Externalizing Problem Behavior in Adolescence: Parenting Interacting with DAT1 and DRD4 Genes

Abstract

The present study extends previous gene-by-environment research through design and methodological advances and examines alternative hypotheses of diathesis stress, vantage sensitivity, and differential susceptibility. In a sample of 984 adolescents and their parents, we examined whether effects of parental support, proactive, punitive, harsh punitive, and psychological control on externalizing problem behavior are moderated by adolescents' genotype for the dopamine transporter (DAT1) or receptor D4 (DRD4) gene. Results provided evidence for main effects of parenting behavior and DRD4, and multiple interaction effects of which one survived Bonferroni correction. Adolescents carrying a long DRD4 variant were more susceptible to the effects of parental proactive control on aggression, for better and for worse. Critical considerations were made regarding the complexity of gene-by-environment research.

Introduction

Adolescence is an important transitional stage in human development, during which individuals undergo multiple physical, psychological, and social changes (Negriff & Susman, 2011). Research indicates an increase in sensation-seeking and reward responsivity in adolescence, relative to childhood and adulthood (Luciana, Wahlstrom, Porter, & Collins, 2012; Sabol et al., 1999). This is considered a normative process as long as it stimulates adolescents' independence and transition to adult roles in the society (Moffitt, 2003). However, adolescents' heightened reward sensitivity as well as punishment insensitivity manifests itself in a higher prevalence of risk-taking behaviors such as delinquency and substance use. An estimated 60% of adolescents gets involved in some kind of problem behavior (Reitz, Deković, & Meijer, 2005). In the present study, we focus on externalizing problem behavior, defined as rule-breaking and aggressive behavior which is externally directed and negatively affects people in the close environment (e.g., parents, peers, teachers) or the society as a whole (Jenson, Harward, & Bowen, 2011). In addition to immediate adverse consequences for both individual and society, adolescent externalizing problems enhance the risk of long-term consequences such as addiction, impaired family relationships, decreased educational and occupational attainment, and criminal activity into adulthood (Huesmann, Dubow, & Boxer, 2009; Reef, Diamantopoulou, van Meurs, Verhulst, & van der Ende, 2011). Although evidence supports an overall increase in risk-taking behavior in adolescence, only a minority develops behavior toward the extreme end of the externalizing continuum. Gene-by-environment (GxE) research enables to investigate whether this individual variability can be explained by the interplay

between genetic and environmental influences. Individuals carrying specific genetic variants might differ in their response to environmental influences or, likewise, the effect of genes on behavior may depend upon the environmental context. In the current study, we examine whether two well-known dopamine polymorphisms in the dopamine transporter (DAT1) and receptor D4 (DRD4) gene moderate the effects of parenting behavior (i.e., parental support, proactive, punitive, harsh punitive and psychological control) on adolescent externalizing problems.

Externalizing Behavior and Parenting Behavior as Environmental Factor

The parent-child relationship is an important context for socialization and is considered either as a protective or risk factor for externalizing problem behavior in children and adolescents (Barber, Stolz, Olsen, Collins, & Burchinal, 2005; Loeber, Slot, & Stouthamer-Loeber, 2008). Parenting behavior, the observable actions of parents towards their children, is most commonly described according to three global dimensions of support, behavioral control, and psychological control (Barber, Stolz, et al., 2005). Parental support includes parental behaviors showing affection, involvement, and responsivity to children's needs. Using behavioral control, parents attempt to influence and control their children's behavior, for example by supervising, setting rules, and punishing misbehavior. Psychological control refers to intrusive parenting behavior that restricts children's psychological and emotional development by manipulating their thoughts, emotions, and feelings (Barber, 1996). In a recent study (Janssens, Goossens, et al., 2015), we refined this well-known tripartite classification by distinguishing, next to parental support and psychological control, three aspects of behavioral control, that is, (a) proactive control, including rule setting and monitoring, (b) punitive control, including non-physical punishments like verbal disapproval or behavioral restrictions, and (c) harsh punitive control, including spanking and other physical punishments.

Parental support and proactive control have been consistently linked to positive child and adolescent development, like prosocial behavior, empathy, and academic competence (e.g., Gray & Steinberg, 1999; Wang, Pomerantz, & Chen, 2007), and also to the absence of problem behavior (e.g., Galambos, Barker, & Almeida, 2003; Pettit, Laird, Dodge, Bates, & Criss, 2001). On the other hand, punitive, harsh punitive and psychological control have been repeatedly associated with both externalizing and internalizing problem behavior (e.g., Bender et al., 2007; Rogers, Buchanan, & Winchell, 2003).

Externalizing Behavior and Dopaminergic VNTRs as Genetic Factors

Externalizing problem behavior has been linked to dopaminergic neurotransmission in the human brain through its involvement in reward-based learning and motivation (Matthys, Vanderschuren, & Schutter, 2013).

Low dopamine activity is thought to be associated with reduced reward sensitivity and under-stimulation by normal rewards. To compensate for the unpleasant state of understimulation, adolescents engage in excessive sensation seeking, which leads to externalizing problem behavior.

Polymorphisms (i.e., multiple variants or alleles at a certain genetic locus) in dopaminergic genes affect the functionality and availability of dopamine in the human brain, resulting in interpersonal differences in neurological reactivity to rewards. The present study focuses on two dopaminergic polymorphisms commonly examined in relation to externalizing behavior, that is, the 40 base pair (bp) variable number tandem repeat (VNTR) in the dopamine transporter (DAT1) gene and the 48 bp VNTR in the dopamine receptor D4 (DRD4) gene. A VNTR is a location in the genome where a short sequence of basic units is repeated a different number of times in different individuals (Haddley et al., 2008).

Dopamine transporter (DAT1) gene. The 40 bp DAT1 VNTR is located in the 3' untranslated region (UTR) of the DAT1 gene. The number of repeats ranges from 3 to 13 copies with the 10-repeat (10R) and 9-repeat (9R) polymorphisms being the two most common alleles in most human populations (Mitchell et al., 2000). There is evidence suggesting the functionality of this VNTR (see Haddley et al., 2008, for a review), with studies indicating more DAT protein availability (e.g., Heinz et al., 2000) and lower binding potential in 10R homozygotes (e.g., Jacobsen et al., 2000). Further, the presence of the 10R allele was correlated with increased levels of DAT1 expression in post-mortem brain tissue (e.g., Brookes et al., 2007; Mill, Asherson, Browes, D'Souza, & Craig, 2002). Higher levels of gene expression seem to promote more DAT protein production, which may result in more effective reuptake of dopamine and eventually in reduced dopamine transmission in the brain (Dreher, Kohn, Kolachana, Weinberger, & Berman, 2009).

Carrying the DAT1 10R allele is considered a risk allele for a wide range of behavioral disorders, such as attention deficit hyperactivity disorder (ADHD) (e.g., Gizer, Ficks, & Waldman, 2009), substance use disorders (e.g., Hopfer et al., 2005; Timberlake et al., 2006), and novelty seeking (e.g., Sabol et al., 1999). However, results are mixed whereas also non-significant (e.g., Johansson et al., 2008; Sullivan et al., 1997) and opposite findings have been reported, the latter suggesting either more problems in 9R carriers (e.g., Kohnke et al., 2005) or less problems in 10R carriers (e.g., Vandenbergh et al., 2002). An early study on externalizing behaviors showed more problems in children carrying the 9R allele (Young et al., 2002), in contrast to later studies in adolescent and adult samples that found associations with the presence of the 10R allele (e.g., Beaver, Wright, & Walsh, 2008; Blum et al., 2011; Burt & Mikolajewski, 2008; Chen et al., 2007; Guo, Roettger, & Shih, 2007; Lee et al., 2007). In line with the latter studies, individuals homozygous for the DAT1 9R were less

likely to exhibit delinquency, substance use, and not wearing a seatbelt compared to 10R carriers (Guo, Cai, Guo, Wang, & Harris, 2010).

Dopamine receptor D4 (DRD4) gene. The 48 bp DRD4 VNTR is located in exon 3, a coding region of the DRD4 gene. The number of repeats ranges from 2 to 11, with the 2-repeat (2R), 4-repeat (4R), and 7-repeat (7R) alleles as the most prevalent in human populations (Chang, Kidd, Livak, Pakstis, & Kidd, 1996). Neurobiological research provided evidence for the functionality of this polymorphism (see Ebstein, 2006, for a review). Studies have linked the longer 7R allele to suppressed gene expression (e.g., Schoots & Van Tol, 2003) and ability to transmit signal information (e.g., Asghari et al., 1995) compared to shorter 2R and 4R alleles. Although results of individual studies are mixed, review studies and meta-analyses suggest that individuals carrying longer variants of the DRD4 VNTR, and especially the 7R allele, show more behavioral disorders like ADHD (e.g., Gizer et al., 2009), substance abuse (see Le Foll, Gallo, Le Strat, Lu, & Gorwood, 2009, for a review), and novelty seeking (e.g., Kluger, Siegfried, & Ebstein, 2002). With regard to externalizing problem behavior, the presence of the 7R or longer DRD4 allele has been associated with more aggression in four-year-olds (Schmidt, Fox, Rubin, Hu, & Hamer, 2002), more externalizing behavior in adolescents (Hohmann et al., 2009), and higher delinquency, short temper, and thrill seeking in adult males (Dmitrieva, Chen, Greenberger, Ogunseitan, & Ding, 2011).

Externalizing Behavior and the Interaction of Parenting and Dopaminergic VNTRs

In many studies the link between externalizing problems and parenting or dopaminergic genes has been investigated separately, but recently, there is a growing body of candidate gene-by-environment interaction (GxE) studies showing that adolescents' genotype plays a role in modifying how they perceive or respond to parenting behaviors. Different hypotheses have been formulated according to which genetic moderation of environmental effects can occur. The most well-known hypotheses are diathesis stress, vantage sensitivity, and differential susceptibility (see Pluess & Belsky, 2013). The classic dual-risk or *diathesis-stress hypothesis* (see Figure 1a), which has largely inspired early GxE research, associates problem behaviors with the combination of both genetic and environmental risk. Therefore, individuals carrying a specific genetic variant (further called carriers) are more vulnerable to environmental adversity than non-carriers, whereas there will be no difference in the absence of adversity. In contrast, the *vantage sensitivity hypothesis* (see Figure 1b) focusses on the beneficial effect of genes by suggesting that carriers are more sensitive than non-carriers to positive, but not negative environmental influences. Both perspectives are combined in the *differential susceptibility hypothesis* (see Figure 1c). According to this developmental theory, carriers are more susceptible to all environmental

influences for better and for worse (Belsky, 2005). This means that adolescents' genotype related to increased risk for externalizing problems when growing up in a low-quality parenting environment may also be associated with positive adjustment when experiencing high-quality parenting.

Only a handful of studies have investigated GxE effects of the DAT1 VNTR and parenting behavior on externalizing behavior. Two studies on children with ADHD showed 9-repeat carriers to be more susceptible to the quality of parental expressed emotion (Sonuga-Barke et al., 2009) and observed maternal parenting (Lahey et al., 2011), resulting in more or less conduct problems. In contrast, a recent study on adolescent serious delinquency shows 10-repeat carriers to be more susceptible to the effect of family closeness (Boardman et al., 2014). Multiple studies have examined DRD4-by-parenting interactions that may affect externalizing behavior. Together, these studies seem to support the hypothesis of differential susceptibility suggesting that children with the DRD4 long or 7-repeat allele are more susceptible to both low and high quality parenting (Bakermans-Kranenburg & van IJzendoorn, 2011). When experiencing low quality parenting (i.e., maternal insensitivity), preschoolers and young children with the DRD4 long or 7R allele, show more oppositional and aggressive behavior (Bakermans-Kranenburg & van IJzendoorn, 2006), more sensation seeking (Sheese, Voelker, Rothbart, & Posner, 2007), and more externalizing problems (DiLalla, Elam, & Smolen, 2009), compared to carriers of other variants. When experiencing high quality parenting (i.e., secure attachment, maternal sensitivity, positive discipline, maternal positivity), children with the DRD4 long or 7R allele show less externalizing problems (Bakermans-Kranenburg, van IJzendoorn, Pijlman, Mesman, & Juffer, 2008) and more prosocial behavior (Bakermans-Kranenburg & van IJzendoorn, 2011; Knafo, Israel, & Ebstein, 2011). A recent study confirmed the differential susceptibility hypothesis with regard to adolescent aggression. Adolescents with the DRD4 7R allele were more negatively affected by maternal hostility and more positively by intervention efforts than non-carriers (Schlomer, Cleveland, Vandenbergh, Feinberg, et al., 2015). However, another study found a decrease in externalizing behavior when experiencing warm-responsive parenting in children with the short DRD4 variant (i.e., 2-6 repeats), instead of the longer 7R variant (Propper, Willoughby, Halpern, Carbone, & Cox, 2007). A more recent study was unable to replicate the interaction effect with the DRD4 7R, but its findings did indicate a protective effect of the 4R allele (Marsman, Oldehinkel, Ormel, & Buitelaar, 2013). Adolescents with the 4R allele who experienced parental overprotection showed less externalizing problem behavior compared to adolescents without the 4R allele.

The Present Study

Based on our literature review, we can conclude that there are many inconsistent findings, failures to replicate, and unexplored research questions. The current ambiguity of results may be related to heterogeneity in design or methodological issues. Concerning design, this pertains to heterogeneity in the externalizing problem behaviors assessed (which may comprise oppositional behavior, delinquency, substance abuse, and hyperactivity), diversity in the age periods examined (which range from childhood to adulthood), and heterogeneity in the parenting concepts used (for example, secure attachment, parental sensitivity, maltreatment, and overprotection). Methodological issues include small sample size, with most earlier samples being underpowered (Duncan & Keller, 2011), the use of different informants (e.g., mothers vs. children), adopting a diathesis stress hypothesis without considering other GxE interpretations, and various statistical problems (e.g., failures to correct for multiple testing and gene-environment correlation or to check for population stratification) (Duncan & Keller, 2011).

The present study aimed to extend previous GxE research by making informed design choices and by incorporating methodological advances. At the design level, we took into account the heterogeneity in externalizing behavior by differentiating subtypes of rule-breaking and aggressive behavior. We focused on adolescence, an important developmental period for externalizing problems (Reitz et al., 2005). In addition, we adopted a comprehensive five-dimensional structure of parenting, including support, psychological control, and three aspects of behavioral control (i.e., proactive, punitive, and harsh punitive control) (Janssens, Goossens, et al., 2015). At the methodology level, we used a large sample of approximately 1,000 adolescents to have sufficient statistical power to find even relatively small gene-environment interactions. We also used multiple informants (i.e., adolescents, mothers, and fathers) for all study variables. Finally, statistical issues and alternative GxE hypotheses which are often neglected in previous GxE research were addressed.

We tested three different hypotheses on the genetic moderation of parenting effects on externalizing problem behavior: diathesis stress, vantage sensitivity, and differential susceptibility (see Pluess & Belsky, 2013). Because most neurobiological and behavioral genetic evidence suggests altered dopamine functioning, increased prevalence of behavior problems, and increased environmental sensitivity for the DAT1 10R allele and the DRD4 long variant, we expect the effects of different parenting dimensions to be larger for adolescents carrying these variants. According to a *diathesis-stress hypothesis* (see Figure 1a), adolescents carrying the DAT1 10R or the DRD4 long variant would be more vulnerable to the effects of a low-quality parenting environment (i.e., low support and proactive control, or high punitive control, harsh punitive control, and

psychological control) than non-carriers. A *vantage sensitivity hypothesis* (see Figure 1b) would be supported when carriers are more sensitive than non-carriers, but only to the benefits of a high-quality parenting environment (i.e., high support and proactive control, or low punitive control, harsh punitive control, and psychological control). Finally, we would find evidence for the *differential-susceptibility hypothesis* (see Figure 1c) when adolescents carrying the DAT1 10R or the DRD4 long variant would show more externalizing behavior than non-carriers when experiencing low-quality parenting, but less externalizing behavior in case of high-quality parenting.

Method

Participants and Procedure

This study is part of the STRATEGIES project (i.e., Studying Transactions in Adolescence: Testing Genes in Interaction With Environments) conducted in Flanders, the Dutch-speaking part of Belgium. The STRATEGIES sample was drawn using a randomized multistage sampling approach. In a first step, we invited Flemish secondary schools, stratified by educational track in order to include students from general, technical, and vocational tracks. Within nine participating schools, 121 classes in Grades 7 to 9 were randomly selected. Within these classes, all students were invited to participate. During school visits, from February till June 2012, researchers assisted participating adolescents in completing questionnaires and donating a saliva sample. Questionnaires for parents were completed at home and returned to the researchers within the following two weeks. Parents and adolescents signed an active informed consent form and permission for the study was obtained from the Institutional Review Board of the Faculty of Medicine at the University of Leuven.

In total 1,116 out of the 2,254 invited adolescents agreed to participate (response rate of 50%). To control for shared genetic background and parental environment, we identified 58 pairs of siblings within the overall sample and in each of these cases randomly selected one sibling for inclusion. Further, we excluded 73 non-European adolescents (i.e., at least one grandparent born out of Europe) to account for population stratification, which refers to possible confounding due to genetic differences between ancestry groups. Our final sample consisted of 985 adolescents of which 51% were boys. The average age was 13.76 years (*SD* = .91), including 35%, 38%, and 27%, seventh, eighth, and ninth graders, respectively. Post-hoc power calculations in QUANTO (Gauderman & Morrison, 2006) indicated that our sample had sufficient statistical power (> 80%) to find even relatively small gene-environment interactions (R^2 = .02 to .03). Parent reports were available for 77% of the adolescents in our sample, which corresponds to 747 mothers (*M* age = 43.59, *SD* = 4.45) and 645 fathers (*M* age = 45.32, *SD* = 4.69). For most adolescents we obtained both mother and father

reports (65%), whereas only a minority was filled out only by mother (11%) or only by father (1%). Family characteristics of our sample were representative for the general population ($\chi2(2) = 2.78$, $p = .25$) with 82% two-parent families, 7% single-parent families and 11% blended families (King Baudouin Foundation, 2008). Parents' educational level and employment activity level differed for both mothers (EDU: $\chi2(3) = 30.34$, $p = .00$; ACT: $\chi2(1) = 15.87$, $p = .00$) and fathers (EDU: $\chi2(3) = 34.19$, $p = .00$; ACT: $\chi2(1) = 15.13$, $p = .00$) with a slight overrepresentation of bachelor degrees and active employees (Research Department of the Flemish Government, 2010, 2011). Although the sample is not entirely representative for the general population, it can be concluded that the participants represent all categories for socio-economic status.

Measures

Parenting behavior. Based on a psychometric study by Janssens, Goossens, et al. (2015) on the same sample, we applied a five-dimensional parenting model including parental support, proactive control, punitive control, harsh punitive control, and psychological control. These dimensions were measured by a combination of subscales derived from multiple validated questionnaires and rated by adolescents, mothers, and fathers. Internal consistency of the subscales in the current sample was satisfactory, as indicated by the Cronbach's alpha's. The *Parental support* dimension (23 items; $\alpha = .94$, .91, and .94, respectively for adolescent, mother, and father) includes the subscales Positive parenting of the Parental Behavior Scale (PBS-S: Van Leeuwen et al., 2013), Responsivity of the Louvain Adolescent Perceived Parenting Scale (LAPPS: Delhaye, Beyers, Klimstra, Linkowski, & Goossens, 2012) and Autonomy support of the Perceptions of Parents Scale (POPS: Grolnick, Ryan, & Deci, 1991) and Research Assessment Package for Schools (RAPS: Institute for Research and Reform in Education, 1998). A sample item is: "When my son/daughter has a problem, I discuss with him/her what exactly is going on". *Proactive control* rates the frequency by which parents show positive and preventive forms of control like establishing rules and limitations or supervising their adolescents' behavior (11 items; $\alpha = .84$, .86, and .85). This dimension includes the subscales Parental expectations for behavior and Parental monitoring of behavior of the Parental Regulation Scale (PRS-YSR: Barber, 2002; Soenens, Vansteenkiste, Luyckx, & Goossens, 2006). A sample item is: "I ask questions about how my son/daughter behaves outside the house". A more reactive form is *Punitive control*, such as verbal punishment, behavioral restrictions or withdrawal of privileges (4 items; $\alpha = .86$, .88, and .88), assessed by the subscale Punishment of the Parental Behavior Scale (PBS-S: Van Leeuwen et al., 2013). A sample item is: "When my son/daughter does something that he/she is not allowed to do, I punish him/her". *Harsh punitive control* refers to physical or harsh punishment, such as slapping, hitting or kicking children (5 items; $\alpha = .89$, .73, and .77), measured by the

subscale Harsh punishment of the Parental Behavior Scale (PBS-S: Van Leeuwen et al., 2013). A sample item is: "I slap my son/daughter when he/she has done something wrong". The *Psychological control* scale consists of 15 items (α = .88, .84, and .83) including the Verbal hostility scale (VHS: Nelson & Crick, 2002) and the Psychological control scale (PCS-YSR: Barber, 1996; Soenens et al., 2006), which both assess intrusive parenting behaviors that threaten the self-esteem and emotional well-being of children. A sample item is: "I make my son/daughter feel guilty when he/she has done something wrong".

Items were rated by adolescents and both parents on a 5-point scale ranging from 1 = *'(almost) never'* to 5 = *'(almost) always'*. Higher scores indicate a higher frequency of the assessed parenting behaviors. Items in the adolescent questionnaire were modified to assess their perspective on parenting behavior of both parents (i.e., "I" was replaced by "My parents").

Adolescent problem behavior. Adolescents rated their own externalizing problem behavior on the Youth Self Report (YSR; Achenbach, 1991b). The broad-band Externalizing Problems scale includes 31 items (α = .83) and can be subdivided into two small-band subscales, Rule-Breaking Behavior (14 items; α = .57; e.g., "I break rules at home, school, or elsewhere") and Aggressive Behavior (17 items; α = .80; e.g., "I fight a lot."). Parents completed the Child Behavior Checklist (CBCL; Achenbach, 1991a), which includes 35 items in the broad-band Externalizing Problems scale (α = .89), 17 items in the small-band subscale of Rule-Breaking (α = .71; e.g., "My child breaks rules at home, school or elsewhere") and 18 items in the small-band subscale of Aggressive Behavior (α = .87; e.g., "My child gets in many fights"). All items were answered on a 3-point rating scale from 0 = *'not true'*, 1 = *'somewhat or sometimes true'*, to 2 = *'very true or often true'*. Higher scores indicate the presence of more externalizing problem behaviors.

Genotyping. We obtained DNA for 99% of our sample (*n* = 972) by taking saliva samples during the first wave of data collection using Oragene DNA collection kits (DNA Genotek; Ontario, Canada). The remaining 13 adolescents were absent during saliva collection (*n* = 7), refused to donate saliva (*n* = 4), or dropped out of the study (*n* = 2). The present study examines the 40-bp VNTR in the 3' UTR of the DAT1 gene (forward primer: 5'-VIC-TGCGGTGTAGGGAACGGCCTGAG-3'; reverse primer: 5'-CTTCCTGGAGGTCACGGCTCAAGG-3') and the 48-bp VNTR in exon 3 of the DRD4 gene (forward primer: 5'-NED-GCGACTACGTGGTCTACTCG-3'; reverse primer: 5'-AGGACCCTCATGGCCTTG-3'). We performed a polymerase chain reaction (PCR) followed by a fragment analysis protocol. The amplification mixture for PCR of both VNTRs included 50 ng genomic DNA, 12.5 µl Master Mix (Promega), 0.5 µmol/l of each forward and reverse primer, 1M Betaine solution (Sigma-Aldrich), and 1.5 µl water. The cycling

conditions for the PCR started with 5 min at 95°C, followed by 35 cycles of 30 sec at 95°C, 30 sec at 60°C, and 90 sec at 72°C, afterwards followed by 7 min at 72°C. After finishing PCR, the DNA mixture was cooled down to 4°C. Fragment analysis was performed with a mix contained 0.5 µl of the PCR product, 0.5 µl GeneScan 600 LIZ Size Standard V2.0 (Applied Biosystems) and 10 µl Hi-Di formamide. After a final denaturation step at 95°C for 3 min, analysis followed on an ABI 3730xl Genetic Analyzer (Applied Biosystems). Results were printed out using the GeneMarker software Version 1.91 (SoftGenetics, 2010). Genetic information was available for 97% of our sample (1% not genotyped; 1% failed on DAT1 only; 0.8% failed on DRD4 only; 0.6% failed on both DAT1 and DRD4).

Analysis Strategy

We centered the parenting dimensions (environmental variables, further referred to as E) around their mean, separately for adolescents and parents. We created an aggregated score for the variables rated by mothers and fathers separately to reduce the potential number of analyses, by calculating the mean. Ratings of mothers and fathers correlated moderately to high (*r* ranged from .38 to .54, $p < .001$). Data from one parent was used when the other parent did not participate. Genetic information (further referred to as G) was dummy coded into carriers and non-carriers using a dominant model and based on existing neurobiological and behavioral genetic research. For the DAT1 gene, adolescents with one or two copies of the 10R allele (90%; i.e., 10R carriers) were distinguished from adolescents with two 9R alleles (8%; i.e., non-10R carriers). Adolescents with alternative genotypes were considered as missing (2%). For the DRD4 gene, adolescents with at least one 7R or longer allele (35%; i.e., long carriers) were distinguished from adolescents with both alleles shorter than 7R (65%; i.e., non-long carriers), in line with previous research (e.g., Dreber et al., 2009; Propper et al., 2007). Both VNTRs were in Hardy-Weinberg equilibrium ($p > .98$), indicating that allele and genotype frequencies of our sample were similar to what would be expected in the population. Control variables included adolescent's gender and age, and mother's highest educational degree. In addition, a gene-environment correlation (*r*GE) coefficient was included in all models, using the WITH-statement in Mplus, to account for the possible direct relation between environmental and genetic influences.

Regression analyses were used to examine conditional main effects and interaction effects of genes (i.e., DAT1 and DRD4) and parenting (i.e., support, proactive control, punitive control, harsh punitive control, and psychological control) on adolescent externalizing problem behavior (i.e., rule breaking and aggressive behavior). Model 1 included control variables, a genetic variable, and an environmental variable, after which the interaction term was added in a second step (Model 2). Analyses were performed using Mplus Version 6.1

(Muthén & Muthén, 1998-2010). Non-normality in our data was accounted for by using robust maximum likelihood estimation (MLR) and missing data by using full information maximum likelihood (FIML). One additional participant was excluded because data on all variables included in the present study were missing (i.e., total sample of 984).

For each significant interaction effect that was found, we performed four critical tests as proposed by Roisman et al. (2012). The first two critical tests evaluate the validity of the interaction effect. First, an additional model including the non-linear predictor terms E^2 and GE^2 was tested to investigate whether a significant interaction effect is not an artifact of enforcing a linear model onto a non-linear phenomenon. Second, significant effects were evaluated using a conservative Bonferroni adjusted alpha value of .001 (α/n = .05/40) to control for multiple testing of 40 different models (i.e., five parenting dimensions, two genetic polymorphisms, and two informants for environmental and outcome variables). Subtypes of externalizing problems were not counted as independent models because they were highly correlated (i.e., *r* ranges from .66 to .97). The third and fourth critical test evaluate alternative GxE hypotheses for the interactions that survived Bonferroni correction. In the third test, Regions of Significance (RoS) were calculated to examine the range of the environmental variable (E) for which the association between the gene (G) and the outcome variable is statistically significant. In the fourth and last test, we calculated the crossover point (C) and two indexes: the Proportion of Interest (PoI) which presents the proportion of the interaction represented on the left versus the right side of C, and the Proportion of Affected (PA) which presents the proportion of cases on E that fall on the left versus the right side of C. Whereas PoI is dependent upon how ranges of E are defined, PA provides a more pragmatic way for evaluation based on the raw data. The criteria for labeling an interaction as evidence for diathesis stress, vantage sensitivity, or differential susceptibility are explained in Figure 1. RoS, PoI, and PA were calculated using the web application designed by Fraley (2012).

Results

Correlations among study variables are presented in Table 1. Control variables were related to adolescent externalizing problems as expected. Boys reported more externalizing problems than girls (t (961) = 3.37, $p < .001$), especially rule-breaking behavior (t (961) = 5.89, $p < .001$). Parents also reported more externalizing problems in boys (t (742) = 4.51, $p < .001$), both aggressive (t (742) = 3.96, $p < .001$) and rule-breaking behavior (t (742) = 4.58, $p < .001$). Older adolescents reported more externalizing problem behavior (r = .10, $p < .01$), especially rule-breaking behavior (r = .16, $p < .001$). A higher degree of mothers' education was related to less adolescent-reported aggression (r = -.07, $p < .05$) and parent-reported rule-breaking behavior (r =

-.08, $p < .05$). Additional t-tests revealed that DAT1 and DRD4 were not associated with parenting behavior, suggesting the absence of a direct link between genes and environment (*r*GE).

Models 1: Conditional Main Effects

Table 2 and 3 present the standardized coefficient estimates of regression analyses including the DAT1 gene or the DRD4 respectively. In the first models (M1), we evaluated the effects of parenting controlled for the effect of genes and covariates, as well as the effect of genes controlled for the effect of environment and covariates. For parenting behavior, support negatively predicted externalizing problem behavior in adolescents (β ranges from -.20 to -.37, $p < .001$), whereas punitive control (β ranges from .08 to .17, $p < .05$), harsh punitive control (β ranges from .24 to .39, $p < .001$), and psychological control (β ranges from .19 to .50, $p < .001$) were positive predictors. These results were present for all informants and for both rule-breaking and aggressive subtypes of externalizing behavior. For proactive control, only parent-report negatively predicted externalizing problems reported by adolescents ($\beta = -.08$, $p < .05$). When differentiating between subtypes, associations were significant for aggressive ($\beta = -.08$, $p < .05$) and marginally significant for rule-breaking behavior ($\beta = -.07$, $p < .10$).

With regard to the effects of genes above environmental influences, DRD4 only predicted parent-reported externalizing behavior (β ranges from -.07 to -.08, $p < .05$), more specifically aggressive behavior (β ranges from -.07 to -.08, $p < .05$). Adolescents carrying at least one long DRD4 allele (i.e., 7R or longer) showed less externalizing and aggressive behavior than adolescents who did not carry a long DRD4 allele. The association between DRD4 and externalizing problem behavior did not reach significance in models including parent-reported punitive control, parent-reported harsh punitive control, and proactive control reported by both adolescent and parents.

Models 2: Interaction Effects

Adding interaction terms to the models resulted into multiple significant findings (see M2 in Table 2 and 3). We found a significant interaction effect of the DAT1 gene and adolescent-reported support on adolescent ($\beta = -.28$, $p < .05$) and parent-reported externalizing problems ($\beta = -.29$, $p < .05$). When differentiating externalizing subtypes, there was a significant interaction for aggressive behavior ($\beta = -.27$ and -.28, $p < .05$), but not rule breaking behavior. Another significant interaction was present between the DAT1 gene and parent-reported punitive control in relation to adolescent-reported rule breaking behavior ($\beta = .21$, $p < .05$). Further, DAT1-by-parent-reported harsh punitive control significantly predicted adolescent-reported externalizing problems ($\beta = .20$, $p < .05$), and more specifically aggressive behavior ($\beta = .26$, $p < .05$). Finally,

adolescent-reported psychological control interacted with the DAT1 gene predicting adolescent-reported externalizing (β = .27, p < .05) and aggressive behavior (β = .29, p < .05).

For the DRD4 gene, we found an interaction effect with adolescent-reported support on parent-reported externalizing problems (β = .11, p < .05), more specifically rule-breaking behavior (β = .11, p < .05). Further, we observed significant interaction effects between DRD4 and parent-reported proactive control on parent-reported externalizing behavior (β = -.13, p < .01), more specifically aggressive behavior (β = -.14, p < .001).

Critical Tests on Significant Interaction Effects

To further evaluate the validity of the significant interaction effects, four critical tests were sequentially performed (Roisman et al., 2012). First, an additional model including the non-linear terms E^2 and GE^2 was tested for each significant interaction effect. These terms were non-significant in all models (p > .05), which indicated that the interaction effects were not the result of the curvilinear nature of the relation. Second, we controlled for multiple testing using a Bonferroni adjusted alpha value of .001. When applying this conservative value only 1 out of the 12 significant interaction effects were strong enough to survive, that is, the interaction between the DRD4 gene and parent-reported proactive control in relation to parent-reported aggressive behavior (β = -.14, p < .001). This interaction is presented in Figure 2 and further investigated to examine alternative GxE models. In the third test, Regions of Significance (RoS) were found on the lower (-.79) and upper bound (.00) of E (min = -2.25; max = .85). These findings indicate that the association between DRD4 and aggression behavior is significant at both sides of the interaction, supporting differential susceptibility. Also the fourth and final test supported differential susceptibility. According to the rules of thumb proposed by Roisman et al. (2012), the Proportion of Interest (PoI = left: 77%; right: 23%) was not highly consistent with differential susceptibility (between 40 and 60%), but the Proportion of Affected (PA = left: 26%; right: 74%) was higher than the threshold of 16%. These results show that the regression lines intersect within the range of environmental values observed in our sample, so that 26% of the adolescents experience less and 74% more parental proactive control than the crossover value.

Discussion

The present study examined the interplay between two dopaminergic gene variants and parenting behavior on externalizing problem behavior in a large sample of adolescents and their parents. We found significant effects of parenting behavior while controlling for genetic effects, supporting decades of research on the importance of the parent-child relationship in the development of children and adolescents (Barber, Stolz, et al., 2005). Adolescents experiencing more support and proactive control from their parents showed less

externalizing problems, whereas the opposite was true for adolescents experiencing more punitive, harsh punitive, and psychological control. Most results were consistent across parent and adolescent ratings, suggesting multi-informant agreement. Further, we found significant effects for the DRD4 gene, but not the DAT1 gene, when taking into account environmental effects. Adolescents with at least one long DRD4 allele (i.e., 7R or longer) showed less externalizing and aggressive behavior according to their parents than adolescents without a long variant. This is opposite to previous research suggesting more externalizing problems in adolescents carrying the 7R allele (Hohmann et al., 2009). However, some other studies on adolescent samples did not support this effect (e.g., Beaver et al., 2007; Marsman et al., 2013).

These conditional main effects need to be reviewed in the presence of the found gene-by-environment interactions. After applying a conservative Bonferroni correction for multiple testing, the interaction between the DRD4 and parent-reported proactive control on aggressive behavior remained significant. Further critical tests showed evidence for differential susceptibility. When experiencing higher levels of proactive control, adolescents with the long DRD4 variant (i.e. 7R or longer) showed less aggressive behavior compared to adolescents without the long variant. On the other hand, when experiencing lower levels of proactive control, adolescents with the long variant showed more aggression compared to their counterparts. These results are in line with research findings on child samples indicating that carriers of the DRD4 long or 7R allele are more susceptible to both low and high quality parenting (Bakermans-Kranenburg & van IJzendoorn, 2011). Also a recent study on adolescent aggression showed that adolescents carrying the DRD4 7R allele are more negatively affected by maternal hostility and more positively by intervention efforts than adolescents without the 7R allele (Schlomer et al., 2015).

Our results support the bio-ecological framework of human development in which biological and environmental influences are intertwined (Bronfenbrenner & Morris, 2006). A stronger awareness of this process might benefit clinicians who work with externalizing problems in adolescents. It might prevent the deterministic idea of ‘bad children’ or ‘bad parents’ and show that genetic variability can be ‘for better and for worse’. Also the effectiveness of prevention and treatment efforts, which can be seen as environmental influences, depends on the genetic make-up of the participants. Due to differences in genetic sensitivity, some adolescents may respond more positively to preventive and clinical interventions than others. Average effects will not show this variability and may therefore underestimate the efficacy of interventions (Mitchell et al., 2013). This way, genetic differences may explain why an intervention works for one adolescent and not for another.

The Complexity of Gene-Environment Research

The excitement about GxE research as a way to integrate both biological and psychological constructs in a single framework has been tempered by many inconsistent and non-replicated findings, and probably publication bias (Duncan & Keller, 2011). In the present study, we tried to overcome some of the recognized design and methodological limitations. Nevertheless, this study warrants attention to certain topics showing the complexity of gene-environment research.

Previous psychological and genetic association studies have introduced genetic variants and environmental variables that are interesting candidates for studying GxE interactions related to externalizing problem behavior. However, current knowledge is not sufficient to formulate specific hypotheses about neurobiological mechanisms involved in gene functioning and gene-by-environment interplay. Genes do not directly code for certain behaviors, but influence the neuronal processes that underlie behavior (Padmanabhan & Luna, 2014). With regard to dopamine genes, such as DAT1 and DRD4, most research suggests mechanisms involving sensitivity to social stimuli such as punishment and reward (Matthys et al., 2013). Individuals with decreased dopaminergic activity have been found less reactive to simulation. Because these individuals need more input for optimal functioning, they are at higher risk for excessive sensation seeking and externalizing problems. However, higher novelty seeking has also been observed in individuals with extremely high dopamine activity (Padmanabhan & Luna, 2014). The impact of dopamine activity has been shown to emerge as an inverted U-shaped function, whereby both increases and decreases from the optimal level lead to impaired functioning (Robbins & Arnsten, 2009). What is considered as an optimal level of dopamine activity is dependent upon the task or environment, because dopamine functioning that is adequate in one situation may be inadequate in another. For example, dopamine levels increase during stressful situations in order to adaptively respond to the environment and to control emotional behavior (Pani, Porcella, & Gessa, 2000). These neurobiological processes are determined by a complex network of genes reciprocally influencing each other (Matthys et al., 2013; Steinberg, 2007). Based knowledge on underlying mechanisms is limited, we might question the common approach in GxE research of genotyping single gene markers according to a dominant model, in which individuals are categorized as sensitive or insensitive based on the presence or absence of a specific allele in a single gene. GxE research might benefit from incorporating a more continuous approach to genetic sensitivity, such as using an additive inheritance model or including multiple genetic markers that determine dopaminergic functioning ranging from abnormally low to abnormally high activity (Mitchell et al., 2013). We recently presented analyses on the same dataset with a biologically informed multilocus genetic score

based on a study of Nikolova, Ferrell, Manuck, and Hariri (2011), combining the effects of DRD2 Taq1A, DRD4 VNTR, DAT1 VNTR and COMT Val/Met. Although this score did not explain much more variance in aggressive, rule-breaking and externalizing behavior than the single genes approach, including this polygenic score revealed a clearer picture with distinct patterns for aggressive and rule-breaking behavior. Significant independent effects indicated that low dopamine signaling was predominantly associated with more aggressive behavior, but not with rule-breaking behavior. Significant G by E interactions were found for rule-breaking behavior, but not for aggressive behavior (Van Leeuwen et al., 2015). In order to gain insight in underlying mechanisms, GxE research must also take into account that both biological and environmental influences differ according to people's developmental stage. Evidence suggests maturational changes in the dopamine system, such as increases in dopamine activity and receptor density during adolescence (Padmanabhan & Luna, 2014). Likewise, brain systems regulating reward processes are more sensitive during puberty, when cognitive control is still maturing, which makes adolescents more vulnerable for risk taking behavior (Steinberg, 2007). In addition, adolescent maturation towards greater autonomy results in changing parent-child relationships and increasing involvement outside the family. Evidence suggests a gradual decline in limit setting (Barber, Maughan, & Olsen, 2005), whereas autonomy support and monitoring are seen as particularly important during this developmental period (Pettit et al., 2001). In contrast, psychological control is assumed to be especially harmful for adolescents, because it endangers their identity formation and emotional development (Wang et al., 2007). Based on this knowledge of changing biological and environmental factors in adolescents, results on child and adult samples may not be comparable to GxE processes in adolescence. We need more research that directly investigates dopaminergic functioning and the interaction with parenting behavior in adolescent samples.

Limitations and Suggestions for Future Research

Besides the strengths of the present study, such as the large sample drawn from the general population, multi-informant data, and a comprehensive GxE framework, some limitations have to be mentioned. First, it was difficult to formulate specific hypotheses due to inconsistency in previous GxE research concerning the age range of study samples, the measurement of externalizing problems and parental behavior, and the categorization of polymorphisms. More studies are needed to replicate our findings and extend them to other samples and measures. For example, only including adolescents of European decent was necessary to account for population stratification, however, this limited the generalizability of our results due to the lack of diversity.

We should develop a nomological network of research findings to increase our understanding on externalizing problem behavior in adolescence.

Second, similar to most GxE research, the present study focused on a selection of two dopaminergic polymorphisms interesting for externalizing problem behavior. However, the predictive power of such a selection might be rather small because they belong to complex networks of genes acting together to influence human behavior (Matthys et al., 2013; Steinberg, 2007). Although a candidate gene approach has important explanatory value (Schlomer, Cleveland, Vandenbergh, Fosco, & Feinberg, 2015), research incorporating more complex networks of genes may shed additional light on the biological basis of human behavior.

Third, although a participation rate of 50% is equivalent to other large-scale population studies in Flanders (e.g., Guérin et al., 2012), we should take into account potential bias due to self-selection. Chi-square tests indicate that our sample is representative for the general population with regard to family characteristics, but differences were found for socio-economic status. Respondents who voluntarily participate may also present less externalizing problems and less inadequate parenting behaviors than actually present in the general population. Therefore, we should be careful not to generalize results. In addition, we should be careful when interpreting results on adolescent-reported rule-breaking behavior because the internal consistency of this scale was questionable. Nevertheless, associations between independent and dependent variables were of similar magnitude and in the same direction for adolescent and parent ratings of rule-breaking behavior.

Finally, the cross-sectional and non-experimental nature of our data does not allow for causal inferences. Evidence suggests bidirectional relations between problem behavior and both parenting behavior and genes. Parenting has been found to influence externalizing problems, whereas these problems reciprocally influence behavior of parents (Kuppens, Grietens, Onghena, & Michiels, 2009; Lansford et al., 2011). Genes underlie human behavior in response to environmental influences, but so-called epigenetic processes show that environmental experiences can alter the expression of genes and thereby influence biological sensitivity to future environments (Mitchell et al., 2013).

Conclusion

In the present study, we simultaneously took into account several design and methodological issues. We found evidence for main effects of parenting behavior and the DRD4 gene, and multiple interaction effects. Despite sufficient power, only one interaction effect survived correction for multiple testing. Adolescents with the long DRD4 variant were more susceptible to both low and high levels of proactive control, resulting in more or less aggressive behavior. These results underscore the fact that genotypic differences are not straightforward

'bad' or 'good' and that optimal parenting is different for each adolescent due to underlying genetic differences. However, to understand the complex underpinnings of human behavior, we need more insight in the neurobiological mechanisms involved in gene functioning and gene-by-environment interplay.

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Table 1

Correlations Among Study Variables

	Externalizing problem behavior						**Parenting behavior**									
Variable	EXTa	EXTp	AGGa	AGGp	RULa	RULp	SUPa	SUPp	PROa	PROp	PUNa	PUNp	HARa	HARp	PSYa	PSYp
EXTa																
EXTp	.44 ***															
AGGa	.95 ***	.43 ***														
AGGp	.41 ***	.97 ***	.41 ***													
RULa	.86 ***	.36 ***	.66 ***	.31 ***												
RULp	.42 ***	.86 ***	.39 ***	.70 ***	.38 ***											
SUPa	-.39 ***	-.31 ***	-.37 ***	-.29 ***	-.34 ***	-.29 ***										
SUPp	-.25 ***	-.30 ***	-.24 ***	-.28 ***	-.21 ***	-.28 ***	.35 ***									
PROa	.01	.00	.01	-.01	.01	.02	.24 ***	.04								
PROp	-.07 †	-.04	-.07 †	-.03	-.05	-.06	.06	.46 ***	.15 ***							
PUNa	.17 ***	.15 ***	.16 ***	.16 ***	.15 ***	.10 **	-.13 ***	-.11 **	.35 ***	.09 *						
PUNp	.17 ***	.19 ***	.15 ***	.18 ***	.16 ***	.17 ***	-.17 ***	-.11 **	.14 ***	.21 ***	.42 ***					
HARa	.34 ***	.29 ***	.33 ***	.28 ***	.28 ***	.26 ***	-.32 ***	-.16 ***	.13 ***	.00	.36 ***	.24 ***				
HARp	.29 ***	.35 ***	.27 ***	.29 ***	.25 ***	.40 ***	-.17 ***	-.26 ***	.00	-.09 *	.06 †	.17 ***	.31 ***			
PSYa	.51 ***	.36 ***	.49 ***	.34 ***	.44 ***	.32 ***	-.57 ***	-.28 ***	.18 ***	-.04	.32 ***	.21 ***	.54 ***	.20 ***		
PSYp	.24 ***	.38 ***	.24 ***	.37 ***	.19 ***	.31 ***	-.25 ***	-.41 ***	.04	.05	.15 ***	.26 ***	.24 ***	.40 ***	.30 ***	
Mean	.27	.13	.30	.18	.23	.07	.03	.02	.01	.01	.00	.01	.00	-.01	-.01	.00
SD	.18	.16	.23	.22	.17	.11	.63	.40	.63	.45	1.01	.82	.55	.23	.64	.43

Note. The table presents correlations among study variables including control variables, externalizing problem behavior, dopaminergic VNTRs, and parenting behavior. ME = mother's highest degree of education; a = adolescent-reported; p = parent-reported; EXT = externalizing problems; AGG = aggressive behavior; RUL = rule breaking behavior; DAT1 = dopamine transporter gene; DRD4 = dopamine receptor D4 gene; SUP = support; PRO = proactive control; PUN = punitive control; HAR = harsh punitive control; PSY = psychological control. † $p < .10$; * $p < .05$; ** $p < .01$; *** $p < .001$.

Table 2

Regression Analyses of DAT1 and Parenting on Externalizing Problem Behavior

			Support							
			Adolescent				Parents			
Outcome	Informant	Model	R^2	E	G	GxE	R^2	E	G	GxE
EXT	Adolescent	M1	.16 ***	-.37 ***	-.02		.09 ***	-.25 ***	-.02	
		M2	.16 ***	-.10	-.01	-.28 *	.09 ***	-.19	-.02	-.06
	Parents	M1	.12 ***	-.30 ***	.01		.13 ***	-.30 ***	.00	
		M2	.13 ***	-.02	.02	-.29 *	.13 ***	-.11	.01	-.20
AGG	Adolescent	M1	.14 ***	-.37 ***	-.02		.07 ***	-.24 ***	-.03	
		M2	.14 ***	-.10	-.01	-.27 *	.07 ***	-.17	-.02	-.08
	Parents	M1	.11 ***	-.29 ***	.00		.11 ***	-.28 ***	.00	
		M2	.11 ***	-.02	.02	-.28 *	.11 ***	-.02	.02	-.27 †
RUL	Adolescent	M1	.15 ***	-.30 ***	-.01		.11 ***	-.20 ***	-.01	
		M2	.15 ***	-.07	.00	-.23 †	.11 ***	-.19 †	-.01	-.01
	Parents	M1	.11 ***	-.28 ***	.01		.12 ***	-.28 ***	.00	
		M2	.12 ***	-.02	.02	-.26	.12 ***	-.27 *	.00	-.01
			Proactive control							
			Adolescent				Parents			
Outcome	Informant	Model	R^2	E	G	GxE	R^2	E	G	GxE
EXT	Adolescent	M1	.03 *	.01	.00		.03 **	-.08 *	-.01	
		M2	.03 **	-.10	.00	.11	.03 **	-.16 †	-.01	.08
	Parents	M1	.04 **	-.01	.02		.04 **	-.06	.02	
		M2	.04 **	.04	.02	-.05	.04 **	-.08	.02	.02
AGG	Adolescent	M1	.01	.01	-.01		.02 †	-.08 *	-.01	
		M2	.01	-.11	.00	.12	.02 †	-.12	-.01	.04
	Parents	M1	.03 *	-.02	.02		.03 *	-.05	.02	
		M2	.03 **	.09	.02	-.11	.03 *	-.05	.02	.00
RUL	Adolescent	M1	.07 ***	.00	.00		.07 ***	-.07 †	.00	
		M2	.07 ***	-.07	.00	.08	.07 ***	-.19 *	.00	.13
	Parents	M1	.04 **	.01	.02		.04 **	-.07	.02	
		M2	.04 **	-.06	.02	.07	.05 **	-.12	.02	.05

(Table 2 continued)

			Punitive control							
			Adolescent				Parents			
Outcome	Informant	Model	R^2	E	G	GxE	R^2	E	G	GxE
EXT	Adolescent	M1	.05 ***	.17 ***	-.01		.05 ***	.16 ***	-.01	
		M2	.05 ***	.07	-.01	.10	.06 ***	-.04	.00	.20 †
	Parents	M1	.05 **	.13 ***	.01		.07 ***	.17 ***	.02	
		M2	.05 **	.13	.01	.00	.07 ***	.11	.02	.06
AGG	Adolescent	M1	.04 **	.16 ***	-.02		.03 **	.15 ***	-.01	
		M2	.04 **	.10	-.01	.07	.03 **	-.02	.00	.17
	Parents	M1	.05 **	.14 ***	.01		.06 ***	.16 ***	.02	
		M2	.05 **	.10	.01	.04	.06 ***	.11	.02	.06
RUL	Adolescent	M1	.08 ***	.13 ***	.00		.09 ***	.15 ***	.00	
		M2	.08 ***	.00	.00	.14	.09 ***	-.06	.01	.21 *
	Parents	M1	.05 **	.08 *	.01		.06 ***	.15 ***	.02	
		M2	.05 **	.17	.01	-.09	.06 ***	.10	.02	.05
			Harsh punitive control							
			Adolescent				Parents			
Outcome	Informant	Model	R^2	E	G	GxE	R^2	E	G	GxE
EXT	Adolescent	M1	.15 ***	.35 ***	-.02		.10 **	.35 ***	-.02	
		M2	.15 ***	.27	-.01	.08	.11 **	.27	-.01	.08
	Parents	M1	.12 ***	.29 ***	.01		.15 **	.29 ***	.01	
		M2	.12 ***	.36	.00	-.07	.16 **	.36	.00	-.07
AGG	Adolescent	M1	.13 ***	.34 ***	-.02		.08 **	.34 ***	-.02	
		M2	.13 ***	.34 †	-.02	.01	.09 **	.34 †	-.02	.01
	Parents	M1	.10 ***	.28 ***	.00		.11 **	.28 ***	.00	
		M2	.11 ***	.42	-.01	-.15	.11 **	.42	-.01	-.15
RUL	Adolescent	M1	.14 ***	.28 ***	-.01		.12 ***	.28 ***	-.01	
		M2	.14 ***	.10	.00	.19	.12 ***	.10	.00	.19
	Parents	M1	.10 ***	.26 ***	.01		.19 **	.26 ***	.01	
		M2	.10 ***	.15	.01	.10	.20 **	.15	.01	.10

(Table 2 continued)

			Psychological control							
			Adolescent				Parents			
Outcome	Informant	Model	R^2	E	G	GxE	R^2	E	G	GxE
EXT	Adolescent	M1	.27 ***	.50 ***	-.03		.08 ***	.24 ***	-.01	
		M2	.28 ***	.24 *	-.01	.27 *	.09 ***	.09	.00	.16
	Parents	M1	.16 ***	.36 ***	-.01		.18 ***	.38 ***	.02	
		M2	.16 ***	.16	.01	.20	.18 ***	.20 †	.02	.19 †
AGG	Adolescent	M1	.25 ***	.49 ***	-.03		.07 ***	.24 ***	-.01	
		M2	.25 ***	.21 †	-.02	.29 *	.07 ***	.12	-.01	.13
	Parents	M1	.15 ***	.35 ***	-.01		.17 ***	.37 ***	.02	
		M2	.15 ***	.13	.01	.23	.17 ***	.21 †	.02	.17
RUL	Adolescent	M1	.23 ***	.41 ***	-.02		.10 ***	.19 ***	.00	
		M2	.23 ***	.24 *	-.01	.18 †	.10 ***	.03	.00	.16
	Parents	M1	.13 ***	.31 ***	-.01		.14 ***	.31 ***	.02	
		M2	.13 ***	.20	.01	.11	.14 ***	.15	.02	.17 †

Note. Environmental variables are the five parenting dimensions of Support (SUP), Proactive control (PRO), Punitive control (PUN), Harsh punitive control (HAR), and Psychological control (PSY). Outcome variables reflect Externalizing problem behavior (EXT), divided in two subcategories of Aggressive behavior (AGG) and Rule breaking behavior (RUL). All variables are reported upon by adolescents and their parents. Model 1 (M1) includes only main effects of the environment (E) and the gene (G). In Model 2 (M2), interaction effects are added (GxE). Values are standardized regression estimates without Bonferroni correction. † $p < .10$; * $p < .05$; ** $p < .01$; *** $p < .001$.

Table 3

Regression Analyses of DRD4 and Parenting on Externalizing Problem Behavior

			Support							
			Adolescent				Parents			
Outcome	Informant	Model	R^2	E	G	GxE	R^2	E	G	GxE
EXT	Adolescent	M1	.16 ***	-.37 ***	-.01		.09 ***	-.25 ***	-.02	
		M2	.16 ***	-.39 ***	-.01	.03	.09 ***	-.23 ***	-.02	-.03
	Parents	M1	.13 ***	-.30 ***	-.07 *		.13 ***	-.30 ***	-.07 *	
		M2	.14 ***	-.37 ***	-.07 *	.11 *	.13 ***	-.30 ***	-.07 *	-.01
AGG	Adolescent	M1	.14 ***	-.37 ***	-.02		.07 ***	-.24 ***	-.02	
		M2	.14 ***	-.38 ***	-.02	.02	.07 ***	-.23 ***	-.02	-.03
	Parents	M1	.12 ***	-.29 ***	-.08 *		.12 ***	-.28 ***	-.08 *	
		M2	.12 ***	-.35 ***	-.08 *	.10 †	.12 ***	-.28 ***	-.08 *	-.01
RUL	Adolescent	M1	.15 ***	-.30 ***	.00		.11 ***	-.20 ***	-.01	
		M2	.15 ***	-.31 ***	.00	.02	.11 ***	-.18 ***	-.01	-.03
	Parents	M1	.12 ***	-.28 ***	-.05		.12 ***	-.28 ***	-.05 †	
		M2	.12 ***	-.34 ***	-.06 †	.11 *	.12 ***	-.27 ***	-.05 †	-.02
			Proactive control							
			Adolescent				Parents			
Outcome	Informant	Model	R^2	E	G	GxE	R^2	E	G	GxE
EXT	Adolescent	M1	.03 **	.01	-.02		.03 **	-.08 *	-.02	
		M2	.03 **	-.01	-.02	.02	.03 **	-.07	-.02	-.01
	Parents	M1	.04 **	-.01	-.07 †		.04 **	-.06	-.07 †	
		M2	.04 **	-.03	-.07 *	.03	.06 ***	.01	-.07 †	-.13 **
AGG	Adolescent	M1	.01	.01	-.02		.02 *	-.08 *	-.02	
		M2	.01 †	-.01	-.02	.02	.02 *	-.07	-.02	-.01
	Parents	M1	.04 **	-.02	-.08 *		.04 **	-.05	-.07 *	
		M2	.04 **	-.04	-.08 *	.04	.05 **	.03	-.07 †	-.14 ***
RUL	Adolescent	M1	.07 ***	.00	-.01		.07 ***	-.07 †	-.01	
		M2	.07 ***	-.01	-.01	.02	.07 ***	-.06	-.01	-.02
	Parents	M1	.04 **	.01	-.05		.05 ***	-.07	-.05	
		M2	.04 **	.00	-.05	.02	.05 ***	-.03	-.05	-.09 †

(Table 3 continued)

			Punitive control							
			Adolescent				Parents			
Outcome	Informant	Model	R^2	E	G	GxE	R^2	E	G	GxE
EXT	Adolescent	M1	.05 ***	.16 ***	-.02		.05 ***	.16 ***	-.01	
		M2	.05 ***	.16 ***	-.02	.01	.05 ***	.18 ***	-.01	-.04
	Parents	M1	.06 ***	.13 ***	-.07 *		.07 ***	.17 ***	-.07 †	
		M2	.06 ***	.12 *	-.07 *	.02	.07 ***	.19 ***	-.07 †	-.04
AGG	Adolescent	M1	.04 **	.16 ***	-.02		.03 **	.15 ***	-.02	
		M2	.04 **	.15 ***	-.02	.02	.03 **	.16 ***	-.02	-.02
	Parents	M1	.05 ***	.14 ***	-.08 *		.06 ***	.16 ***	-.07 †	
		M2	.05 ***	.14 **	-.08 *	.00	.06 ***	.19 ***	-.07 †	-.04
RUL	Adolescent	M1	.08 ***	.13 ***	-.01		.09 ***	.15 ***	.00	
		M2	.08 ***	.14 **	-.01	.00	.09 ***	.18 ***	.00	-.06
	Parents	M1	.05 **	.09 *	-.05		.06 ***	.14 ***	-.05	
		M2	.05 ***	.05	-.05	.07	.06 ***	.16 **	-.05	-.02
			Harsh punitive control							
			Adolescent				Parents			
Outcome	Informant	Model	R^2	E	G	GxE	R^2	E	G	GxE
EXT	Adolescent	M1	.15 ***	.35 ***	-.02		.11 **	.28 ***	.01	
		M2	.15 ***	.38 ***	-.02	-.05	.11 **	.28 ***	.01	.01
	Parents	M1	.13 ***	.29 ***	-.08 *		.15 **	.34 ***	-.05	
		M2	.13 ***	.32 ***	-.08 *	-.04	.15 **	.32 ***	-.04	.05
AGG	Adolescent	M1	.13 ***	.34 ***	-.02		.08 **	.27 ***	.00	
		M2	.13 ***	.36 ***	-.02	-.03	.08 **	.27 ***	.00	.00
	Parents	M1	.11 ***	.28 ***	-.08 *		.11 ***	.28 ***	-.05	
		M2	.11 ***	.30 ***	-.08 *	-.03	.11 ***	.25 ***	-.05	.07
RUL	Adolescent	M1	.14 ***	.28 ***	-.01		.12 ***	.24 ***	.01	
		M2	.14 ***	.32 ***	-.01	-.06	.12 ***	.24 **	.01	.01
	Parents	M1	.11 ***	.26 ***	-.06 †		.19 **	.39 ***	-.02	
		M2	.11 ***	.30 ***	-.06 †	-.05	.19 **	.39 **	-.02	.00

(Table 3 continued)

			Psychological control							
			Adolescent				Parents			
Outcome	Informant	Model	R^2	E	G	GxE	R^2	E	G	GxE
EXT	Adolescent	M1	.27 ***	.50 ***	-.01		.09 ***	.24 ***	-.01	
		M2	.27 ***	.49 ***	-.01	.01	.09 ***	.23 ***	-.01	.01
	Parents	M1	.17 ***	.36 ***	-.07 *		.19 ***	.38 ***	-.07 *	
		M2	.17 ***	.38 ***	-.08 *	-.03	.19 ***	.36 ***	-.07 *	.04
AGG	Adolescent	M1	.24 ***	.49 ***	-.02		.07 ***	.24 ***	-.02	
		M2	.25 ***	.48 ***	-.02	.02	.07 ***	.23 ***	-.02	.03
	Parents	M1	.16 ***	.35 ***	-.08 *		.17 ***	.37 ***	-.07 *	
		M2	.16 ***	.36 ***	-.08 *	-.02	.17 ***	.35 ***	-.07 *	.04
RUL	Adolescent	M1	.23 ***	.41 ***	.00		.10 ***	.19 ***	.00	
		M2	.23 ***	.41 ***	.00	.00	.10 ***	.19 ***	.00	-.01
	Parents	M1	.14 ***	.31 ***	-.05 †		.14 ***	.31 ***	-.05	
		M2	.14 ***	.34 ***	-.06 †	-.05	.14 ***	.30 ***	-.05	.02

Note. Environmental variables are the five parenting dimensions of Support (SUP), Proactive control (PRO), Punitive control (PUN), Harsh punitive control (HAR), and Psychological control (PSY). Outcome variables reflect Externalizing problem behavior (EXT), divided in two subcategories of Aggressive behavior (AGG) and Rule breaking behavior (RUL). All variables are reported upon by adolescents and their parents. Model 1 (M1) includes only main effects of the environment (E) and the gene (G). In Model 2 (M2), interaction effects are added (GxE). Values are standardized regression estimates without Bonferroni correction. † $p < .10$; * $p < .05$; ** $p < .01$; *** $p < .001$.

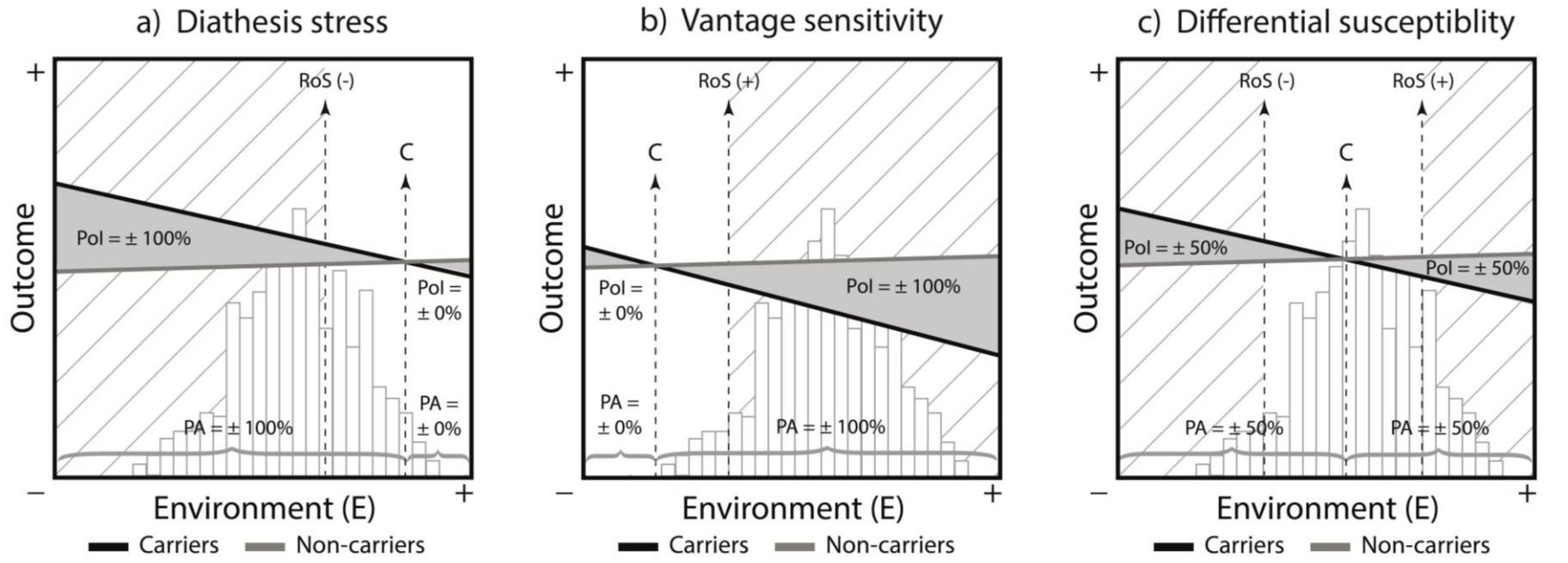

Figure 1. This figure shows a schematic representation of Roisman criteria to evaluate alternative GxE models. First, diathesis stress (model a) is supported if only a negative Region of Significance [RoS(-)] is found, indicating that the association between gene and outcome is only significant at the negative side of the environmental variable (E). The crossover point (C) is situated at the positive side of E, which causes that almost the entire proportion of the interaction (PoI; Proportion of Interest) and cases (PA; Proportion of Affected) falls on the negative side of C. Second, the opposite pattern suggests vantage sensitivity (model b): finding only RoS(+), C situated at the negative side of E, and almost the entire proportion of PoI and PA on the positive side of C. Finally, differential susceptibility (model c) is supported when boundaries of both positive and negative RoS as well as C fall within the range of E, indicating a significant association between gene and outcome at both ends of E. PoI and PA are present on both sides of C. According to Roisman et al. (2012), strong evidence for differential susceptibility is supported by a PoI value from 40% to 60% and a PA value of at least 16%. Adapted from "Externalizing Problem Behavior in Adolescence: Dopaminergic Genes in Interaction with Peer Acceptance and Rejection" by Janssens et al., 2015, *Journal of Youth and Adolescence, 44*, p. 1443. Copyright 2015 by Springer US.

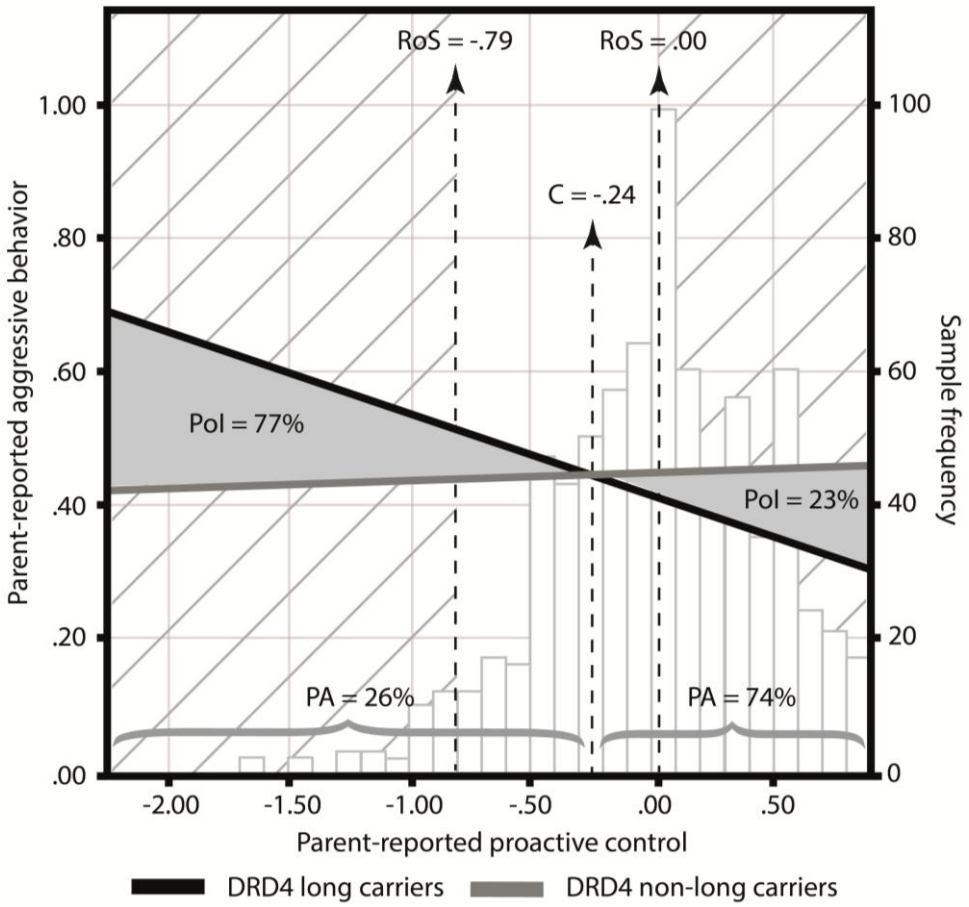

Figure 2. DRD4 interacts with parent-reported proactive control (x-axis) in predicting parent-reported aggressive behavior (left y-axis). Adolescents with the long DRD4 allele (black line) whose parents report less proactive control show more aggressive behavior, compared to non-carriers (grey line). In case of high proactive controlling parents, these adolescents show less problem behavior. Critical tests proposed by Roisman and colleagues (2012) provide evidence for differential susceptibility. The hatched regions of significance (RoS) show that the two regression lines significantly differ on both sides of the interaction. The crossover point (C = -.24) fell within the range observed for proactive control (min = -2.25; max = .85). The Proportion of Interest (PoI), presented by the grey area between the regression lines (PoI = left: 77%; right: 23%), was not highly consistent with differential susceptibility (between 40 and 60%), but the Proportion of Affected (PA), calculated on the sample frequency of parent ratings on proactive control (right y-axis), was higher than the threshold of 16% proposed by _ENREF_70Roisman et al. (2012) as evidence for differential susceptibility (PA = left: 26%; right: 74%).