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Authors

van Ijzendoorn, MH

Belsky, J

Bakermans-Kranenburg, MJ

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Serotonin transporter genotype 5HTTLPR as a marker of differential susceptibility? A meta-analysis of child and adolescent gene-by-environment studies

MH van IJzendoorn¹, J Belsky² and MJ Bakermans-Kranenburg¹

We present results of a meta-analysis of gene-by-environment ($G \times E$) studies involving the serotonin transporter genotype 5HTTLPR to evaluate empirical support for two competing conceptual frameworks in developmental psychopathology: diathesis-stress and differential susceptibility. From a diathesis-stress perspective, the cumulative negative effects of the short allele (ss and sl genotypes) and adverse environments on development have been stressed. From a differential-susceptibility perspective, carriers of the s allele are predicted to be more open to adverse as well as positive environments, for better and for worse. Studies with children and adolescents up to 18 years of age ($N = 9361$) were included. We found 41 effect sizes ($N = 5863$) for the association between negative environments and developmental outcomes with or without significant moderation by 5HTTLPR genotype and 36 effect sizes ($N = 3498$) for the potentially 5HTTLPR-moderated association between positive environments and developmental outcomes. Five moderators were examined: age, ethnicity, genotyping (biallelic or triallelic) and methods used to assess environment and outcome. In the total set of studies, including studies with mixed ethnicities, we found that ss/sl carriers were significantly more vulnerable to *negative* environments than ll carriers, thus supporting the diathesis-stress model. In the Caucasian samples, however, ss/sl carriers also profited significantly more from *positive* environmental input than ll carriers. Associations between (positive or negative) environment and (positive or negative) developmental outcome were absent for ll carriers. The meta-analytic findings support the hypothesis that in Caucasian samples 5HTTLPR is a genetic marker of differential susceptibility. $G \times E$ interactions might be critically dependent on ethnicity.

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Introduction

Most gene-by-environment ($G \times E$) studies of the interaction of measured genes by measured environments emphasize the cumulative *negative* effects of specific 'risk' genes and adverse environments, whereas potentially cumulative positive effects of the same 'risk' genes (better called 'susceptibility' or 'plasticity' genes) interacting with positive environments remain understudied.^{1–4} From a diathesis-stress perspective, the potentially cumulative negative effects of the 5HTTLPR short allele (ss and sl genotypes) and adverse environments have been stressed in many studies, as in the association between negative childhood experiences and adult depression.^{5–7} The differential-susceptibility perspective highlights the need to examine the 5HTTLPR-moderated associations between negative *and* positive environmental influences and developmental outcomes from the position that certain individuals are not just more vulnerable to adversity because of their genetic make-up, but disproportionately responsive to positive *and* negative environmental experiences and exposures. Here we present the first meta-analytic evidence addressing the question whether the 5HTTLPR genotype should be considered a marker of vulnerability or susceptibility.

Central to the differential-susceptibility hypothesis is the proposition that individuals vary in their susceptibility to the same environmental influences. From an evolutionary perspective, it seems implausible that 'risk' alleles would have survived if they did not promote fitness in some circumstances or contexts.⁸ It is thus a bold but also intuitively plausible conjecture that widespread human characteristics such as a 'reactive' temperament or a 'risky' genotype are, in fact, markers of susceptibility to *positive* and negative circumstances, for better and for worse.^{2,9,10} Susceptibility markers would not have emerged, survived and spread across a substantial minority of the population if they did not advance adaptation to at least some ecological niches for at least some individuals,¹⁰ although random genetic drift cannot be excluded as a possible explanation of their existence. Recent years have witnessed a growing body of correlational evidence consistent with differential-susceptibility thinking.³ The first such work documenting genetic differential susceptibility focused on the dopamine D4 receptor gene,¹¹ with a recent meta-analysis of $G \times E$ studies involving dopamine-related genes and children under 10 years of age indicating that associations between positive environments and positive developmental outcomes were as strong as the negative associations in case of the

¹Centre for Child and Family Studies, Leiden University, Leiden, The Netherlands and ²University of California at Davis, King Abdulaziz University, Birkbeck University of London, Jeddah, Saudi Arabia

Correspondence: Dr MH van IJzendoorn or Dr MJ Bakermans-Kranenburg, Centre for Child and Family Studies, Leiden University, PO Box 9555, Leiden 2300 RB, Netherlands.

E-mail: vanijzen@fsw.leidenuniv.nl or E-mail: bakermans@fsw.leidenuniv.nl

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so-called 'risk' polymorphisms.¹² Here we test whether the same is the case for the short versus long allele of 5HTTLPR, focusing on children under the age of 18.

Hypotheses

A series of meta-analyses tested two contrasting hypotheses about the role of 5HTTLPR in $G \times E$ interactions. The dominant diathesis-stress or cumulative-risk hypothesis stipulates that carriers of the s allele are more vulnerable to the negative effects of adverse environments (double risk). The emerging differential-susceptibility model predicts that carriers of the s-allele are not only more vulnerable to the influence of negative environments but also profit more from the beneficial influences of positive environments. From a differential-susceptibility perspective, we expect the interactive effects of the 5HTTLPR genotype and positive environments on development to be as large as the interaction effects of the same genotype and risk environments.

Materials and methods

Data sources. For our meta-analysis, we systematically searched the PsycLit, Medline and ISI web of knowledge databases, with the key words 'serotonin' or '5HTT*', and 'human' in the title or abstract. The asterisk indicates that the search contained the word or word fragment. In addition, references of three recently published review papers on the same topic were scrutinized.^{3,4,10}

Study selection. The search was restricted to studies with behavioral, psychiatric or developmental outcomes for children under the age of 18 years, thereby excluding purely medical or physical parameters of child development as outcomes for analysis. We finished the search on 1 March 2012. Medical treatment, as an environmental factor, and also nonempirical papers or papers with insufficient statistics were excluded. Only refereed reports in the English language were included. Studies reporting the presence or absence of a significant $G \times E$ interaction with 5HTTLPR were included even if the main goal of the research was the presentation of a genetic or environmental main effect. Therefore the literature search was 'blind' for the kind of $G \times E$ outcome and unbiased as to theoretical perspective (see Table 1 for a list of studies).

Data extraction. We identified 77 pertinent effect sizes on 9361 subjects from 30 reports, providing data for two meta-analyses on the moderating role of 5HTTLPR, when it comes to the impact of the environment on development. Forty-one effect sizes ($N=5863$) concerned vulnerability, that is, moderation by 'risk alleles' (ss or sl) of the association between adverse environment and negative developmental outcomes. Examples of such studies were the associations between bullying victimization experiences and emotional problems,¹³ between family risk and depression,¹⁴ between prenatal maternal anxiety and infant negative emotionality¹⁵ and between early institutional deprivation and emotional problems in adolescence.¹⁶ Thirty-six effect sizes ($N=3498$)—enabling a focus on the 'bright side'—pertained

Table 1 Characteristics of studies included in the meta-analyses

Study	N	Positive/ negative ^a	Age	Ethnicity ^b	Genotyping triallelic	Assessment	
						environment	outcome
Bakermans <i>et al.</i> (2012)	37	Negative	< 10	Caucasian	No	Observation	Observation
Benjet <i>et al.</i> (2010)	78	Negative	≥ 10	Mixed	No	Self-report	Self-report
Brody <i>et al.</i> (2009)	419	Positive	≥ 10	Mixed	No	Observation	Self-report
Cicchetti <i>et al.</i> (2010)	850	Negative	< 10	Mixed	No	Observation	Self-report
Cicchetti <i>et al.</i> (2011)	92	Positive	< 10	Mixed	No	Observation	Observation
Drury <i>et al.</i> (2012)	100	Positive	< 10	Caucasian	No	Observation	Other report
Eley <i>et al.</i> (2004)	220	Negative	≥ 10	Caucasian	No	Other report	Self-report
Eley <i>et al.</i> (2011)	344	Positive	< 10	Caucasian	No	Observation	Observation
Fox <i>et al.</i> (2005)	73	Positive	< 10	Caucasian	No	Other report	Observation
Gibb <i>et al.</i> (2011)	74	Negative	< 10	Caucasian	No	Observation	Observation
Gilissen <i>et al.</i> (2008)	87	Positive	< 10	Caucasian	No	Observation	Observation
Hankin <i>et al.</i> (2012)	220	Negative	≥ 10	Mixed	Yes	Other report	Self-report
Ivorra <i>et al.</i> (2010)	317	Negative	< 10	Caucasian	No	Other report	Other report
Jacobs <i>et al.</i> (2011)	123	Negative	≥ 10	Caucasian	Yes	Other report	Observation
Kaufman <i>et al.</i> (2004)	101	Negative	≥ 10	Mixed	No	Observation	Self-report
Kochanska <i>et al.</i> (2011)	88	Positive	< 10	Caucasian	No	Observation	Other report
Luijk <i>et al.</i> (2011)	512	Positive	< 10	Caucasian	No	Observation	Observation
Kumsta <i>et al.</i> (2010)	64	Negative	≥ 10	Caucasian	No	Observation	Other report
Mueller <i>et al.</i> (2011)	115	Negative	< 10	Caucasian	Yes	Self-report	Observation
Nijmeijer <i>et al.</i> (2010)	194	Negative	≥ 10	Caucasian	No	Other report	Other report
Nilsson <i>et al.</i> (2005)	196	Positive	≥ 10	Caucasian	No	Self-report	Self-report
Nobile <i>et al.</i> (2007)	689	Negative	≥ 10	Caucasian	No	Other report	Other report
Paaver <i>et al.</i> (2008)	435	Positive	≥ 10	Caucasian	No	Self-report	Self-report
Pauli-Pott <i>et al.</i> (2009)	69	Positive	< 10	Caucasian	No	Observation	Observation
Pluess <i>et al.</i> (2011)	1513	Negative	< 10	Caucasian	No	Other report	Other report
Sadeh <i>et al.</i> (2010)	296	Positive	≥ 10	Mixed	No	Other report	self-report
Sonuga <i>et al.</i> (2009)	681	Positive	≥ 10	Caucasian	No	Observation	Other report
Spangler <i>et al.</i> (2009)	94	Negative	< 10	Caucasian	No	Observation	Observation
Sugden <i>et al.</i> (2010)	1174	Negative	≥ 10	Caucasian	No	Self-report	Other report
Sulik <i>et al.</i> (2012)	106	Positive	< 10	Caucasian	No	Observation	Other report

Notes. ^aPositive = study providing effect size of the association between supportive environment and positive developmental outcomes; negative = study providing effect size of the association between adverse environment and negative developmental outcome. ^bCaucasian = > 80% of the sample Caucasian.

Table 2 Combined effect sizes for the associations between positive or negative environmental factors and child outcomes for the various 5HTTLPR genotypes in the total set of studies ($k = 77$)

Genotype	Positive environment					Negative environment					Contrast	
	K	N	r	95% CI	Q	k	N	r	95% CI	Q	Q	P
(1) ss	7	312	0.17**	0.07~0.25	5.12	10	715	0.31**	0.24~0.37	6.51	6.17	.01
(2) ss/sl	9	1004	0.27**	0.09~0.43	110.81**	6	1312	0.09	-0.13~0.30	20.16**	1.59	.21
(3) sl	4	568	0.17*	0.01~0.33	9.36*	9	1772	0.20**	0.08~0.31	30.71**	0.07	.80
(4) sl/ll	3	415	0.06*	0.01~0.11	0.33	1	170	0.00	-0.15~0.15	<i>n.a.</i>	<i>n.a.</i>	<i>n.a.</i>
(5) ll	13	1199	0.11**	0.04~0.19	24.80*	15	1894	0.06	-0.01~0.12	12.34	1.30	.26
(6) all ss/sl (1+2+3)	20	1884	0.21**	0.12~0.30	135.48**	25	3739	0.22**	0.14~0.31	79.86**	0.03	.86

* $P < 0.05$, ** $P < 0.01$. Note: direction of effect sizes was labeled according to the *a priori* hypotheses of this meta-analysis.

to the relation between supportive contexts (for example, warm-responsive parenting) and positive developmental outcomes. These studies concerned, for example, the effect of mothers' positive emotions expressed about their children with attention deficit/hyperactivity disorder,¹⁷ the effects of a family-centered prevention program on adolescents' risky behaviors,¹⁸ the decrease in anxiety in response to cognitive behavior therapy¹⁹ or the association of high-quality family functioning (as opposed to neutral or low-quality family functioning) with adolescent alcohol consumption.²⁰ As the 5HTTLPR genotype consists of three variants (ss, sl, and ll), studies sometimes reported on the three variants separately, but in other cases the sl group was combined with either the ss or the ll group. Thus, each of five possible combinations can be found in the literature (see Table 2). The associations of interest were those between (positive or negative) environment and child outcome within each of the five genotype groups, consisting of carriers of the short (putative 'risk') allele (ss and sl genotypes) and carriers of two long alleles (ll). All effect sizes were computed through consensus of two coders (MHvIJ, MBK).

Moderators. We included five moderators to test whether effect sizes varied significantly across moderator categories. First, age was coded in two categories: below 10 years (parallel to a previous meta-analysis on $G \times E$ with dopamine-related genes¹²), and 10 years and older. Second, as 5HTTLPR ss genotype has been found associated with higher CSF 5-HIAA levels in African Americans, but with lower levels in Caucasians,²¹ we categorized the studies into those involving >80% Caucasian participants, and studies involving more than 20% other ethnicities. Third, a single-nucleotide polymorphism (SNP) in the L allele (rs25531) has recently led to differentiation between the high functioning L_a variant versus the L_g variant that is more functionally equivalent to the S allele (the triallelic approach²²). We differentiated between the studies using the traditional biallelic approach and studies applying the triallelic method. Fourth, the method of assessing the environment was categorized into studies using observations, questionnaires or interviews completed by persons other than the children (for example, parents), or self-report questionnaires or interviews. Fifth, the same categorization (observation, other-report, self-report) was used for the assessment of the developmental outcomes. Inter-coder reliability was adequate (mean 94%, range 80–100%). Disagreements were discussed to reach consensus.

Data synthesis. The Comprehensive Meta-Analysis (CMA) program was used to transform the results of the individual studies (for example, means and s.d. in both genotype groups) into the common metric of correlations and to combine effect sizes.²³ Heterogeneity across studies was assessed using the Q -statistic. As most of our data sets were heterogeneous in their effect sizes, and as random effects models are somewhat more conservative than fixed effects parameters in such cases, combined effect sizes and confidence intervals (CIs) from random effects models are presented. We also tested the influence of the five moderators on the variation of effect sizes between studies with the $Q_{contrast}$ statistic in a random effects model.²³ The $Q_{contrast}$ statistic is based on the logic of analysis of variance, with the total variance Q_{total} partitioned into $Q_{between}$ and Q_{within} . Q_{total} is the variance with any grouping factors ignored, and Q_{within} for each group refers to the variances in the specific subsets of studies. $Q_{between} = Q_{total} - Q_{within}$, and is tested for significance using the χ^2 distribution.²³ A significant $Q_{contrast}$ value indicates that the difference in effect size between subsets of studies is significant.

Results

In Table 2, the combined effect sizes for each of the five genotype groups are presented. The effect sizes represent the associations between variations in the environmental and developmental outcomes. Here we discuss the contrast between the carriers of one or two s alleles (the combination of the groups with ss, ss/sl or sl carriers) and the carriers of two l alleles (ll carriers), separately for the effect of adverse and supportive environments.

Adverse environments. The combined effect size for developmental problems in the presence of negative environmental influences (that is, 'the dark side') amounted to $r = 0.22$ ($P < 0.01$, 95% CI 0.14, 0.31) for ss/sl carriers, in a heterogeneous set of effect sizes ($Q = 79.86$, $P < 0.01$). The combined effect size for the ll carriers was $r = 0.06$ (NS, 95% CI -0.01, 0.12) in a homogeneous set ($Q = 12.34$, NS). Using a random effects test, the difference was significant ($Q_{contrast} = 8.35$, $P < 0.01$), supporting the diathesis-stress idea that ss/sl carriers are more vulnerable to environmental adversity than ll carriers.

Positive environments. Turning to the ‘bright side’—the association between positive environments and better child outcomes—we found a combined effect size of $r=0.21$ ($P<0.01$, 95% CI 0.12, 0.30) for ss/sl carriers in a heterogeneous set of effect sizes ($Q=135.48$, $P<0.01$). The combined effect size for ll carriers was $r=0.11$ ($P=0.04$, 95% CI 0.04, 0.19) in a marginally heterogeneous set ($Q=24.80$, $P<0.05$). Although this differential pattern of associations was consistent with differential susceptibility, the difference in effect sizes across the two genetic groups was nonsignificant ($Q_{\text{contrast}}=0.54$, NS). Thus, although children with s alleles were more negatively affected by adverse contexts than ll carriers with regard to negative outcomes (see above), they did not benefit significantly more from positive environments than children homozygous for the l allele. It should be noted that only in the case of the carriers of the short allele in negative environments did the funnel plot reveal potential publication bias, which, when corrected with the Duval and Tweedie trim and fill method,²³ changed only marginally the point estimate of the combined effect size.

Moderators. Moderator analyses focused on age, use of triallelic genotyping, the type of assessment of the environment and the outcome were not significant, and thus did not change our main findings of ss/sl carriers being significantly more vulnerable to negative environments, but not profiting significantly more from positive environments compared with ll carriers, all $ps>0.14$. However, ethnicity proved to be a significant moderator of the association between positive environmental influences and positive developmental outcome for carriers of the ll alleles ($Q_{\text{contrast}}=6.49$, $P=0.01$).

Caucasian samples. As ethnicity was a significant moderator, we recomputed the combined effect sizes for the ss/ll carriers versus the ll carriers using only studies with (mostly) Caucasian participants.

Adverse environments. In the Caucasian samples, the combined effect size for developmental problems in the presence of adverse environmental influences amounted to $r=0.18$ ($P<0.01$, 95% CI 0.11, 0.25) for ss/sl carriers, in a heterogeneous set of effect sizes ($Q=63.06$, $P<0.01$). The combined effect size for the ll carriers was $r=0.04$ (NS, 95% CI -0.07 , 0.14) in a homogeneous set ($Q=9.98$, NS). The difference between the ss/sl versus ll carriers was significant ($Q_{\text{contrast}}=4.58$, $P=0.03$). In adverse contexts and consistent with diathesis-stress thinking, ss/sl carriers were more at risk for negative developmental outcomes than ll carriers.

Positive environments. The association between positive environments and better child adaptation amounted to a combined effect size of $r=0.17$. ($P<0.01$, 95% CI 0.10, 0.24) for ss/sl carriers, in a heterogeneous set of studies ($Q=29.26$, $P<0.01$), whereas the combined effect size for ll carriers was nonsignificant, $r=0.05$ (95% CI -0.05 , 0.14), in a homogeneous set of studies ($Q=5.73$, NS). The difference between the ss/sl versus ll carriers was significant ($Q_{\text{contrast}}=3.92$, $P=0.048$). Children with ss/sl genotypes

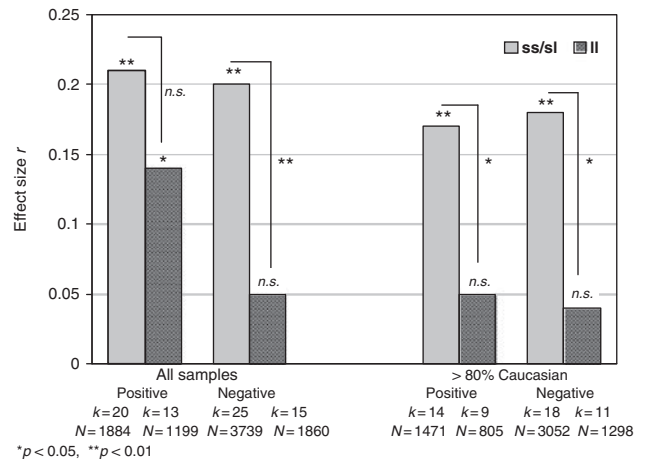


Figure 1 Combined effect sizes for the associations between positive and negative environmental factors and child outcomes for the 5HTTLPR ss/sl and ll genotypes, in the total set of studies (except sl/ll, $k=73$) and in studies with $>80\%$ Caucasian participants ($k=52$). * $P<0.05$, ** $P<0.01$. Note: In the total set of studies, the combined effect sizes for positive environmental factors are significant for both ss/sl and ll carriers. The difference between the combined effect sizes for ss/sl and ll is not significant, $Q_{\text{contrast}}=0.54$, $P=0.46$. The combined effect size for negative environmental factors is significant for ss/sl carriers, but not for ll carriers. The combined effect sizes for ss/sl and ll differ significantly, $Q_{\text{contrast}}=8.35$, $P<0.01$. In the set of studies with mostly Caucasian participants, the combined effect sizes for positive and negative environmental factors are significant for the ss/sl carriers, but not for the ll carriers. The differences between the combined effect sizes for ss/sl and ll carriers are significant, $Q_{\text{contrast}}=3.92$, $P=0.048$ for positive environmental factors and $Q_{\text{contrast}}=4.58$, $P=0.03$ for negative environmental factors.

gained more from positive environments than children homozygous for the l allele, consistent with differential susceptibility. In summary, then, for children with the ll genotype, the associations between positive or negative environment and positive or negative developmental outcome were absent. Thus, in samples with $>80\%$ Caucasian children, ss/sl carriers were more open to environmental influences than ll carriers, for better and for worse, consistent with differential susceptibility. Figure 1 illustrates these findings.

Discussion

In this series of meta-analyses on 77 effect sizes with 9361 children and adolescents who were the subject of 30 pertinent research reports, we found some support for 5HTTLPR as a genetic marker of differential susceptibility or plasticity rather than vulnerability. Carriers of the s alleles (ss/sl) were not only at risk for developing poorly in an adverse environment, consistent with the diathesis-stress model, but they were also significantly more influenced by supportive environments enabling them to develop in a more positive way than ll carriers, consistent with differential susceptibility. Indeed, the latter finding is incompatible with the diathesis-stress framework that has informed, implicitly or explicitly, most $G \times E$ research to date.^{2,3} Ethnicity was an important moderator in the total set of 5HTTLPR $G \times E$ studies involving child and adolescent samples. Some evidence for differential susceptibility only emerged in studies with (mostly) Caucasian participants. Caucasian participants with the ll genotype were less influenced by environmental factors, whether supportive

or adverse. The mixed studies with a higher percentage of non-Caucasians may have resulted in population stratification or admixture, which may seriously elevate the type I error rate for detecting genes underlying complex traits, and in the end may lead to non-replicable $G \times E$ findings.

The support for the differential susceptibility theory chronicled here in the case of the 5HTTLPR genotype must be regarded as tentative owing to the fact that the set of studies available for inclusion in our meta-analysis was rather small. Most importantly, the $G \times E$ studies conducted thus far are quite heterogeneous in terms of environments and outcomes studied. The heterogeneity creates relatively large confidence intervals (CI) around the point estimates of combined effect sizes, which may make the meta-analytic results somewhat unstable. More studies using similar assessments of environments and outcomes will afford stronger tests of the hypothesis that 5HTTLPR is a marker of differential susceptibility, the conclusion drawn here. Furthermore, including assessments of positive environments does not exclude the possibility that the resulting associations with (positive) developmental outcomes are driven by the lower scores on these assessments, thereby representing, perhaps, the higher end of negative environmental input. Evidence that carriers of short versus long allele of 5HTTLPR prove more susceptible to experimental interventions promoting development by enhancing the quality of the environment would counter this alternative interpretation.

Most $G \times E$ studies included in the current meta-analyses are correlational in design, making causal inferences impossible. Correlational $G \times E$ studies are limited in their control of gene–environment correlations that might wrongly be interpreted as $G \times E$ interactions. Only experimental manipulations of the environment in randomized control trials afford valid conclusions about $G \times E$ interactions independent of gene–environment correlations.²⁴ Protocolled interventions also create standardized and observable changes in the environment; in so doing, they reduce the error component in the measurement of the environment. This should increase the chance of replicable $G \times E$ findings,²⁴ as these have been found to be greatly dependent on the quality of the assessment of the environment.⁷ Furthermore, in most developmental studies, 5HTTLPR was the only candidate genetic marker of differential susceptibility. However, differential susceptibility will not depend on one genotype only; other genotypes have already been successfully examined as markers of differential susceptibility (perhaps most compelling dopamine-system related genes¹²). In future studies, genetic pathways related to the serotonin system might be included in the $G \times E$ equation, and the combined effects of serotonergic and dopaminergic pathways may be examined. This requires studies with large samples that only consortia of researchers are able to conduct.

The diathesis-stress model still dominates the field of developmental psychopathology and psychiatric genetics more generally, stressing the negative developmental impact of a vulnerable genetic make-up interacting with adverse environments. The current meta-analyses show, however, just like our earlier one on dopamine-related genes and child development,¹² that genetic vulnerability might also imply greater susceptibility to the influences of positive (changes in)

environments. At least in the case of children under the age of 18 years, the exclusive ‘dark-side’ view of some genotypes (for example, 5HTT s allele, DRD4-7 repeat allele) as risk factors for psychopathology appears on the basis of this and our previous meta-analysis undeserved and incompatible with emerging empirical evidence. Similar to the diathesis-stress model, differential susceptibility theory acknowledges the negative effects of cumulative genetic and environmental risks, but at the same time draws attention to the bright side of development. The so-called vulnerability genes might make individuals not only vulnerable to negative environmental influences but also more open to the positive developmental effects of positive changes in the environment.

Conflict of interest

The authors declare no conflict of interest.

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Disclaimer. MJBK and MHvIJ had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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