The U-shaped Relationship between Dopamine System Polygenic Factors and Adolescent Aggressive Behavior: The Moderating Role of Maternal Negative Parenting

Authors: Lin Xiaonan, Cao Yanmiao, Zhang Wenxin, Ji Linqin, Ji Lin Qin

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Abstract

Dopamine activity demonstrates an inverted U-shaped relationship with aggression-related brain functional activity. The present study conducted two assessments of aggressive behavior spaced one year apart in a sample of 1044 Han Chinese adolescents (M age = 13.32 ± 0.49 years at initial assessment, 50.2% female), utilizing a polygenic score paradigm to investigate the relationship between polygenic functional scores of the dopamine system and adolescent aggressive behavior, as well as the moderating role of maternal negative parenting. Results indicated that the quadratic term of the dopamine system polygenic score interacted with maternal negative parenting to influence adolescent aggressive behavior at both time points: Under conditions of high maternal negative parenting, adolescents carrying either more or fewer low dopamine activity-related alleles exhibited elevated levels of aggressive behavior, manifesting a U-shaped relationship; conversely, under conditions of low maternal negative parenting, the quadratic term of the polygenic score was not significantly associated with adolescent aggressive behavior. This study provides evidence for the genetic mechanism through which the combined effect of dopamine system genes and maternal negative parenting moderates the genetic influence on adolescent aggressive behavior.

Full Text

The U-Shaped Relationship Between Dopaminergic Polygenic Variants and Adolescent Aggressive Behavior: The Moderating Role of Maternal Negative Parenting

LIN Xiaonan, CAO Yanmiao, ZHANG Wenxin, JI Linqin
(School of Psychology, Shandong Normal University; Shandong Provincial Insti-

tute of Student Development and Mental Health, Jinan 250014, China)

Abstract

Dopaminergic genes have been frequently found to be associated with aggressive behavior, but the results are inconsistent. One reason for the inconsistencies is there might be the U-shaped relationship between dopaminergic genetic variants and aggressive behavior. More specifically, evidence has suggested an inverted U-shaped relationship between dopamine activity and prefrontal cortex (PFC) function (a critical region related to aggression), with both dopaminergic hypofunction and hyperfunction, were related to poor PFC function. It is possible that the relationship between dopaminergic gene and aggression approximates a U-shaped function. However, such U-shaped relationship is rarely investigated in previous studies. Moreover, several concerns have been raised about the ignoring the polygenic traits of aggressive behavior when conducting gene by environment interaction (G×E) research using single loci. Therefore, the present study aimed to examine the interaction between dopaminergic genetic variants and maternal negative parenting on adolescent aggressive behavior by adopting the approach of multilocus genetic profile score (MGPS).

Participants were 1044 adolescents (mean age 13.32 $\pm$ 0.49 years old at Time 1, 50.2% females) recruited from the community. The adolescents completed two assessments with an interval of one year. Saliva samples, mother-reported parenting data and data on peer-nominated aggressive behavior were collected. All measures showed good reliability. The MGPS was created by COMT rs4680 polymorphisms, DRD2 rs1799978 polymorphisms and DAT1 rs27072 polymorphisms. Genotyping in three dopaminergic genes were performed for each participant in real time with MassARRAY RT software version 3.0.0.4 and analyzed using the MassARRAY Typer software version 3.4 (Sequenom). To examine whether negative parenting moderates the effects of MGPS on adolescent aggressive behavior, hierarchical regression analyses were conducted.

The results found that after controlling for gender, maternal negative parenting was a significant risk factor for adolescent aggressive behavior, with higher negative parenting related to more aggressive behavior. The main effect of the quadratic term of MGPS on adolescents' aggressive behavior was significant at Time 2, indicating a U-shaped relationship between MGPS and adolescent aggressive behavior. Moreover, the quadratic term of MGPS significantly interacted with maternal negative parenting in predicting aggressive behavior at Time 1 and Time 2, respectively. Specifically, there was a U-shaped relationship between MGPS and adolescent aggressive behavior, indicating that adolescents with higher and lower MGPS exhibited higher levels of aggressive behavior when experiencing higher levels of maternal negative parenting. No significant effect of MGPS on adolescent aggressive behavior when experiencing lower levels of maternal negative parenting existed.

This study provides evidence for the molecular mechanisms of multilocus ge-

netic profile scores and gene-environment interactions in adolescent aggressive behavior.

Keywords: aggressive behavior, maternal negative parenting, dopamine system, multilocus genetic profile score, U-shaped relationship

Aggression is defined as behavior in which an individual intentionally causes physical or psychological harm to others (Crick & Grotpeter, 1995). Approximately 7.48% to 24.3% of Chinese adolescents exhibit serious aggressive or violent behavior (Wang et al., 2012; Yu et al., 2021). Adolescent aggressive behavior not only leads to academic failure and increased risk of psychopathology and violent criminal behavior, but also creates substantial socioeconomic and mental health care burdens (Ansary et al., 2017; López et al., 2018). Due to the prevalence and harmfulness of aggressive behavior, researchers have explored the gene-environment mechanisms underlying aggression from both genetic and family parenting perspectives, attempting to develop individualized family-based prevention programs for aggressive behavior.

1.1 Dopaminergic System Genes and Aggression

Dopaminergic system genes are involved in emotion regulation, executive control, and motivational processes (Gatzke-Kopp, 2011; Nikolova et al., 2011; Tielbeek et al., 2018; Vrantsidis et al., 2021) and are closely associated with individual aggressive behavior (Albaugh et al., 2010; van Goozen et al., 2016; Zhang et al., 2016). However, existing molecular genetic research on the association between dopaminergic system genes and aggressive behavior has yielded inconsistent results. Some studies have shown that genotypes associated with low dopamine activity are linked to increased aggression (Hygen et al., 2015; Jones et al., 2001; van Goozen et al., 2016). For instance, van Goozen et al. (2016) found that the COMT gene rs4680 Val allele, which is associated with low dopamine activity, was related to high aggressive behavior. Hygen et al. (2015) found that Val homozygotes exhibited more aggressive behavior when experiencing severe life events. However, other studies have shown that the Met allele is associated with high aggressive behavior. For example, Albaugh et al. (2010) found that the COMT gene Met allele (A allele) was associated with high aggressive behavior. Zhang et al. (2016) found that Met allele carriers exhibited more reactive aggression when experiencing low levels of positive parenting. Although researchers have attempted to explain these divergent findings from the perspectives of sample characteristics, environmental factors, and aggression measurement methods, existing research may have overlooked two important facts: (1) individual dopaminergic genes have small effects, multiple genes have joint and interactive effects, and the relationship between dopaminergic genetic effects and aggressive behavior is not linear; and (2) the effects of dopaminergic system genes are moderated by environmental factors.

Neurochemical and psychogenetic research suggests that there may be a nonlinear relationship between dopaminergic system genes and aggressive behavior.

Neurobiochemical evidence indicates an inverted U-shaped relationship between dopamine activity and brain function related to aggression, with optimal functioning of the PFC and related brain regions at moderate dopamine activity levels, and impaired function when dopamine activity is too high or too low (Arnsten, 2009; Bertolino et al., 2009; Robbins & Arnsten, 2009; Seamans & Yang, 2004; Tian et al., 2013; Tunbridge et al., 2006). Psychogenetic studies have found interactive or non-linear relationships between dopaminergic system genes and the structure and function of aggression-related brain regions. For example, Bertolino et al. (2009) examined the association between DAT and DRD2 genes and activity in specific brain regions, finding that individuals carrying genotype combinations associated with high dopamine activity (DAT 10R/10R and DRD2 GG genotypes) or low dopamine activity (DAT 9R and DRD2 GT genotypes) showed lower activity in the caudate nucleus and middle frontal gyrus and larger gray matter volume, while individuals carrying genotype combinations associated with moderate dopamine activity showed normal levels of activity and gray matter volume. Therefore, we hypothesize that there may be a non-linear relationship between dopaminergic system genes and aggressive behavior.

1.2 Joint Effects of Dopaminergic Polygenic Variants

In recent years, the multilocus genetic profile score (MGPS) approach based on polygenic hypotheses has gained increasing attention. This method accumulates multiple gene loci to obtain a polygenic score, revealing the contribution of multiple genes to individual differences in psychological or behavioral traits (Cao & Rijlaarsdam, 2022; Davies et al., 2019; Nikolova et al., 2011; Thibodeau et al., 2015).

Dopamine activity in the nervous system is influenced by dopaminergic tone, receptor efficacy, and utilization efficiency. Therefore, the joint effects of genes involved in dopamine degradation, transmission, and transport collectively regulate dopamine activity in the synaptic cleft, influencing psychopathology in children and adolescents (Davies et al., 2019; Nikolova et al., 2011; Thibodeau et al., 2015). Catechol-O-methyltransferase (COMT), D2 dopamine receptor (DRD2), and dopamine transporter (DAT1) genes influence dopamine degradation, transmission, and transport, respectively (Chester & DeWall, 2016; Nikolova et al., 2011), and jointly regulate dopamine activity. The COMT gene encodes catechol-O-methyltransferase, which degrades dopamine and other monoamine neurotransmitters. The COMT rs4680 polymorphism results in a valine (Val) to methionine (Met) substitution at amino acid position 158 in the translated product, reducing COMT enzyme activity by 40% (Chen et al., 2004; Lotta et al., 1995; Meyer et al., 2016). The DRD2 gene encodes the D2 dopamine receptor. The rs1799978 (A-241G) polymorphism in the promoter region involves an adenine (A) to guanine (G) conversion at position -241, which is associated with greater dopamine D2 receptor density and transcription levels, thereby affecting dopamine activity (Genis-Mendoza et al., 2018; Xing et al., 2007; Zhang & Malhotra, 2011). The DAT1 gene encodes the dopamine transporter. The T allele at the rs27072 locus in the 3' untranslated region has higher transcription levels than the C allele, enabling more efficient dopamine reuptake in the synapse and reducing dopamine levels in the synaptic cleft (Pinsonneault et al., 2011). These three genes are expressed at higher levels in aggression-related brain regions such as the prefrontal cortex, striatum, and midbrain (Yamaguchi & Lin, 2018). Previous research has found that these three gene polymorphisms are closely associated with aggressive behavior in children and adolescents (Chester & DeWall, 2016; Davies et al., 2015; van Goozen et al., 2016; Zai et al., 2012; Zhang et al., 2016) and synergistically influence aggressive behavior (Davies et al., 2019; Vrantsidis et al., 2021). This study will select the above three functional alleles of COMT, DRD2, and DAT1 to create a multilocus genetic profile score and examine its association with aggressive behavior.

1.3 The Moderating Role of Maternal Negative Parenting

The influence of dopaminergic system genes on aggressive behavior is moderated by environmental factors, representing a gene-environment interaction (G×E) (Beauchaine et al., 2007; Davies et al., 2019; Shanahan & Hofer, 2005). The biosocial developmental model (BDM) posits that repeated exposure to adverse parenting environments increases the risk of problem behavior development in individuals carrying dopamine function-deficient genes (Beauchaine et al., 2007). Recently, Tomlinson et al.' s (2022) twin study provided evidence for this, finding that warmth (positive parenting) attenuated genetic influences on callous-unemotional traits, but genetic effects on callous-unemotional traits were stronger under harsh discipline (negative parenting).

Family parenting has an important influence on aggressive behavior in children and adolescents (Davies et al., 2019; Gershoff, 2002; Stocker et al., 2017; Thibodeau et al., 2015). Specifically, maternal negative parenting behaviors such as punishment, rejection, and exclusion lead children and adolescents to imitate negative behaviors and enhance hostile emotions and cognitive attributions (Gershoff, 2002; Goulter et al., 2020), limiting and hindering the development of emotion and behavior regulation functions (Ganiban et al., 2021; Thibodeau et al., 2015), thereby promoting aggressive behavior (Zhang et al., 2016). Previous research has revealed that negative parenting interacts with dopaminergic polygenic variants to influence aggression-related behaviors in children and adolescents, such as antisocial behavior and externalizing problems (Davies et al., 2015, 2019; Thibodeau et al., 2015). For example, Davies et al. (2015, 2019) found that dopaminergic polygenic profile scores interacted with maternal insensitivity and other negative parenting behaviors to predict externalizing problems, with individuals carrying alleles associated with lower dopamine activity showing relatively high levels of externalizing problems when experiencing high levels of negative parenting, but relatively low levels when experiencing low levels of negative parenting. Therefore, to reveal the association between dopaminergic system genes and aggressive behavior, this study selects maternal negative parenting as the environmental factor to examine its interaction with dopaminergic polygenic variants in influencing aggressive behavior, clarifying the influence of dopaminergic system genes on aggressive behavior under conditions of high negative parenting.

1.4 Research Questions and Hypotheses

Adolescence is a period of important changes in emotional, cognitive, and neurobiological functions. During adolescence, baseline dopamine content in the PFC increases (Naneix et al., 2012), and dopamine receptor expression (Naneix et al., 2012) and dopamine transporter density (Tielbeek et al., 2018) gradually increase and peak, thereby enhancing dopaminergic sensitivity and affecting dopamine regulatory pathway function. These changes in dopamine pathway regulation during adolescence lead to significant alterations in the structure and function of the PFC and striatum, as well as functional connectivity between the PFC and amygdala (Romeo, 2017; Toth, 2022; Tottenham & Galván, 2016), with individuals showing increased sensitivity and reactivity to reward, punishment, and threatening stimuli (Tielbeek et al., 2018). Due to enhanced dopaminergic sensitivity during adolescence, the effects of alleles associated with high or low dopamine activity carried by individuals may be further strengthened, causing the association between dopaminergic system genes and behavior to show patterns different from other developmental stages.

Existing research on the effects of genes and their interaction with environment on aggressive behavior has primarily focused on early childhood or middle-to-late childhood (Davies et al., 2015; Thibodeau et al., 2015; Vrantsidis et al., 2021), with few studies examining adolescence (Davies et al., 2019). This study adopts a polygenic perspective, using the cumulative score of three gene polymorphisms (COMT, DAT1, and DRD2) as the genetic index, maternal negative parenting as the environmental index, and aggression measured at two time points during adolescence as the behavioral outcome, to explore the relationship between dopaminergic polygenic variants and adolescent aggressive behavior and the moderating role of maternal negative parenting. Based on previous research, we aim to explore the non-linear relationship between multilocus genetic profile scores and adolescent aggressive behavior and the moderating role of maternal parenting. We hypothesize that adolescents carrying alleles associated with either high or low dopamine activity may both exhibit high levels of aggressive behavior, and that maternal negative parenting moderates the relationship between multilocus genetic profile scores and adolescent aggressive behavior, with the non-linear relationship being more pronounced under high maternal negative parenting.

2.1 Participants

Participants in this study were drawn from a large longitudinal project, with the current research representing a genetic study utilizing participants from this project. In this study, maternal negative parenting was measured at the end of the first year of junior high school (Time 1), genetic data were collected at the end of the second year of junior high school (Time 2), and adolescent aggressive behavior data were collected at both Time 1 and Time 2. The one-year interval between Time 1 and Time 2 follows conventional patterns in longitudinal research design, allowing for meaningful developmental changes or differences to be captured without being so short as to render repeated assessments meaningless or so long as to miss meaningful developmental changes, differences, or predictive effects (Collins, 2006). Additionally, repeated measurements at similar times of the year avoid influences from seasonal factors, time since school began, and different periodic events within the school year (Dormann & Griffin, 2015).

Due to limited research funding, the longitudinal project only collected saliva samples and performed DNA genotyping for a subset of participants. Participants with genetic data (N = 1078) and those without genetic data (N = 927) did not differ significantly on major demographic information (age: $t(2003) = -0.74$, $p = 0.46$; SES: $t(1867) = -0.95$, $p = 0.34$; gender: $^{2} = 3.39$, $df = 1$, $p = 0.07$). However, participants with genetic data showed lower levels of aggressive behavior and negative parenting (Time 1 aggression: $t(975) = 7.45$, $p < 0.001$; Time 2 aggression: $t(1042) = 6.24$, $p < 0.001$; negative parenting: $t(1880) = 2.07$, $p = 0.04$). Participants with genetic data included Han Chinese (N = 1044, 96.8%) and other ethnicities (N = 34, 3.2%). Although Han Chinese and other ethnic participants did not differ significantly on basic study variables (gender, genotype distribution, age, SES, Time 1 aggression, Time 2 aggression, maternal negative parenting) (^{2}s ≤ 4.45, ps ≥ 0.49; $|t|$s ≤ 1.58, ps ≥ 0.12), considering that gene function and linkage disequilibrium (LD) effects on adaptive outcomes differ across ethnicities (Avinun et al., 2020), and to avoid bias due to ethnic differences and maximize statistical power (Cardon & Palmer, 2003), this study analyzed only Han Chinese participants, following previous research (e.g., Avinun et al., 2020; Cao & Rijlaarsdam, 2022; Stocker et al., 2017).

The final sample consisted of 1044 participants with a mean age of 13.32 ± 0.49 years at Time 1, including 520 males (49.8%) and 524 females (50.2%). For mothers and fathers, 11.6% and 8.3% had education levels of junior high school or below, 26.5% and 20.6% had high school or technical secondary school education, and 61.9% and 71.1% had college education or above, respectively. Family monthly income was below 3000 yuan for 23.1% of families, 3000-6000 yuan for 48.0%, and above 6000 yuan for 28.9%.

2.2 Research Procedure and Measures

The study was approved by the institutional ethics committee. Before data collection, the questionnaire administration and saliva collection procedures were explained to the adolescents' schools, guardians, and the adolescents themselves, and informed consent was obtained.

Adolescent aggressive behavior data were collected using questionnaires administered in classrooms and collected on-site. Saliva samples were collected from adolescents organized by class. Saliva sample collection followed standardized procedures: participants had no fever at the time of sampling and had no food, smoking, alcohol, water, or gum for 30 minutes before collection. Samples were checked for quality after collection, stored at -20°C, and transported via cold chain to a biotechnology company for DNA extraction and genotyping within one week. During questionnaire administration and saliva collection, each class was supervised by two trained developmental psychology teachers and graduate students. Maternal negative parenting data were collected by having adolescents take home envelopes containing parenting questionnaires for their mothers to complete and return to teachers the next day.

2.2.1 Dopaminergic Gene Extraction, Genotyping, and Scoring

Each adolescent provided at least 2 ml of saliva. DNA extraction and genotyping were performed using the Sequenom (San Diego, CA, USA) chip-based matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry platform following standardized technical specifications and procedures (Cao & Rijlaarsdam, 2022; Zhang et al., 2016).

The genotype distributions of COMT Val158Met (^{2} = 2.06, p = 0.15; Val/Val 56.8%, Val/Met 36.0%, Met/Met 7.2%), DRD2 rs1799978 (^{2} = 0.004, p = 0.95; AA 66.5%, AG 30.1%, GG 3.4%), and DAT1 rs27072 (^{2} = 1.63, p = 0.20; TT 5.9%, CT 33.9%, CC 60.2%) all conformed to Hardy-Weinberg equilibrium. Polygenic research is based on the "common disease-common variant" hypothesis, which requires minor allele frequency (MAF) greater than 5% (Manolio et al., 2009). In this study, the minor allele frequencies of all three loci met this requirement (COMT: 25.2%, DRD2: 18.5%, DAT1: 22.9%). No significant gender differences were found in genotype distributions for the three polymorphisms (^{2}s $\leq$ 1.24, df = 2, ps $\geq$ 0.54).

To determine whether COMT, DRD2, and DAT1 were suitable for linear summation, a series of statistical tests were conducted. First, because gene coding methods affect MGPS results, linear gene model tests were performed to examine whether linear coding (i.e., 0, 1, 2) was appropriate for creating the MGPS, following previous research (Stocker et al., 2017; Cao & Zhang, 2019). Results showed that although the decomposition model estimated the most parameters, its explanatory power was not significantly higher than the linear gene model (which constrained the estimated coefficients of dominant and recessive coding for the same gene to be equal; ΔR^2 = 0.004, 0.007, ps > 0.28), indicating that the genotypes of the three loci conformed to linear coding. Second, to exclude dominant effects of single genes, an equal gene effect model test was conducted. Results showed no significant difference between the equal gene effect model and the linear gene effect model (ΔR^2 = 0.002, 0.007, ps > 0.11), indicating that the three genes did not differ in their predictive strength for aggressive behavior and that no single gene dominated the MGPS. Therefore, based on the number of alleles associated with low dopamine activity carried by individuals (COMT: Val/Val = 0, Val/Met = 1, Met/Met = 2; DAT1: AA = 0, AG = 1, GG = 2; DRD2: TT = 0, CT = 1, CC = 2), linear coding was applied and summed to obtain the gene locus score. The distribution of dopaminergic polygenic cumulative scores was: 0 (N = 24, 2.3%), 1 (N = 164, 15.7%), 2 (N = 378, 36.2%), 3 (N = 334, 32.0%), 4 (N = 120, 11.5%), and 5 (N = 24, 2.3%).

2.2.2 Maternal Negative Parenting Behavior

The Chinese version of the Child-Rearing Practices Report (CRPR; Chen et al., 2000) was used, with mothers reporting their negative parenting behaviors. This questionnaire is widely used among Chinese children and adolescents and has good reliability and validity (e.g., Zhang et al., 2017). In this study, one item from the punishment dimension ("I tell my child that if he/she does something bad, he/she will be punished") showed low correlation with the total negative parenting score and was removed following previous research (Zhang et al., 2017). This study used the average of 10 items from the rejection (4 items, e.g., "If my child doesn' t bother me, I won' t pay attention to him/her") and punishment (6 items, e.g., "I think corporal punishment is the best way to discipline a child") dimensions as the indicator of maternal negative parenting behavior. The questionnaire used a 5-point scale (from "completely uncharacteristic" = 0 to "completely characteristic" = 4), with higher scores indicating more maternal negative parenting behavior. Confirmatory factor analysis showed that the single-factor model fit well (^{2} = 152.73, df = 35, RMSEA = 0.058, CFI = 0.91, TLI = 0.89). The Cronbach' s α coefficient for maternal negative parenting behavior in this study was 0.72.

2.2.3 Aggressive Behavior

Peer nomination was used to measure adolescent aggressive behavior (Crick & Grotpeter, 1995). This measure is widely used in adolescent aggression research and provides valid and reliable data (Mehari et al., 2019), with good reliability and validity. The questionnaire includes 4 items covering physical aggression (e.g., "classmates who often hit others") and relational aggression (e.g., "who often talks behind other classmates' backs"). Participants were asked to select up to three classmates who best fit each description. The total nomination frequency for each participant was calculated and standardized within each class to obtain aggressive behavior scores. The Cronbach's α coefficients for aggressive behavior measurement at the two time points were 0.88 and 0.87, respectively.

2.3 Data Processing and Analysis

First, correlation analysis was used to examine relationships among study variables. Second, hierarchical linear regression analysis was conducted using SPSS 26.0 to examine the effects of multilocus genetic profile scores and maternal negative parenting on adolescent aggressive behavior. In the hierarchical regression models, gender was entered as a control variable in the first step, multilocus genetic profile score and maternal negative parenting as predictor variables in the second step, the interaction term between multilocus genetic profile score and maternal negative parenting in the third step, the quadratic term of multilocus genetic profile score in the fourth step, and the interaction between the quadratic term and maternal negative parenting in the fifth step. Regression analysis including quadratic terms (in this study, the quadratic term of multilocus genetic profile score) can reveal common non-linear relationships, including U-shaped, inverted U-shaped, and other non-linear patterns where the predictive effect of the predictor on the outcome strengthens or weakens as the predictor increases. A significant positive quadratic term indicates a U-shaped relationship, while a significant negative quadratic term indicates an inverted U-shaped relationship (Cohen et al., 2003; Haans et al., 2016). If any interaction term was significant, simple slope tests were conducted (Cohen et al., 2003). Simple slope tests were performed by dividing maternal negative parenting into high and low groups based on +1 SD and analyzing the association between multilocus genetic profile score, its quadratic term, and aggressive behavior under high and low maternal negative parenting conditions. Following recommendations from previous research (Kochanska et al., 2011; Roisman et al., 2012; Zhang et al., 2015), maternal negative parenting was also divided into high and low groups based on +2 SD to explore and clarify significant interactions beyond +1 SD.

To avoid multicollinearity, both multilocus genetic profile score and maternal negative parenting were standardized. To verify the robustness of results, a series of sensitivity analyses were conducted: (1) repeating the above regression models for any single gene and comparing differences in significance between single-gene and multilocus genetic profile score models (Cao & Rijlaarsdam, 2022); (2) conducting k-fold cross-validation using the regress and crossvalind functions in MATLAB R2013b (Marcot & Hanea, 2021; Zhang et al., 2021); and (3) randomly splitting the sample into two subsamples (50% each) to conduct the above regression analyses for internal validation (Cao & Rijlaarsdam, 2022; Zhang et al., 2016).

3.1 Descriptive Statistics

Descriptive statistics and correlations for all variables are presented in Table 1 . Multilocus genetic profile score was not significantly correlated with maternal negative parenting, ruling out gene-environment correlation. Multilocus genetic profile score was not significantly correlated with aggression at either time point, while maternal negative parenting was significantly positively correlated with aggression at both time points. Independent samples t-tests showed significant gender differences in aggressive behavior and maternal negative parenting at both time points (Time 1 aggression: $t(782) = -7.13$, Time 2 aggression: $t(772) = -6.68$, negative parenting: $t(958) = -3.65$, $ps < 0.001$), with males showing significantly higher aggressive behavior and maternal negative parenting than females.

3.2 Effects of Multilocus Genetic Profile Score and Maternal Negative Parenting on Adolescent Aggression

To examine the effects of polygenic variants and maternal negative parenting on adolescent aggression, hierarchical regression analyses were conducted with Time 1 adolescent aggressive behavior and Time 2 adolescent aggressive behavior as dependent variables, respectively, controlling for gender and including multilocus genetic profile score, maternal negative parenting, the interaction between multilocus genetic profile score and maternal negative parenting, the quadratic term of multilocus genetic profile score, and the interaction between the quadratic term and maternal negative parenting as predictor variables.

Results for Time 1 adolescent aggressive behavior as the dependent variable are shown in Table 2 . Maternal negative parenting significantly positively predicted Time 1 aggressive behavior. The main effect of multilocus genetic profile score and its interaction with maternal negative parenting on Time 1 aggressive behavior were not significant. The quadratic term of multilocus genetic profile score did not significantly predict Time 1 aggressive behavior, but the interaction between the quadratic term and negative parenting significantly predicted Time 1 aggressive behavior. Simple slope analysis (see Figure 1 [Figure 1: see original paper]) showed that when maternal negative parenting was high (+1 SD), the quadratic term of multilocus genetic profile score significantly and positively predicted Time 1 aggressive behavior (quadratic term: $b = 0.05$, $t = 2.75$, $p = 0.006$; linear term: $b = -0.06$, $t = -1.92$, $p = 0.055$), showing a U-shaped relationship between multilocus genetic profile score and Time 1 aggressive behavior, with adolescents with high or low multilocus genetic profile scores exhibiting high aggressive behavior. When maternal negative parenting was low (-1 SD), the quadratic term of multilocus genetic profile score did not significantly predict Time 1 aggressive behavior (quadratic term: $b = -0.03$, $t = -1.33$, $p = 0.18$; linear term: $b = 0.01$, $t = 0.17$, $p = 0.86$).

Results for Time 2 adolescent aggressive behavior as the dependent variable are shown in Table 3 . Maternal negative parenting significantly positively predicted Time 2 aggressive behavior. The main effect of multilocus genetic profile score and its interaction with maternal negative parenting on Time 2 aggressive behavior were not significant. The quadratic term of multilocus genetic profile score significantly predicted Time 2 aggressive behavior (quadratic term: $b = 0.03$, $t = 1.98$, $p = 0.048$; linear term: $b = -0.02$, $t = -0.78$, $p = 0.44$), indicating that adolescents with excessively high or low multilocus genetic profile scores showed high aggressive behavior (see Figure 2 [Figure 2: see original paper]). The quadratic term of multilocus genetic profile score significantly interacted with negative parenting in predicting Time 2 aggressive behavior. Simple slope analysis showed that when maternal negative parenting was high (+1 SD), the quadratic term of multilocus genetic profile score significantly and positively predicted Time 2 aggressive behavior (quadratic term: $b = 0.07$, $t = 3.20$, $p = 0.001$; linear term: $b = -0.04$, $t = -1.33$, $p = 0.18$), showing a U-shaped relationship between multilocus genetic profile score and Time 2 aggressive behavior, with adolescents with excessively high or low multilocus genetic profile scores exhibiting high aggressive behavior (see Figure 3 [Figure 3: see original paper]). When maternal negative parenting was low (-1 SD), the quadratic term of multilocus genetic profile score did not significantly predict Time 2 aggressive behavior (quadratic term: $b = -0.02$, $t = -0.70$, $p = 0.49$; linear term: $b = -0.002$, $t = -0.06$, $p = 0.95$).

3.3 Sensitivity Analyses

Regression analyses of any single gene and maternal negative parenting on Time 1 and Time 2 aggressive behavior showed that the quadratic term of any single gene (ΔR^2s ≤ 0.004; $|b|$s ≤ 0.03, ps ≥ 0.16) and its interaction with maternal negative parenting were not significant (ΔR^2s ≤ 0.002; $|b|$s ≤ 0.04, ps $\geq$ 0.13, see Appendix Tables S1 and S2), indicating that multilocus genetic profile scores have greater advantage than single-gene studies in increasing genetic explanatory power and significance. k-fold cross-validation results showed that model-predicted aggression scores were significantly correlated with actual aggression scores (rs ≥ 0.21, ps $\leq 1.46 \times 10^{-11}$), and the r values remained stable and significant after 10 repetitions (rs = 0.20 ~ 0.24, ps = 3.91×10^{-14} ~ 2.87×10^{-10}, see Appendix "2 k-fold cross-validation"). Internal validation results from randomly splitting the total sample into two subsamples showed that the interaction between the quadratic term of multilocus genetic profile score and maternal negative parenting was significant or marginally significant in both subsamples (see Appendix Tables S3 and S4). In summary, the main findings of this study were supported by sensitivity analyses.

4.1 Maternal Negative Parenting Moderates the Association Between Dopaminergic Genes and Aggression

The U-shaped relationship between dopaminergic genes and aggression was more pronounced under high maternal negative parenting. Under conditions of high maternal negative parenting, the quadratic term of dopaminergic multilocus genetic profile score significantly predicted both Time 1 and Time 2 aggressive behavior, with adolescents carrying more or fewer alleles associated with low dopamine activity showing high aggressive behavior. Under low maternal negative parenting, alleles associated with low dopamine activity were not significantly associated with aggressive behavior. These results are consistent with G×E interaction theory and related empirical research (Beauchaine et al., 2007; Shanahan & Hofer, 2005; Tomlinson et al., 2022; Zhang et al., 2016), indicating that high negative parenting environments can trigger or exacerbate the association between dopaminergic polygenic variants and aggressive behavior, while relatively positive environments (i.e., low maternal negative parenting in this study) can prevent or attenuate genetic predisposition expression.

The mechanism by which maternal negative parenting enhances the association between dopaminergic polygenic variants and aggressive behavior may involve the following processes. Maternal negative parenting, as an adverse environmental factor, affects baseline dopamine levels in the brain, causing numerous changes in the dopaminergic system, such as reduced DRD2 receptor density and overactivation of the mesocortical dopamine pathway (Tielbeek et al., 2018). Due to enhanced dopaminergic sensitivity and stress reactivity during adolescence, the impact of adverse environmental factors like maternal negative parenting on the brain dopaminergic system is more pronounced during this period. Therefore, adolescents with excessively high or low dopaminergic multilocus genetic profile scores, when experiencing high levels of maternal negative parenting, show impaired function in brain regions such as the PFC due to dual genetic and environmental influences, leading to increased risk of aggressive behavior. At the behavioral level, maternal negative parenting leads adolescents to imitate aggression or hostility, enhances angry or hostile emotions, and impairs emotion regulation abilities (Gershoff, 2002; Goulter et al., 2020). These behavioral influences interact with excessively high or low dopamine function to increase adolescent aggressive behavior levels (Zhang et al., 2016).

The relationship between dopaminergic multilocus genetic profile score and aggressive behavior conforms to a U-shape, with adolescents having excessively high or low polygenic scores associated with low dopamine activity both showing high aggressive behavior. This is consistent with previous neurobiochemical research findings (e.g., Bertolino et al., 2009; Robbins & Arnsten, 2009; Tian et al., 2013; Tunbridge et al., 2006), which show that both excessively high and low dopamine levels cannot effectively maintain the balance between cortical excitation and inhibition, leading to impaired PFC function, abnormal functional connectivity with other brain regions, and dysregulation of mesocortical and mesolimbic dopamine pathways (Arnsten, 2009; Bertolino et al., 2009; Robbins & Arnsten, 2009; Seamans & Yang, 2004; Tian et al., 2013), thereby limiting executive control and emotion regulation functions and increasing sensitivity to reward and punishment (Romeo, 2017), resulting in aggressive behavior (Achterberg et al., 2020; Chester & DeWall, 2016; Padmanabhan & Luna, 2014; Raine, 2008; Rosell & Siever, 2015; Sadeh et al., 2019; Tielbeek et al., 2018). Although these findings require further verification from future neurobiochemical and brain science research, they suggest that to understand how dopaminergic system genes influence aggressive behavior, we cannot simply judge genes as "good" or "bad" based on high or low dopamine activity, but must consider the complexity of genes themselves and the possible U-shaped relationship between dopaminergic polygenic combinations and aggressive behavior.

4.2 Innovations, Limitations, and Future Directions

An important innovation of this study is the use of the multilocus genetic profile approach, which accumulates multiple gene loci involved in dopamine metabolism, transmission, and transport, to reveal the non-linear relationship between dopaminergic system genes and adolescent aggressive behavior. This has important implications for understanding the complex physiological mechanisms of aggressive behavior. Although gene-environment interactions explained less than 1% of the variance, they remain significant for developmental behavioral genetics research (Evans, 1985; Hasan & Afzal, 2019). Based on gene-environment interactions, researchers can focus on physiological mechanisms or environmental sensitivity characteristics regulated by dopaminergic system genes to further reveal the physiological-environmental mechanisms underlying aggressive behavior. In health decision-making and medical interventions, based on individuals' candidate gene information or physiological mechanism characteristics and their environmental sensitivity, attention can be paid to differential responsiveness to environments (interventions) among individuals with different genetic backgrounds, thereby forming more targeted treatment or intervention programs. For example, providing positive parenting environments for adolescents with aggressive behavior who are more environmentally sensitive can prevent genetic predisposition expression and reduce aggressive behavior to some extent.

This study reveals that the influence of dopaminergic polygenic variants on aggressive behavior during adolescence shows a non-linear pattern, different from findings from studies with childhood samples (Davies et al., 2015; Thibodeau et al., 2015; Vrantsidis et al., 2021). This is related to the developmental dynamics of the brain dopaminergic system (Naneix et al., 2012; Tielbeek et al., 2018; Toth, 2022), as well as the fact that adolescents need to make complex decisions and learn to inhibit inappropriate behaviors and impulses (Tielbeek et al., 2018), while key brain regions (e.g., PFC) are not yet fully developed and PFC regulatory functions are overloaded (Toth, 2022). These results suggest that adolescence may be a critical period when gene-environment interaction patterns change. Future research should employ longer-term longitudinal designs to more fully explore and compare relationship patterns between dopaminergic polygenic variants and aggressive behavior across different age stages, further revealing the developmental dynamics of aggressive genetic mechanisms and sensitive periods for genetic effects.

Additionally, in this study, the quadratic term of multilocus genetic profile score and its interaction with maternal negative parenting predicted aggressive behavior levels at Time 1 and Time 2, but could not predict developmental changes in aggressive behavior from Time 1 to Time 2. However, this does not mean that gene-environment interactions are unrelated to the development of aggressive behavior. Future research should deeply examine the effects of genetics and environment on aggressive behavior and its developmental changes.

This study has several limitations. First, based on the neurophysiological mechanisms and related theories of aggressive behavior, we selected three functional loci involved in dopamine metabolism, transport, and transmission, covering multiple physiological processes affecting dopamine activity and avoiding data-driven and overfitting risks. However, the dopaminergic system includes numerous genes, and this study could not include all dopaminergic system genes or candidate genes for aggressive behavior, thus limiting explanatory power.

Future research should still adopt polygenic approaches to examine other candidate genes in the dopaminergic system or joint effects between dopaminergic and other systems to more comprehensively reveal the polygenic genetic basis of aggressive behavior. Second, although this study conducted multiple internal replication validations, providing evidence for result reliability, random grouping reduced sample size and may have decreased statistical power. No external sample using the same measurement tools and similar participant characteristics was available for external validation. Future research should conduct external validation in other samples, especially larger ones. Third, this study only focused on urban, typically developing adolescents, and the results may not generalize to high-risk adolescent populations such as those with low socioeconomic status or clinical samples. In high-risk populations, maternal negative parenting levels may be higher and comorbidities beyond aggression may exist (Davies et al., 2019; Gard et al., 2022; Stocker et al., 2017), and the strength and pattern of associations between genes and aggressive behavior may differ from typically developing adolescents. Fourth, this study only examined maternal negative parenting and did not include paternal parenting. Paternal parenting behavior also has important effects on adolescent problem behavior (e.g., Cao & Rijlaarsdam, 2022). Future research should examine both paternal and maternal parenting to more comprehensively reveal the influence of parenting on adolescent aggressive behavior. Fifth, this study only focused on adolescent genes, but considering that parental genes may be associated with parenting behavior and intergenerational transmission issues, future research should also assess parental genes to more comprehensively explore the effects of genes and environment on adolescent aggressive behavior.

5 Conclusion

This study provides evidence for the polygenic genetic basis of aggressive behavior and the non-linear relationship between dopaminergic system genes and adolescent aggressive behavior. In early-to-mid adolescence, there is a non-linear relationship between dopaminergic system genes and aggressive behavior, and high negative parenting environments can exacerbate or amplify this relationship. These results suggest that interventions for aggressive behavior should focus on reducing negative parenting and increasing positive parenting.

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Appendix: Series of Sensitivity Analyses

1 Single-Gene Effect Tests

Regression analyses were conducted for any single gene and maternal negative parenting on Time 1 and Time 2 aggressive behavior. Results showed that maternal negative parenting significantly predicted Time 1 and Time 2 aggressive behavior, while any single gene, its interaction with maternal negative parenting, its quadratic term, and the interaction between its quadratic term and maternal negative parenting were all non-significant (see Tables S1 and S2), indicating that multilocus genetic profile scores have greater advantage than single-gene studies in increasing genetic explanatory power and significance.

Table S1 Effects of Single Genes and Maternal Negative Parenting on Time 1 Aggressive Behavior

Variable	ΔR^2	p	b	95% CI
COMT Val158Met	0.22	<0.001		
COMT×NP	0.05***	<0.001		
$COMT^2$	0.01**	<0.001		
$COMT^2$×NP	0.007**	<0.001		
DRD2 rs1799978	0.22	<0.001		
DRD2×NP	0.05***	<0.001		
$DRD2^2$	0.01**	<0.001		
$DRD2^2$×NP	0.007**	<0.001		
DAT1 rs27072	0.22	<0.001		
DAT1×NP	0.05***	<0.001		
$DAT1^2$	0.01**	<0.001		
$DAT1^2$×NP	0.007**	<0.001		

Note: NP = maternal negative parenting behavior. Significant and marginally *significant results are bolded.*

Table S2 Effects of Single Genes and Maternal Negative Parenting on Time 2 Aggressive Behavior

Variable	ΔR^2	p	b	95% CI
COMT Val158Met	0.21	<0.001		
COMT×NP	0.04***	<0.001		
$COMT^2$	0.01**	<0.001		
$COMT^2$×NP	0.004*	<0.001		
DRD2 rs1799978	0.21	<0.001		
DRD2×NP	0.04***	<0.001		
$DRD2^2$	0.01**	<0.001		
$DRD2^2$×NP	0.004*	<0.001		
DAT1 rs27072	0.21	<0.001		
DAT1×NP	0.04***	<0.001		
$DAT1^2$	0.01**	<0.001		
$DAT1^2$×NP	0.004*	<0.001		

2 k-Fold Cross-Validation

To further verify model generalizability and predictive power, k-fold cross-validation (k = 10; Marcot & Hanea, 2021; Zhang et al., 2021) was conducted using the regress and crossvalind functions in MATLAB R2013b, with 9 groups as the training set and 1 group as the test set. The regression model was: y = c + β_1 × MGPS + β_2 × maternal negative parenting + β_3 × MGPS × maternal negative parenting + β_4 × MGPS × MGPS + β_5 × MGPS × MGPS × maternal negative parenting + β_6 × gender + e. Results showed that model-predicted aggression scores were significantly correlated with actual aggression scores (Time 1 aggression: r = 0.24, p = 3.45×10^{-14}; Time 2 aggression: r = 0.21, p = 1.46×10^{-11}). To test result stability, this process was repeated 10 times, with r values remaining stable and significant (Time 1 aggression: r = 0.22 ~ 0.24, p = 3.91×10^{-14} ~ 1.74×10^{-11}; Time 2 aggression: r = 0.20 ~ 0.22, p = 9.81×10^{-12} ~ 2.87×10^{-10}).

3 Internal Validation

The sample was randomly split into two subsamples (50% each; n_{subsample1} = 500, n_{subsample2} = 544) for regression analysis to conduct internal validation. The two subsamples did not differ significantly on major variables (gender: ^{2} = 2.23, p = 0.14; multilocus genetic profile score: ^{2} = 3.20, p = 0.67; maternal negative parenting: t = 0.49, p = 0.62; Time 1 aggression: t = -0.24, p = 0.81; Time 2 aggression: t = -0.14, p = 0.89). As shown in Tables S3 and S4, the interaction between the quadratic term of multilocus genetic profile score and maternal negative parenting in predicting Time 1 aggressive behavior was significant in subsample 1 ($p = 0.03$) and marginally significant in subsample 2 ($p = 0.059$), and marginally significant in both subsamples for Time 2 aggressive behavior ($p = 0.06$ and $p = 0.056$).

For Time 1 aggressive behavior, in subsample 1, when maternal negative parenting was high ($\geq$ 1.90 SD), the quadratic term of multilocus genetic profile score significantly and positively predicted Time 1 aggressive behavior ($b = 0.09$, $t = 1.97$, $p = 0.05$), showing a U-shaped relationship where adolescents with excessively high or low multilocus genetic profile scores exhibited high aggressive behavior. When experiencing low maternal negative parenting (-1 SD), the quadratic term did not significantly predict Time 1 aggressive behavior ($b = -0.06$, $t = -1.72$, $p = 0.09$). In subsample 2, when maternal negative parenting was high (+1 SD), the quadratic term significantly and positively predicted Time 1 aggressive behavior ($b = 0.07$, $t = 2.40$, $p = 0.02$), showing a U-shaped relationship. When maternal negative parenting was low (-1 SD), the quadratic term did not significantly predict Time 1 aggressive behavior ($b = -0.01$, $t = -0.38$, $p = 0.70$).

For Time 2 aggressive behavior, when maternal negative parenting was high (+1 SD), the quadratic term of multilocus genetic profile score significantly and positively predicted Time 2 aggressive behavior (subsample 1: $b = 0.059$, $t = 1.92$, $p = 0.055$; subsample 2: $b = 0.08$, $t = 2.66$, $p = 0.008$), showing a U-shaped relationship where adolescents with excessively high or low multilocus genetic profile scores exhibited high aggressive behavior. When maternal negative parenting was low (-1 SD), the quadratic term did not significantly predict Time 2 aggressive behavior (subsample 1: $b = -0.04$, $t = -1.00$, $p = 0.32$; subsample 2: $b = -0.006$, $t = -0.18$, $p = 0.86$).

Table S3 Effects of Multilocus Genetic Profile Score and Maternal Negative Parenting on Time 1 Aggressive Behavior in Subsamples

Variable	Subsample 1 ΔR^2	p	95% CI	Subsample 2 ΔR^2	p	95% CI
MGPS×NP	0.05***	<0.001	[0.14, 0.35]	0.05***	<0.001	[0.18, 0.40]
$MGPS^2$	0.01**	<0.001	[-0.08, 0.06]	0.02*	<0.001	[-0.03, 0.11]
$MGPS^2$×NP	0.006+	<0.001	[-0.06, 0.05]	0.007+	<0.001	[-0.10, 0.02]

Table S4 Effects of Multilocus Genetic Profile Score and Maternal Negative Parenting on Time 2 Aggressive Behavior in Subsamples

Variable	Subsample 1 ΔR^2	p	95% CI	Subsample 2 ΔR^2	p	95% CI
MGPS×NP	0.04***	<0.001	[0.11, 0.34]	0.05***	<0.001	[0.18, 0.41]
$MGPS^2$	0.007+	<0.001	[-0.07, 0.07]	0.01*	<0.001	[-0.03, 0.11]
$MGPS^2$×NP	0.006+	<0.001	[-0.06, 0.07]	0.007+	<0.001	[-0.10, 0.02]

Note: MGPS = multilocus genetic profile score.

Note: Figure translations are in progress. See original paper for figures.

Source: ChinaXiv —Machine translation. Verify with original.