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Dopamine Functioning and Child Externalizing Behavior: A Longitudinal Analysis of Polygenic Susceptibility to Parenting

Karen Fischer, MSc,*† Alithe L. van den Akker, PhD,*† Helle Larsen, PhD,†‡
Terrence D. Jorgensen, PhD,* Geertjan Overbeek, PhD*†

ABSTRACT: *Objective:* This study investigated how genetic susceptibility may affect children's sensitivity to parenting practices in their development of externalizing behavior. We created a continuous polygenic index composed of 5 dopamine polymorphisms to investigate the moderating role of dopamine-related genes in shaping parent-child gene-by-environment (Gc×E) interactions. Accumulating research supports that differences in children's dopamine neurotransmission make certain children more susceptible to both negative and positive parenting practices, a "for-better and for-worse" effect. *Methods:* Data from a 3-wave longitudinal study (4 months between waves) on 190 at-risk families with children aged 4 to 8 were used to investigate whether a heightened polygenic index score amplified the associations between negative and positive parenting and later children's externalizing behavior. Parenting practices and child externalizing behavior were assessed by parent-reported questionnaires. *Results:* Findings were not in line with the expectation that there was a stronger association between positive and negative parenting and later externalizing behavior for children with higher scores on the polygenic susceptibility index. Rather, children with a lower score on the polygenic susceptibility index showed more later externalizing behavior in response to positive parenting behavior, whereas for children with a higher score on the polygenic index, positive parenting was predictive of relatively lower levels of later child externalizing behavior. *Conclusion:* The results indicate that not only are children with higher but also lower scores on the polygenic index sensitive to parenting, they suggest that different phenotypical characteristics related to reward processing might underlie these genetic susceptibilities to parenting practices.

(*J Dev Behav Pediatr* 41:628–636, 2020) **Index terms:** differential susceptibility, polygenic, longitudinal, externalizing behavior, parenting.

Early onset of disruptive behavior is a robust predictor of impairing externalizing psychopathology in later life. Externalizing problems during early childhood predict a range of maladaptions in later life, such as academic problems, impaired social relationships, and cognitive development.¹ Factors implicated in the development of child externalizing behaviors are dysfunctional parenting practices. Parenting research has shown that dysfunctional parenting practices play a key role in eliciting externalizing and disruptive behavior problems in children. Specifically, many studies showed that parental punishment, inconsistent discipline, and lack of reward-

based parenting function as longitudinal predictors of externalizing behaviors (e.g., see meta-analysis²). Interestingly, accumulating research shows that not all children may be equally affected by parenting. Although some children may be highly reactive to parenting practices and in return elicit strong reactions in their parents, other children may do so to a lesser extent. Within the past decade, research has shown that susceptibility to parenting may have a biological basis, such as in genetic and physiological pathways.

The idea that some individuals may be more vulnerable to negative environmental influences than others, also known as the "diathesis stress" model,³ has been challenged over the past years. In the last decade, several evolutionary-inspired theories emerged that posit that some individuals might not only be highly sensitive to adverse environmental influences but may also profit to a greater extent from the effects of environmental enrichment than less sensitive individuals. Some of the most prominent theoretical perspectives advocating for such a "for-better and for-worse" effect entail sensory processing sensitivity,⁴ biological sensitivity to context,⁵ and differential susceptibility theory.⁶

The sensory processing sensitivity perspective finds its roots in biology research on so-called animal "personalities" in the late 1990s, which provides strong

From the *Research Institute of Child Development, University of Amsterdam, Amsterdam, Netherlands; †Research Priority Area Yield, University of Amsterdam, Amsterdam, Netherlands; ‡Research Institute of Psychology, Department of Developmental Psychology, University of Amsterdam, Amsterdam, Netherlands.

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Address for reprints: Karen Fischer, MSc, Research Institute of Child Development and Education, Postbus 15776, 1001NG Amsterdam, Netherlands; e-mail: k.fischer@uva.nl.

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support for the existence of general traits of sensitivity to the environment across time and contexts in a wide array of species.^{4,7} Sensory processing sensitivity is proposed to be a genetically informed trait in human beings that is linked to deeper cognitive processing of stimuli of negative and positive valence.⁴ Relatedly, the concept of “biological sensitivity to context” holds that high-reactivity phenotypes have bivalent effects on psychiatric and biomedical outcomes, which can enhance and buffer risk depending on the environmental condition.⁵ This reactivity is assumed to be a phenotypic property of individuals, of both genetic and environmental origins, developed through calibration of biological stress response systems during early development. As such, biological sensitivity to context can exacerbate the effects of negative environmental conditions or promote the beneficial effects of supportive and protective environments.⁵ Similar to this perspective, the differential susceptibility hypothesis⁶ emerged, in which sensitivity to the environment is operationalized at the behavioral level. In this framework, the focus lies on individual differences in susceptibility to rearing influences that are assumed to be rooted in heritable susceptibility factors such as genetics. This idea is of great interest to developmental researchers, as the same children who are at risk of developing the most unfavorably in a dysfunctional family environment may profit the most from an increase in rewarding parenting practices. We aim to test this framework in this study.

PHENOTYPICAL EXPRESSIONS OF GENETIC SUSCEPTIBILITY

These theoretical perspectives find common ground in the notion that children differ in their reactivity to their environment and that this may in part be gene-based. Specifically, polymorphisms in the serotonin transporter, dopamine receptors (e.g., see meta-analysis⁸ and review⁹), and those related to degradation of brain dopamine and serotonin (e.g., see meta-analysis¹⁰) have consistently emerged as genes that render children more sensitive to both positive and negative environmental influences. Regarding susceptibility to dysfunctional parenting, polymorphisms related to dopamine functioning are of primary interest because they modulate children’s reward^{8,11} and punishment-based learning.¹²

Indeed, children with certain dopamine polymorphisms have been shown to be more reactive to parents’ punishment cues but also more responsive to reward cues^{8,9} (for more, see review⁶). The literature suggests that differential susceptibility is related to heightened sensitivity to rewards and punishment.^{6,8} Specifically, higher susceptibility seems to be related to various relevant phenotypes such as emotional reactivity and impulse control problems. For example, certain allelic variations of the 5 prominent dopaminergic susceptibility genes (MAOA, DAT1, DRD2, COMT, and DRD4) have been empirically linked to the development

of externalizing behavior in the context of family adversity, with a common denominator being their phenotypical expression of problem behavior related to impulse control problems and disinhibition.¹³ However, it remains unclear what specifically the underlying neurobiological mechanisms are (e.g., dopamine hypersensitivity vs hyposensitivity), through which these polymorphisms may be related to behavioral outcomes such as impulse control problems.

CONCEPTUALIZATION OF GENETIC SUSCEPTIBILITY

The functional contribution of dopamine-related genes in shaping parent-child gene-by-environment (Gc×E) interactions is probably polygenic in nature.¹⁴ Although earlier studies regarding differential susceptibility took a single candidate gene approach, research has recently moved to a polygenic approach and provides support for children’s differential susceptibility to parenting.^{15–18} Compared with a candidate-gene approach, a polygenic index may explain a greater amount of genetic variance, even if this index contains only a few more polymorphisms from the same circuitry. This is because these polymorphisms do not function in isolation and might, in aggregation, exert not linear, but nonlinear, larger effects.¹⁴ We used a continuous rather than a dichotomous genetic index given that genetic susceptibility operates most likely in a cumulative fashion, with individual genes having small effects.¹⁴ Furthermore, a continuous index allows for greater variability and thereby favorably affects power and provides more information on the magnitude of genetic susceptibility. By using a continuous polygenic approach in this study, we aim to investigate the genetic roots of how children respond to parenting behaviors.

The index was created by assigning a point for the presence of a particular allelic variant of polymorphisms, for which the literature suggested an association with heightened susceptibility to family adversity in the development of externalizing behavior.^{15,16} The selected genes have empirically been related to heightened levels of externalizing behavior and susceptibility to environmental influences in a cumulative fashion,^{15,16} which suggests that children may be influenced by parenting in a for-better and for-worse manner the more susceptibility genes they dispose over.⁵ Therefore, rather than examining a single genetic marker, we examined a composite measure of cumulative genetic susceptibility,^{15,16} which allows testing the hypothesis that a child becomes more susceptible the more susceptibility markers it carries.

THIS STUDY

The aim of this study was to investigate whether a heightened polygenic index score amplifies the associations between negative and positive parenting and later children’s externalizing behavior. In line with the differential susceptibility hypothesis, we hypothesized

that for children with a higher polygenic index, the longitudinal associations between both negative and positive parenting behavior and child externalizing behavior would be significantly stronger than for children with a lower polygenic index.

We used a 3-wave longitudinal dataset (Observational Randomized Controlled Trial on Childhood Differential Susceptibility [ORCHIDS] study¹⁵) on 190 at-risk families with children aged between 4 to 8 years old to examine the relationship between parenting practices and child externalizing behavior. To assess genetic susceptibility, a continuous polygenic index was created based on relevant polymorphisms related to dopamine functioning (DRD4, DRD2, DAT1, MAOA, and COMT), which have been associated with children's heightened susceptibility to both positive and negative environmental influences.⁵ To conduct a stringent and complete prospective test of children's differential susceptibility to parenting, both negative and positive parenting practices, representing the for-better and for-worse environment, were examined.

Previous analyses on the ORCHIDS dataset including all 387 at-risk families of the control and intervention condition showed that for boys with higher scores on the genetic susceptibility index, parent-reported externalizing behavior decreased significantly because of the Incredible Years parenting-intervention.¹⁵ These results support the "for-better" effect of the differential susceptibility hypothesis. There were no significant changes in externalizing behavior, neither parent-reported nor observed, in boys with low scores on the genetic susceptibility index in the experimental group, nor for boys in the control group, regardless of their score on the genetic susceptibility index. Interestingly, children in the control group with higher genetic susceptibility index scores did not show the greatest increase (or smallest decline) in externalizing behavior over time. These findings were thus not in line with the "for-worse" effect of the differential susceptibility hypothesis.

METHOD

Participants and Procedure

This study made use of 3-wave longitudinal data from the Observational Randomized Controlled Trial on Childhood Differential Susceptibility (ORCHIDS) study,¹⁶ a randomized controlled trial in which 387 at-risk families participated, with 1 parent (Mage = 38.09, SD = 4.84; 91% mothers) and their 4- to 8-year-old child (Mage = 6.21, SD = 1.33; 55.30% boys). The time between waves was 4 months. Before the beginning of the study, the study received approval by the research ethics committee. Approval for this study protocol, entitled The ORCHIDS, was received from the institutional review board in Medisch Ethische Toetsingscommissie Universitair Medisch Centrum Utrecht (protocol number 11-320/K).

Half of the parents were enrolled in an intervention condition (n = 197), and the other half in a control

condition (n = 190). This study made use of the control sample exclusively to assess the natural development of parent and child behaviors over time. Participating children were screened for being at risk of externalizing behavior. At-risk status was determined with a cutoff score at the 75th percentile on the Eyberg Child Behavior Inventory (ECBI),¹⁹ which parents filled out before the study. Over 84% of the parents were born in the Netherlands. Among the mothers, 50.5% were of a high educational status, whereas 27.5% and 21.2% had medium and low status, respectively (for fathers: 45.6% high, 26.2% medium, 25.6% low educational status). Parents were mostly either married or living together (87%), whereas 8.8% were single, and 4.1% classified as other. Of the 26.4% of parents who were not employed, 44.4% were a stay-at-home parent, 23.3% were unemployed, and 32.3% classified as other. Approximately 39% of the families were Christian, 5.45% were Islamic, 21.2% affiliated with other religions, and 34.2% were nonreligious. In the ORCHIDS study, child externalizing behavior and parenting practices were assessed at 3 time points (T₁, T₂, and T₃), with measurement intervals of 6 and 4 months, respectively. There was a 93% retention rate at T₃.

Measures

Questionnaire Measures

Both negative and positive parenting practices were assessed with the Parenting Practices Inventory²⁰ (PPI). We used the subscales of Harsh and Inconsequent Discipline (15 items) and Physical Punishment (6 items) to construct a measure of negative parenting practices, and the subscales Positive Verbal Discipline (9 items) and Praise and Incentives (11 items) to construct a measure of positive parenting practices. The other subscales of the PPI did not exclusively measure positive or negative parenting practices and were therefore not included. The variables for negative and positive parenting practices and child externalizing behavior at each of the 3 time points were created by summing up and averaging all items assessing the respective construct. All items were scored on a 7-point Likert scale, which assessed parents' perception of how often they used a certain parenting practice, ranging from 1 (*never*) to 7 (*always*). Cronbach's alpha for the negative parenting practices measure was 0.79, 0.83, and 0.80 at T₁, T₂, and T₃, respectively. Cronbach's alpha for the positive parenting practices measure was 0.74, 0.77, and 0.80 at T₁, T₂, and T₃.

Child externalizing behavior was assessed by parent reports on the ECBI,¹⁹ a measure designed to assess externalizing problems in children aged 7 to 16 years. This study used the Intensity Scale of the ECBI, which consists of 36 items and demonstrated a Cronbach's alpha of 0.85, 0.86, and 0.88 at T₁, T₂, and T₃, respectively. All items were scored on a 7-point Likert scale, assessing how often a certain child externalizing behavior occurred, ranging from 1 (*never*) to 7 (*always*).

Genetic Susceptibility Measure

Genetic susceptibility was determined at Wave 1 of the study with saliva samples. The dopamine polymorphisms of interest for this study were *DRD4* (7R allele), *DRD2* (A1 allele, rs1800497), *DAT1* (10R allele), *MAOA* (low-activity allele), and *COMT* (val allele, rs4680) because these polymorphisms have been related to children's differential susceptibility to both positive and negative environmental influences.^{5,7,15,16} For a detailed account of the individual polymorphisms extraction procedure, see Supplemental Material, Supplemental Digital Content 1, <http://links.lww.com/JDBP/A259>.

Polygenic Index

A continuous polygenic susceptibility index was created by yielding a sum score by assigning a point for each polymorphism that disposed over at least one of the susceptibility alleles. This polygenic index ranged from a score of 0 to 5. The higher the sum score, the higher the genetic susceptibility.^{15,16}

Statistical Procedure

All analyses in this study were conducted in the program R. Interaction plots were generated with the R package "interactions."²¹ Regression analyses were conducted on uncentered data with the polygenic index as a moderator on the longitudinal associations from parenting to later child externalizing behavior. We ran 4 individual regression analyses on the following associations: negative parenting at T1 to child externalizing behavior at T2, negative parenting at T2 to child externalizing behavior at T3, positive parenting at T1 to child externalizing behavior at T2, and positive parenting at T2 to child externalizing behavior at T3. To answer our research question of whether these longitudinal associations were moderated by polygenic index, we conducted piecewise tests of the models that incorporate multiplicative terms involving the specific predictors and a dimensional polygenic composite. Specifically, we conducted a multiple regression analysis for each outcome variable (child externalizing behavior at T2 and T3), with the parenting variable (either positive or negative parenting) and child externalizing behavior at the previous time point as predictor variables. We tested for moderation by polygenic index by including a main effect of polygenic index score and an interaction between polygenic index score and parenting at T1. Running these regressions allowed us to investigate whether associations from parenting practices to later child externalizing behavior were moderated by children's polygenic index. For the interactions that were significant, we probed the interaction to identify for which children (i.e., at which specific value of the polygenic index score) the association from parenting practices to later child externalizing behavior was statistically significant (i.e., nonzero). To identify lower and upper bounds for (non)significant associations, we used the Johnson-Neyman procedure. Briefly, a Johnson-Neyman in-

terval can be interpreted as follows: The parenting-externalizing association was significant among children whose polygenic index score either fell below the lower bound or above the upper bound. Among children whose polygenic index score fell within the Johnson-Neyman interval, the parenting-externalizing association was not statistically significant ($p > 0.05$). Although the reverse situation (in which significant associations occur only for those values within the interval rather than outside it) is also possible, that interpretation did not arise in our results.²¹

RESULTS

Table 1 displays the means, standard deviations, and the bivariate correlations for negative and positive parenting practices and for child externalizing behavior. For the individual subscales of negative parenting practices, mean scores for the subscale of Physical Punishment were in the at-risk range at each of the 3 measurement points and in the clinical range for the subscale Harsh and Inconsequent Discipline.²⁰ For positive parenting practices, mean scores for the subscales of Positive Verbal Discipline were in the at-risk range, and for the subscales of Praise and Incentives, they were in the clinical range at all 3 time points. Taken together, these scores reflect the at-risk nature of our sample, with moderately high scores on negative parenting practices and low scores on positive parenting practices. For child externalizing behavior, the clinical scores at the first measurement point and the at risk scores on the second and third measurement points confirm the at-risk characteristic for child externalizing behavior in this sample.¹⁵ Seven of 9 zero-order correlations between child externalizing behavior and negative parenting practices were significant, with all respective correlations being positive. Thus, as expected, parents' use of negative parenting practices was related to more externalizing behavior in children, both concurrently and over time. For positive parenting practices, no significant correlations were found with children's externalizing behavior. No correlations between polygenic index and the other constructs were significant.

The regression analyses (Tables 2 and 3) showed the following main effects: Child externalizing behavior was not predicted by negative parenting but was at T3 (but not T2) predicted by positive parenting at the previous time point. The association indicated that lower levels of positive parenting at T2 were predictive of relatively higher levels of externalizing behavior at T3, controlling for T2 differences. Furthermore, child externalizing behavior at both T2 and T3 was predicted by child externalizing behavior at the previous time point for both the positive and negative parenting model. Last, there was a main effect of polygenic index at T2 on child externalizing behavior at T3.

Regarding our main research question on genetic moderation of the associations between parenting and

Table 1. Descriptive Statistics and Correlations for Child Externalizing Behavior and Negative and Positive Parenting

Variable	M	SD	1	2	3	4	5	6	7	8	9	10
1 Neg. PB at T1	2.699	0.591	—									
2 Neg. PB at T2	2.572	0.660	0.697**	—								
3 Neg. PB at T3	2.538	0.568	0.607**	0.612**	—							
4 Pos. PB at T1	4.772	0.563	-0.080	-0.066	-0.054	—						
5 Pos. PB at T2	4.729	0.578	-0.084	-0.027	-0.009	0.669**	—					
6 Pos. PB at T3	4.714	0.626	-0.167*	-0.152*	-0.067	0.593**	0.675**	—				
7 CEB at T1	3.650	0.514	0.335**	0.249**	0.123	0.013	-0.037	-0.028	—			
8 CEB at T2	3.514	0.545	0.236**	0.162*	0.111	0.078	0.045	0.144	0.650**	—		
9 CEB at T3	3.403	0.551	0.226**	0.174*	0.203**	-0.038	-0.006	-0.021	0.606**	0.721**	—	
10 G	2.732	0.930	-0.027	0.049	0.028	0.008	0.101	0.040	-0.053	-0.035	-0.119	—

** $p < 0.01$, * $p < 0.05$ (2-tailed). CEB, child externalizing behavior; G, genetic susceptibility; Neg. PB, negative parenting; Pos. PB, positive parenting.

child externalizing behavior, we found that children's polygenic index score moderated the associations between positive parenting at T2 and child externalizing behavior at T3. Specifically, the results showed a cross-over interaction for the effect of children's polygenic index score on the association between positive parenting at T2 and child externalizing behavior at T3 (Fig. 1). The Johnson-Neyman interval indicated that when polygenic index score was outside the interval (0.82–3.62), the slope of positive parenting at T2 was significant at $p < 0.05$. Thus, when children's polygenic index score was 0 (<0.82), positive parenting at T2 was associated with a relative increase of child externalizing behavior at T3, and when children's polygenic index score was 4 or 5 (>3.62), positive parenting at T2 was predictive of relatively lower levels of child externalizing behavior at T3, controlling for T2 differences. Figure 2 displays the Johnson-Neyman interval. The simple slopes analysis demonstrated a slope of -0.34 (standard error [SE] = 0.15, $p = 0.03$) for a polygenic index score of 5, a slope of -0.20 (SE = 0.09, $p = 0.03$) for a polygenic index score of 4, a slope of -0.06 (SE = 0.05, $p = 0.24$) for a polygenic index score of 3, a slope of 0.07 (SE = 0.06, $p = 0.25$) for a polygenic index score of 2, a slope of 0.21 (SE = 0.11, $p = 0.06$) for a polygenic index score of one, and a slope of 0.35 (SE = 0.16, $p = 0.04$) for a polygenic index score of 0.

DISCUSSION

In this study, we found 1 effect of parenting on later child externalizing behavior, with positive parenting at T2 predicting more externalizing problems at T3, controlling for previous levels of externalizing problems. This finding was in contrast to our hypothesis that positive parenting would be associated with less rather than more externalizing behavior over time. Although speculative, it is possible that in at-risk families, parents attempt to deal with children's oppositional and defiant behavior with more positive parenting practices (e.g., temporary relief from disruptive behavior) and in such a way be associated with higher externalizing behavior in children in the long run.²³ Although this general explanation may hold true, it cannot inform conclusions about parent-child interactions at the microlevel, such as with coercive cycles of mutual reinforcement between parent and child.

Regarding our main research question, we expected to find a differential susceptibility effect, namely that a heightened polygenic index score would amplify the associations between negative and positive parenting and later children's externalizing behavior. We expected a cumulative susceptibility gene effect, namely that the more susceptibility genes a child carries, the more susceptible they would be to parenting effects. We did not find an interaction between children's polygenic index

Table 2. Regression Analysis Results for Child Externalizing Behavior at T2 and at T3 for Negative Parenting

Regression	Externalizing Behavior at T2				Externalizing Behavior at T3				
	<i>b</i>	SE	<i>t</i> (171)	<i>p</i>	Regression	<i>b</i>	SE	<i>t</i> (175)	<i>p</i>
Intercept	0.18	0.56	0.32	0.75	Intercept	0.25	0.45	0.56	0.58
Neg. PB at T1	0.29	0.19	1.52	0.13	Neg. PB at T2	0.30	0.16	1.84	0.07
G	0.26	0.18	1.45	0.15	G	0.17	0.14	1.22	0.23
CEB at T1	0.70	0.06	10.94	<0.001	CEB at T2	0.72	0.05	13.31	<0.001
Neg. PB at T1 × G	-0.10	0.07	-1.48	0.14	Neg. PB at T2 × G	-0.09	0.05	-1.63	0.11

CEB at T2: multiple $R^2 = 0.44$; $F(4, 178) = 34.63$, $p < 0.001$; CEB at T3: multiple $R^2 = 0.53$; $F(4, 172) = 49.46$, $p < 0.001$. CEB, child externalizing behavior; G, genetic susceptibility; Neg. PB, negative parenting; SE, standard error.

Table 3. Regression Analysis Results for Child Externalizing Behavior at T2 and at T3 for Positive Parenting

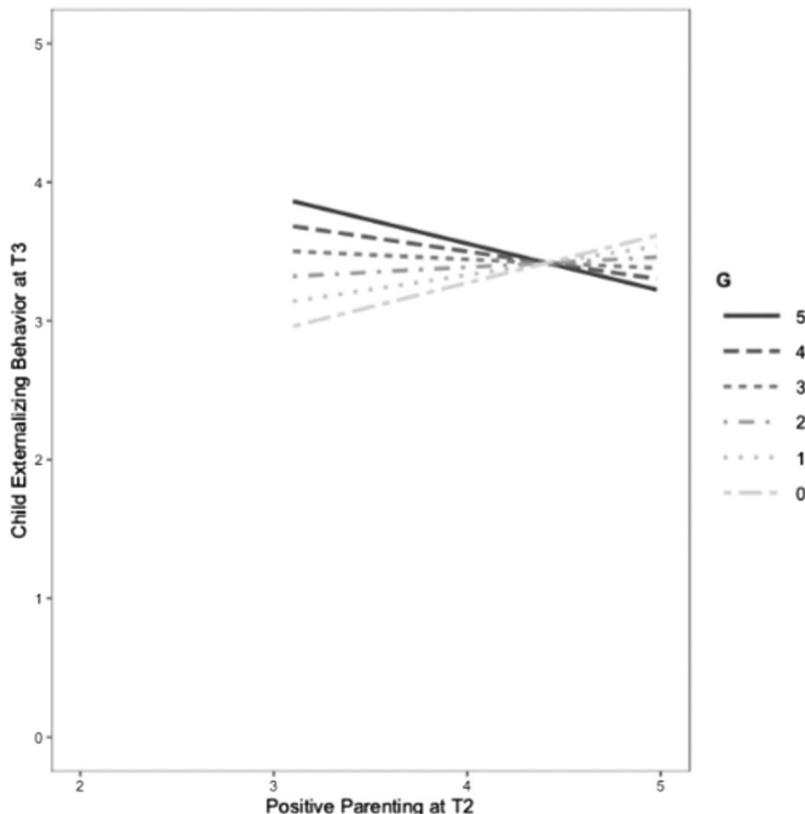
Regression	Externalizing Behavior at T2				Regression	Externalizing Behavior at T3			
	<i>b</i>	SE	<i>t</i> (177)	<i>p</i>		<i>b</i>	SE	<i>t</i> (171)	<i>p</i>
Intercept	-0.04	0.90	-0.05	0.97	Intercept	-0.73	0.82	-0.90	0.37
Pos. PB at T1	0.21	0.18	1.14	0.26	Pos. PB at T2	0.35	0.16	2.12	0.03
G	0.22	0.30	0.74	0.46	G	0.61	0.28	2.14	0.03
CEB at T1	0.70	0.06	11.61	<0.001	CEB at T2	0.74	0.05	13.96	<0.001
Pos. PB at T1 × G	-0.05	0.06	-0.75	0.46	Pos. PB at T2 × G	-0.14	0.06	-2.32	0.02

CEB at T2: multiple $R^2 = 0.41$; $F(4, 178) = 34.72$, $p < 0.001$; CEB at T3: multiple $R^2 = 0.54$; $F(4, 172) = 50.44$, $p < 0.001$. CEB, child externalizing behavior; G, genetic susceptibility; Pos. PB, positive parenting; SE, standard error.

score and negative parenting in the prediction of externalizing problems. However, we did find an interaction between children's polygenic index score and *positive* parenting in the prediction of externalizing problems. We found that when children's polygenic index score was higher, positive parenting at T2 was associated with lower child externalizing behavior at T3 than when polygenic susceptibility was lower. However, for the children with the lowest polygenic susceptibility, we found that the association was in another direction: for them, positive parenting at T2 was associated with more child externalizing behavior at T3. Therefore, we cannot conclude that the children with a higher polygenic index score were more susceptible to positive parenting than children with a low index score; rather, they reacted differently. Specifically, these children may all be af-

ected by positive parenting, but this translates into different outcome behaviors as a function of the effect that the susceptibility genes may have on phenotypical expressions in children with higher and lower polygenic index scores, respectively.

Specifically, to explain these results, the literature shows that the examined dopaminergic susceptibility variants in our study are not only related to higher susceptibility to positive and negative environmental influences but also to various relevant phenotypes such as increased impulse control/disinhibition problems. Our finding that the greatest reduction of externalizing behavior was found in children with the highest polygenic index score could reflect the reward-dominant response style in increased impulse control problems associated with heightened susceptibility. This could be associated

**Figure 1.** Positive parenting at T2 interacts with children's genetic susceptibility score (G) in predicting child externalizing behavior at T3.

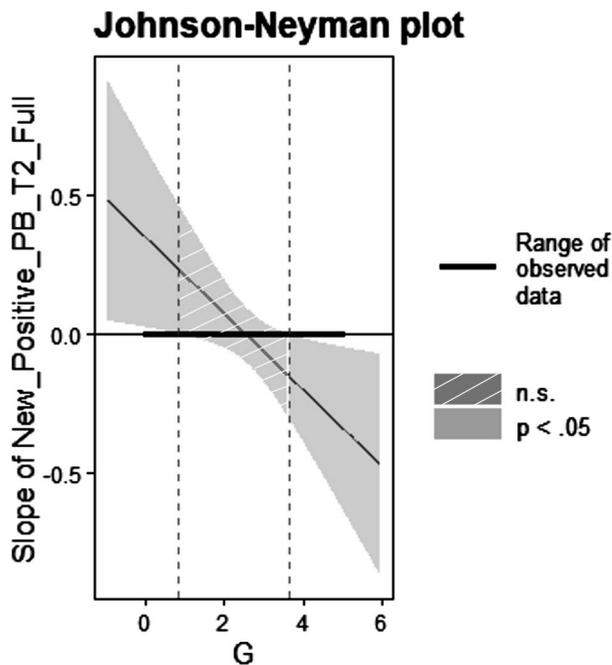


Figure 2. Positive parenting at T2 interacts with children’s genetic susceptibility score (G) in predicting child externalizing behavior at T3. n.s., not significant.

with a heightened behavioral activating system, which is a system that is activated by stimuli of reward or non-punishment and has been shown to be associated with impulse control problems.²⁴ Similarly, other research has shown that behavioral impulsivity is associated with a reward-dominant response style in younger children and a strong motivation to obtain rewards in one’s environment.²⁵ In light of this literature, children with greater impulse control problems might be more responsive to rewards in their environment than their lower susceptibility counterparts. At the same time, for children with lower polygenic susceptibility, the results seem to suggest that these children, perhaps because of a lowered reward responsivity, benefit less or not at all from positive parenting—which parents may upregulate in the context of their child’s burgeoning oppositional and defiant behavior. Thus, for these children at risk for the development of externalizing behavior problems, parents may upregulate praise and positive reinforcement in the wake of their child’s difficult, and difficult-to-change, behavior, but to no avail. In this subgroup of children, then, higher positive parenting is perhaps more of a marker or correlate of a detrimental family process and illustrates how externalizing behavior tends to exacerbate over time if left untreated.²⁶ More research is necessary to illuminate how impulse control problems and reward responsivity may be involved in shaping susceptibility to parenting in the backdrop of genetic susceptibility. In essence, looking at the effect that different levels of polygenic index score had on children’s susceptibility to positive parenting shows us that parenting practices are related to later changes in externalizing behavior for children with both lower and

higher polygenic index scores. However, they are related in different ways, which may depend on relevant phenotypes such as an individual’s impulse control as a function of reward responsivity, determining the manner in which positive parenting is processed, and the effect it has. However, because we did not assess impulse behavior and disinhibition in this study, we can only speculate, based on previous empirical research, that these findings may represent a function of impulsivity and inhibition problems.

Ultimately, the study did not provide evidence supporting the differential susceptibility framework, but rather indicates that several different mechanisms may be necessary to explain how parent-child interactions produce child externalizing behavior, depending on children’s polygenic index score and respective differences in phenotypical expressions. This highlights the importance of differentiating between subtypes of children with externalizing behavior (e.g., nonresponsive callous children vs active-impulsive/disinhibited children and how different types and/or intensities of externalizing behaviors may lead to different parental reactions in the backdrop of their polygenic index). To account for different levels of susceptibility, a susceptibility terminology may be more descriptive if it is not quantitative (e.g., “higher to lower” conveys the idea that high susceptibility necessarily translates into greater adversity), but rather qualitative.

Finally, we want to highlight that there is limited knowledge about the specific neurobiological mechanisms through which susceptibility genes may exert an effect on developmental outcomes such as externalizing behavior and impulse control problems. Some researchers propose that externalizing problem behavior is perpetuated by an excess of dopamine, with higher activity of brain dopamine systems being linked to hypersensitivity to reward and higher stress reactivity to punishment cues from the environment.¹¹ Thus, hyperarousal to reward and punishment may be an underlying mechanism via which genetically more susceptible children are more affected by both negative and positive parenting. By contrast, other research proposes that a dopamine deficiency may underlie these developmental problems,^{10,27} which may occur by means of a greater appetitive disposition of sensation seeking fostered by a lower dopamine availability in those children.¹⁰ This divergence in the literature raises the interesting hypothesis that both a deficiency and an excess of dopamine in different parts of the brain can function as risk mechanisms and may even work symbiotically to produce gene-gene interactions.^{10,11} Insights into these processes would also shed more light onto how differences in polygenic index score seem to be related to various other relevant phenotypes such as impulse control and disinhibition problems, which may play a relevant role in explaining externalizing outcome behaviors because of their high comorbidity. A few discussion points regarding the genetic index used in this study need to be raised. The polygenic index score used in this study is different from genetic

scores based on a genome-wide perspective because it only includes 5 polymorphisms of the dopaminergic circuitry, which represents a smaller subset of the variation available within that circuit. However, testing several large-effect polymorphisms that have aggregated strong a priori evidence from meta-analysis, systematic reviews, well-powered genome-wide association studies, or polymorphisms that have shown large main effects can produce more robust and reliable findings.¹⁴ Future research can benefit from using advanced polygenic risk score (PRS) approaches. Currently, the use of genome-wide PRS offers new insights into how individuals' genetic make-up may interact with specific environmental factors in the development of psychopathology. For example, recent studies showed that parents with higher genome-wide PRS showed more warmth, sensitivity, and stimulating caregiving to their children²⁸ and that PRS predicted antisocial phenotypes in a sample of 2536 men and 3684 women.²⁹ Thus, future research may benefit specifically from incorporating PRS in their analyses of gene-environment interactions in the development of externalizing behavior.

These results show that the associations between positive parenting and child externalizing behavior were significant for lower and higher polygenic index scores but nonsignificant for medium index scores. This raises the question of what collapsing a genetic index into genetic groups does (e.g., "high" and "low" susceptibility) because it is commonly done in the field for producing or canceling out certain effects.^{14,15} Finally, it should be noted that although a genetic index of 0 in our present study suggests the absence of any of the genetic susceptibility markers that we included, the children with this score most likely carry other genetic susceptibility polymorphisms that were not measured in this study.¹⁴ In fact, because we only measured 5 from the many dopamine-related polymorphisms that exist, some of the children with a polygenic index score of 0 in this study could, theoretically, carry more susceptibility genes than any of the other children. This also means that there is a greater amount of unmeasured variability in children with a polygenic index score of 0 and ultimately questions whether children in this group should be truly regarded as nonsusceptible. Clearly, there seems to be more differentiation rather than just higher and lower genetic susceptibility levels; providing more nuanced genetic indexes, such as continuous polygenic indices, can provide important information that would otherwise get lost. Therefore, compared with previous candidate gene and polygenic studies, instead of using a dichotomous genetic index, we used a continuous index, which allows pinpointing specific regions of significance where the genetic score becomes significant in moderating the association. Finally, despite research indicating that dopamine circuitry may play the most prominent role in children's reward and punishment susceptibility, other circuits may also be implicated in these processes and should be examined in this framework of genetic susceptibility.

Although our analytical approach, using a continuous polygenic index, may have favorably affected power, it is essential that future studies try to replicate our findings using larger samples. Furthermore, we recommend that future studies test the gene-based susceptibility of both children and parents. Not having included a measure of parents' genetic susceptibility did not allow us to assess whether parents had a higher gene-based susceptibility to children's externalizing behavior. This is because susceptibility to child effects would be mostly because of the parent's, not child's, genetic make-up. Presently, the existing literature on differential susceptibility in the parenting context still mainly focuses on *children's* genetic susceptibility to parenting, whereby as a result there has been less interest and/or necessity in assessing parents' genetic make-up as well. We recommend that future research also includes measures of parent's genetic susceptibility, thereby also addressing other relevant but currently relatively unexplored points, such as how genetic susceptibility of parent and child combined may predict the strongest effect (i.e., a double-whammy effect).¹⁴ Finally, strengths of the study were that we used an at-risk sample, which inherently exhibits higher proportions of dysfunctional parent and child behavior than population samples. This increases power and yields a less skewed variance.⁸ What makes the study different from most studies on parenting practices and child externalizing behavior is the focus on *both* positive and negative parenting practices. There is not a strong, explicit focus on positive parenting in parenting research, and when there is, it is often falsely conceptualized as the absence of negative parenting. With this study, we conducted a stringent test of longitudinal relationships for both positive and negative dimensions of parenting and were thereby able to test the differential susceptibility hypothesis. The design was strengthened by a very low attrition rate of participants in this study (retention rate of 93%). Furthermore, we would also like to note that although assessing parent-child behaviors with the self-report method can be criticized, self-reports are necessary to assess parents' *perceptions* of their child's behavior, which have been shown to represent one of the strongest predictors of child externalizing behavior.³⁰ Furthermore, self-reports are indispensable when assessing behaviors that do not occur—or cannot practically or ethically be elicited—in experimental paradigms. However, it needs to be kept in mind that using parent report measures has the limitation that parents may report in a socially desirable way about their parenting. This may have resulted in an underestimation of children's externalizing behavior in this study and therefore may have also underestimated the interaction effects of parenting and genetic susceptibility in the prediction of externalizing behavior.

In conclusion, the findings suggest that polygenic index score may be an indicator for differences in children's sensitivity to parental practices and shows us that both a higher and a lower polygenic index score can

influence how children are affected by parenting in their development of externalizing behavior. However, the way polygenic index score affects an individual may be the function of other mediating mechanisms taking place, such as differences in children's reward-processing, which may alter the manner in which positive parenting is processed. Successful distinctions in the way genetic susceptibility expresses itself in these different mechanisms could inform intervention practice for better differentiation between subtypes of externalizing behavior and thereby allow approaches to be tailored to the individual, making them more efficient and cost-efficient in the long run.

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