hostility is mean maternal hostility

aggressive behavior problems was not significant for adolescents at +1 SD as plotted (high hostility), the RoS test indicated that aggressive behavior problems increased significantly at +1.20 SD's and above (see Table 3). Among adolescents included in this study, 13 % ($n = 75$) had a mother whose hostility was within this range. For adolescents in the control group with highly hostile mothers, rates of change were significantly different across genotypes (control 7− vs. control 7+ with high maternal hostility, $b = .093$, $p < .05$). No difference was found between genotypes at moderate maternal hostility ($b = .008$, *ns*). Notably, among adolescents with low hostile mothers, aggressive behavior problems declined at nearly twice the rate for 7+ compared to 7− adolescents ($b = -.165$ vs. $b = -.087$). This difference was marginally significant ($b = -.078$, $p < .10$).

Turning to the intervention, 7− adolescents, on average, showed significant decline in aggressive behavior problems irrespective of maternal hostility (Fig. 2c; see Table 3). Tests comparing intervention and control growth curves within 7− adolescents showed no significant differences at low, moderate, or high maternal hostility (difference in slope, $b = -.042$, $-.012$, $.019$, respectively). Thus, although 7− adolescents in the intervention showed significant declines in aggressive behavior problems even at high hostility—7− control adolescents did not (Fig. 2a)—these differences between intervention versus control were not significant. In contrast, differences were found between intervention and control for 7+ youth (see Table 3). In particular, 7+ adolescents at high maternal hostility showed a decline in aggressive behavior problems ($b = -.105$; Fig. 2d) that was significantly different from the increasing aggressive behavior problems found in control 7+ adolescents (difference in slopes, $b = .163$, $p < .01$). No other differences were found (see Table 2).

Supplemental Analyses

Additional analyses were conducted to test potential differences by sex and to explore possible population stratification. First, in separate unconditional growth models, aggressive behavior problems declined for both boys ($b = -.073$, $p < .05$; $n = 262$) and girls ($b = -.044$, $p < .05$; $n = 318$). The difference in these slopes was not significant in a follow-up analysis, however ($b = .029$, *ns*). Sex was also added to the final 3-way interaction model described above and used to predict both the intercept and

slope. The coefficient for the 3-way interaction was essentially unchanged ($b = -.126$, $p < .05$). Lastly, cross-sectional t tests (results not shown) within the control and intervention groups comparing boys and girls indicated that although aggression was consistently higher among boys at each wave, significant differences were not detected.

In molecular genetic studies, population stratification may confound G-E associations due to allele frequency differences across populations and *DRD4* 7-repeat effects may differ by ethnicity (see Propper et al. 2007). Several steps were undertaken to consider and account for possible stratification confounds. First, principal coordinates (PC) analysis was conducted on approximately 41,000 polymorphic SNPs to assess genetic variability due to geographical ancestry and admixture. In short, we were able to extract a factor (PC1) that represented variation in European ancestry, whereby higher values indicated more non-European genetic ancestry. Further, PC1 was used to categorize participants with and without substantial non-European genetic ancestry (see Cleveland et al. in press). When PC1 was added as a covariate, the coefficient for the 3-way interaction slightly increased ($b = -.133$, $p < .05$). In addition, when genetic non-Europeans were excluded ($n = 56$), the coefficient remained statistically significant although somewhat smaller ($b = -.109$, $p < .05$ vs. $b = -.125$, $p < .05$). Similar results were found when self-reported non-Europeans were omitted from the analysis ($b = -.105$, $p < .05$). Taken together, these results indicate that the findings in this study were not due to population stratification.

In addition, we explored the possibility that the primary findings might be explained by intervention effects on either substance use or maternal hostility. Because the intervention primarily targets substance use, it was important to examine whether the findings reported above were independent of potential changes in substance use. To test this proposition, three items measuring substance use (have you ever been drunk, have you ever smoked marijuana, and have you ever used hard drugs or medications that were prescribed by a doctor to someone else; 0 = No, 1 = Yes), were summed for each of the five assessments. Five regression models where conducted within each wave using substance use to predict adolescent aggressive behavior problems. Unstandardized residuals were saved from each model. These residuals represent aggressive behavior problems after controlling for substance use at each wave and growth models were estimated using residualized aggressive behavior problems. Result showed that the 3-way interaction remained significant ($b = -.025$, $p < .05$). Note, however, that since the scale of the dependent variable—and as a result the scale of the b-weights—is different due to residualizing, the value of this coefficient and the coefficient reported in the primary analyses are not directly comparable. However, further inspection of simple effects showed that the pattern of results was similar to that described in the primary analyses.

Lastly, differences between intervention and control groups in aggressive behavior problems might be due, at least in part, to changes in Maternal Hostility by the Intervention. However, a Maternal Hostility growth model including Intervention as the only fixed effect showed no differences in growth between control and intervention groups ($b = -.006$, *ns*). This result suggests the intervention effect was not mediated by changes in maternal hostility; rather intervention efficacy differed for adolescents, at least in part, by maternal hostility severity (i.e. moderation), the level of which was unaffected by Intervention status. In addition, comparing Fig. 2b with Fig. 2d reveals a somewhat higher intercept for intervention adolescents at high maternal hostility (.67) compared to similar adolescents in the control condition (.48) and could plausibly explain the difference in these two slopes. However, the intercept difference was not statistically significant in the multilevel growth model ($b = .19$, *ns*). Further, individual intercepts and slopes for each participant were exported from the unconditional growth model for cross-sectional analysis. Regression results showed a significant difference between control and intervention slopes for 7+ adolescents at high maternal hostility ($n = 32$) controlling for intercepts ($\beta = -.32$, $p < .05$).

Discussion

Aggressive behavior problems during adolescence and young adulthood present a significant problem for the health and well-being of members of this age group including persistent risk of disability and mortality (CDC 2012a, 2014). Interventions aimed at reducing aggressive behavior problems during early adolescence have the potential to reduce long-term developmental pathways toward later problems such as poor self-control and intimate partner violence (Kokko et al. 2009; O'Donnell et al. 2006). Cross-sectional research suggests that maternal hostility influences adolescent aggressive behavior problems (e.g., Burt et al. 2006). However, little research specifically examines developmental change in aggressive behavior problems (as opposed to more general externalizing), its association with maternal hostility, and factors related to reducing, or exasperating, this association. In this study, we examined the association between maternal hostility and growth in aggressive behavior problems during early- to mid-adolescence and tested the effectiveness of an intervention at reducing the negative effect of maternal hostility. In addition, drawing on prior genetic

research, we tested the hypothesis that adolescents with the *DRD4* 7-repeat would be more affected by both the intervention and maternal hostility than adolescents without the 7-repeat allele. Additional analyses were conducted to test the robustness of our findings including gender differences and controls for population stratification.

Results of this study showed that neither maternal hostility, intervention status, nor the *DRD4* 7-repeat allele was associated with developmental changes in aggressive behavior problems when considered alone. When considered together, however, coactive associations on adolescent aggressive behavior problems were found. Specifically, the intervention moderated the association between maternal hostility and aggressive behavior problems. Adolescents in the intervention appeared less impacted by high levels of maternal hostility compared to similar adolescents in the control condition. This difference was evidenced by the decline from early- to mid-adolescence in aggressive behavior problems found among intervention adolescents that were not mirrored among adolescents in the control condition.

A second important finding was that *DRD4* variation conditioned how maternal hostility and the intervention worked together to impact aggressive behavior problems. Adolescents who carry the 7-repeat allele within the control condition showed *increasing* aggressive behavior problems if they were exposed to high maternal hostility. In fact, these adolescents were the only group who showed an increase in aggressive behavior problems. These adolescents differed significantly from 7− youth in the control condition who had similarly hostile mothers. Perhaps most importantly, although 7+ youth in the control condition with highly hostile mothers showed increasing aggressive behavior problems, similar 7+ adolescents in the intervention condition showed significant *decline* in aggressive behavior problems. Additional analyses indicated that the difference in these slopes was not an artifact of population stratification or baseline differences in aggressive behavior problems.

Related to this latter point, the steepest decline in aggressive behavior occurred among 7+ adolescents in the control condition with mothers low on hostility, although similar youth in the intervention showed no significant decline. Although this finding may seem at odds with what might be expected, our follow-up analyses suggested these differences are a modeling artifact since they were predicted to occur beyond the range of the current data (i.e. >age 18). Indeed, cross-sectional analyses showed no group differences within our data (age 11–16). It is unclear whether these predicted differences would be reflected in data that extend beyond age 16 and therefore should be the subject of future research.

Lastly, two important points should be noted about separating time-varying and time-invariant aspects of maternal hostility in this study. First, our results indicated that lability in maternal hostility parallels adolescent aggressive behavior problems; however, the direction of effects (hostility causes aggression or aggression causes hostility) could not be empirically evaluated. Maternal hostility liability should be the subject of future research as a determinant (or consequence) of adolescent aggressive behavior. Second, findings for the fixed effects of maternal hostility are net of cross-time lability, lending evidence for the robustness of these findings.

One implication for prevention research is that even though PROSPER was not primarily designed to influence aggressive behavior, the PROSPER intervention moderated the association between maternal hostility and aggressive behavior problems. This finding suggests that evidence-based interventions that effect how adolescents negotiate life choices and peer relationships can positively effect a wide range of life outcomes, consistent with the PROSPER team's prior research (Spoth et al. 2000). It also is possible, however, that decreased levels of substance use due to the intervention affected aggressive behavior problems since: (1) substance use and aggressive behavior problems tend to be correlated, and (2) the intervention was primarily designed to reduce substance use. For example, self-regulatory failure associated with alcohol consumption has been linked to adolescent dating violence (e.g., Foshee et al. 2014). Feelings of anger that might result from otherwise minor interpersonal squabbles may lead to violence in adolescents (and adults) with impaired self-regulation due to alcohol consumption. Our inspection of substance use as a possible mediator suggested, however, these findings are independent of substance use during early- to mid-adolescence. However, this question should be formally tested in future research.

Critiques of cGxE Research and the Current Findings

This study also adds to the growing body of research on intervention efficacy in the context of genetic moderation. Our results suggest that the intervention may be effective at modifying long-term developmental change in aggressive behavior problems, particularly for 7+ youth who were at most risk due to high maternal hostility. Despite these promising results, it should be noted that cGxE studies have been the subject of criticism due, in part, to replication problems of primarily two studies (Caspi et al. 2002, 2003; see Munafò et al. 2009; Risch et al. 2009). There has been active debate about this criticism, however. For example, several publications have called this criticism into question on methodological (Rutter et al. 2009) and theoretical (Uher 2009) grounds; other studies have found the findings in question reliable (e.g., Byrd and Manuck 2014; Karg et al. 2011). In contrast, others have

generalized the criticism as a reflection of all cGxE research (e.g., Duncan et al. 2014). We note that although the present study had a modest sample size for some between group comparisons, the pattern of results was generally consistent with theoretical expectations and previous empirical research. Specifically, several studies have demonstrated that *DRD4* moderates effects of parenting (Bakermans-Kranenburg and van IJzendoorn 2007; van IJzendoorn and Bakermans-Kranenburg 2006), interventions (e.g., Brody et al. 2013b), and their combination (Cleveland et al. in press). Moreover, randomized controlled trials present a powerful method for studying cGxE by ruling out self-selection into the intervention. PROSPER's randomized prevention design supports causal interpretation that the intervention reduced the combined risks linked to adolescents carrying the *DRD4* 7-repeat allele and experiencing maternal hostility. The randomized design is also important in reducing Type II errors, as randomization substantially increases statistical power to detect moderation (McClelland and Judd 1993). Additional power to detect effects in the context of multilevel growth modeling also was provided by PROSPER's within-person longitudinal design (Singer and Willett 2005). Lastly, our well-measured constructs may help increase power to a greater extent than would increasing sample size (Manchia et al. 2013). These strengths provide additional confidence that our findings are not unique to these data and suggest that the generalization that all cGxE research is unreliable (an extreme view) is not justified.

In addition, there has been increased emphasis on better characterizing statistical interactions in GxE research (Reiss et al. 2013; Roisman et al. 2012). In conjunction with region of significance tests, increased attention has been given to explaining the form of the interaction more precisely (Reiss et al. 2013). For example, moderators and outcomes that range from negative to positive allow for interactions that conform to a differential susceptibility pattern (Ellis et al. 2011); however, a reading of this literature reveals that measures used in many studies referencing differential susceptibility theory do not necessarily encompass this range. Relevant to the current report, the absence of aggression does not equate to healthy adjustment. Likewise, lack of maternal hostility does not equate to warm parenting. Nor does inclusion in the control group mean exposure to adversity. As a result, the current findings should not be interpreted as support for differential susceptibility, per se. Nonetheless, these results do suggest an inherited sensitivity (Reiss et al. 2013) to the combined influence of maternal hostility and preventive intervention in altering developmental change in aggressive behavior problems in connection with the *DRD4* 7-repeat allelic variation. Measures and samples that more fully capture the range of positive and negative experiences and behaviors are needed in future studies before rendering conclusions about differential susceptibility.

Lastly, in the current study, we chose to examine the *DRD4* VNTR because this gene is well characterized biologically and showed replication evidence in studies that used measures similar to ours (Bakermans-Kranenburg and van IJzendoorn 2006; Bakermans-Kranenburg et al. 2008a, b; Brody et al. 2013a). However, this choice introduces a potential study limitation by using a single candidate gene. A few recent studies have addressed this critique by utilizing gene-scores and aggregating several candidate genes into a genetic risk score (GRS). The basis of choosing which genes to include in a GRS is not well established, however, and researchers rely on a variety of different methods to combine markers such as aggregating based on meta-analyses (Belsky et al. 2013), putative susceptibility markers, (Belsky and Beaver 2011), biolgical risk (Kotte et al. 2013), or neurotransmitter functioning (Nikolova et al. 2011). A strength of candidate gene studies is their greater specificity regarding potential genetic functioning, especially when considered across multiple studies such as in meta-analyses (e.g., Bakermans-Kranenburg and van IJzendoorn 2011).

Strengths, Limitations, and Future Directions

This study has several notable strengths. First, these findings were made possible by the longitudinal measures in the PROSPER study and we were able take advantage of growth modeling that grants additional power over cross-sectional designs (Singer and Willett 2005). Second, the analyses focused on aggressive behavior problems, rather than externalizing behaviors, as in prior studies. Lastly, the randomized intervention provides an environmental context that avoids the rGE cofound within much cGxE research (see Brody et al. 2013b). These strengths made it possible to provide new insight into the combined impact of parenting, intervention experiences, and genetics on patterns of aggressive behavior problems during adolescence.

Although this study has several strengths, some limitations are worth pointing out. For example, we were not able to empirically determine the direction of effects between maternal hostility and adolescent aggression. We note, however, that prior research and theory suggest that this association is not unidirectional, but rather is mutually influential (e.g., Dishion et al. 1992). A second limitation was our inability to distinguish between subtypes of aggression such as proactive versus reactive. However, the distinction between proactive and reactive aggression is somewhat blurred by the fact that the two tend to be strongly correlated (Mayberry and Espelage 2007). Additional research is needed to determine if there are differences in developmental change in more specific forms of

aggressive behavior. Lastly, to maintain consistency with prior research, we used parent report of adolescent aggressive behavior problems. However, reliance on parent report, as opposed to child or teacher report, may underestimate the actual occurrence of some of these behaviors (e.g., attacks others). Additional research is needed that compares possible measurement differences in developmental change in aggression based on different reporters.

Conclusions

This study finds evidence that intervening during early adolescence can change the course of adolescent aggressive behavior problems among those at-risk due to high maternal hostility. Although parental hostility is only one of several factors that render risk for increased aggressive behavior among adolescents, parental hostility is linked with a number of other factors also associated with risk (Farrington 2005). Thus, our findings likely extend to other domains of risk for aggressive behavior problems during adolescence such as low parental monitoring (Low et al. 2012), psychological control (Murray et al. 2014), and neighborhood and socioeconomic disadvantage (Karriker-Jaffe et al. 2013).

Related to the above, these results should not be taken as evidence for a unidirectional process, beginning with maternal hostility and ending with adolescent aggressive behavior problems. Much prior research suggests that this association is mutually influential (e.g., Moilanen et al. 2014). However, our genetic sensitivity orientation implies that maternal hostility is directed from parent to child. How can our findings and the mutual influence model be resolved? Although the parent hostility-adolescent externalizing association is dyadic in nature, it is likely that our child report measure of maternal hostility captures at least a portion of this parent–adolescent process. The driver for associations found in this study may be that portion that is, in fact, directional from parent-to-child.

This study also finds evidence that intervention effectiveness is conditioned by *DRD4* 7-repeat genotype. It is important to emphasize that molecular genetic studies, including cGxE, are a relatively new endeavor in adolescent research and, more broadly, developmental science. As such, the genetic findings of this study should be interpreted as contributing to the basic science of how genes and environment work together in adolescent development. Much more work is needed before we can begin to think about actionable strategies based on the molecular genetic literature, including the findings of this study (e.g., Ellis et al. 2011). Nonetheless, this initial work is needed to lay the foundation for what will no doubt lead to new and exciting discoveries for adolescent development as methods and technologies continue to evolve.

Acknowledgments The authors would like to thank Dr. Deborah Grove and Ms. Ashley Price of the Penn State Genomics Core Facility for DNA purification and genotyping. For participant recruitment we recognize the efforts of Shirley Huck, Cathy Owen, Debra Bahr, and Anthony Connor of the Iowa State University Survey and Behavioral Research Services; Rob Schofield and Dean Stankowski of the Penn State University Survey Research Center; and Lee Carpenter, Kerry Hair, and Amanda Griffin of Penn State. Work on this paper was supported by the National Institute of Drug Abuse (Grants DA030389 and DA013709).

Author Contributions G.S. conceived the analyses, drafted the manuscript, and analyzed and interpreted the data; H.C., D.V., M.F., J.N., M.G., R.S., and C.R. conceived of the study, participated in its design and coordination, and helped draft the manuscript. All authors read and approved the final manuscript.

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