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Does 5-HTTLPR moderate the effect of the quality of environmental context on maternal sensitivity? Testing the differential susceptibility hypothesis

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Evidence documenting associations between 5-HTTLPR and parenting behavior led to testing the hypothesis that this polymorphism moderates the effect of the quality of environmental context on maternal sensitivity. Participants were 210 Portuguese mothers and their preschool children, recruited from the community. An index reflecting the quality of the environmental context was derived based on nine markers (e.g. single parenthood; parental education, economic difficulties, family conflict, maternal psychopathology). Maternal sensitivity was measured observationally. Maternal saliva was collected with OraGene kits for genetic analysis. Results revealed a gene-X-environment interaction, such that short-allele homozygotes proved more sensitive to the family context than long-allele carriers (i.e. sL/LL), displaying the highest and lowest levels of maternal sensitivity, depending on, respectively, low and high quality levels of the environmental context. Because even mothers carrying the long allele evinced similar responsiveness to

the environmental context, but to a lesser extent, findings proved consistent with the weak differential susceptibility model of person-X-context interaction. Results are discussed in light of prior and related gene-X-environment findings. *Psychiatr Genet* 30: 49–56 Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

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Keywords: 5-HTTLPR, differential susceptibility, family context, gene-X-environment interaction, maternal sensitivity, quality of environmental context

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Introduction

The serotonergic system is one of the biological systems thought to influence parenting, based on both animal and human studies. As a modulator of neural circuitry regulating several physiological and behavioral processes, this system has widespread effects on cognition and mood (cf. Homberg and Lesch, 2011), conceivably affecting parenting, the focus of this report. Serotonin may also be linked to parental behavior because of its association with oxytocin, which itself is associated with affiliation and social interaction. For example, Galfi *et al.* (2005) observed that oxytocin secretion was directly influenced by the serotonergic system in rats (Jorgensen *et al.* 2003); and Lee *et al.* (2003) found that stimulation of the hypothalamus by serotonin resulted in the release of oxytocin as a precursor molecule. For these reasons, interest in the relation between serotonin and parenting has been increasing (Bakermans-Kranenburg and van IJzendoorn, 2008; Mileva-Seitz *et al.*, 2011; Cents *et al.*, 2014; Sturge-Apple *et al.*, 2012).

Within the serotonergic system, the gene encoding the serotonin transporter, and in particular the Serotonin Transporter-Linked Polymorphic Region (5-HTTLPR), has been one of the most extensively studied

polymorphisms in research on mood, cognition and parental behavior. It consists of two functional alleles, long (*L*) and short (*s*), with the *s*-allele associated with a decrease in the transcription of the serotonin transporter gene, resulting in increased levels of serotonin in the synaptic cleft. The presence of this *s*-allele has been associated with increased anxiety (Gunthert *et al.*, 2007), depression and suicidality (Caspi *et al.*, 2003), negative emotion processing (for a review Jonassen and Landrø, 2014) and improved social cognition (Homberg and Lesch, 2011). Nonetheless, these, like many other genotype-phenotype associations, have proven inconsistent across studies (e.g. Taylor *et al.*, 2006; Wilhelm *et al.*, 2006; Mesquita *et al.*, 2015 for combined *ss* vs. *sL/LL* genotypes; Caspi *et al.*, 2003; Gunthert *et al.*, 2007; Brummett *et al.*, 2008 for *ss* vs. *sL/LL* combined genotypes).

This seems to be so also in the case of research on parenting. In the first relevant study focused on middle-class mothers whose toddlers were at risk for externalizing behavior problems, Bakermans-Kranenburg and van IJzendoorn (2008) found that mothers homozygous for the *s*-allele provided less sensitive care than other mothers. Somewhat similar results were reported by Morgan *et al.* (2016): Carriers of the *s*-allele (i.e. either *ss*

or *sL*) exhibited less positive parenting when interacting with their 6–9-year-old children than *LL* homozygotes. Yet in a third study, mothers carrying the *s*-allele displayed greater sensitivity than others when observed interacting with their 6-month olds (Mileva-Seitz *et al.*, 2011). Results similar to these emerged when Cents *et al.* (2014) examined the effects of *5-HTTLPR* on sensitive parenting in a large cohort study in which mother-child dyads were observed at three-time points—when children were 14, 36 and 48 months of age. Another study reports on the failure to detect any *5-HTTLPR*-parenting association when high-risk mothers were observed interacting with their 2-year-old children (Sturge-Apple *et al.*, 2012).

Regarding genotype-phenotype inconsistency of the kind just outlined, Caspi *et al.* (2002) based their pioneering work on the proposition that it might result from the interplay of genes (G) and environment (E). Especially notable in this regard is that three of the just-cited studies discerned gene-X-environment (GXE) effects. Mileva-Seitz *et al.* (2011) found that mothers carrying the *s*-allele provided higher quality care than other mothers when they had experienced positive parenting in their own childhoods. Morgan *et al.* (2016) observed that *s*-carrying parents engaged in more negative and less positive parenting than other parents when experiencing disruptive child behavior. And Sturge-Apple *et al.* (2012) reported that *s*-carrying mothers displayed the most and least supportive parenting depending, respectively, on whether they experienced low or high levels of interparental conflict. The latter findings are particularly noteworthy in that they suggest that the *s*-allele may be associated with heightened sensitivity to both supportive and adverse environmental conditions, thus being consistent with the differential-susceptibility hypothesis (Belsky *et al.*, 2009; Belsky and Pluess, 2009; Ellis *et al.*, 2011).

Just as notable is that GXE research involving *5-HTTLPR* and other non-parenting phenotypes also provides support for the differential-susceptibility model of person-X-environment interaction. This includes work predicting depression (Caspi *et al.*, 2003; Taylor *et al.*, 2006; Wilhelm *et al.*, 2006; Zalsman *et al.*, 2006; Brummett *et al.*, 2008), anxiety (Gunthert *et al.*, 2007) and Attention deficit hyperactivity disorder (Retz *et al.*, 2008). Indeed, all these studies found that *s*-carriers proved most responsive to both positive and negative contextual conditions (with positive conditions often operationalized as low levels of negative ones); and this was so even as they focused on diverse contextual factors, including parental education (Brummett *et al.*, 2008), daily stressors (Gunthert *et al.*, 2007), childhood environment (Retz *et al.*, 2008) and positive life events (Wilhelm *et al.*, 2006).

To be noted, however is that none of this GXE work, including the three aforementioned studies on parenting (Mileva-Seitz *et al.*, 2011; Sturge-Apple *et al.*, 2012; Morgan *et al.*, 2016), formally tested the differential-susceptibility hypothesis, especially against the competing

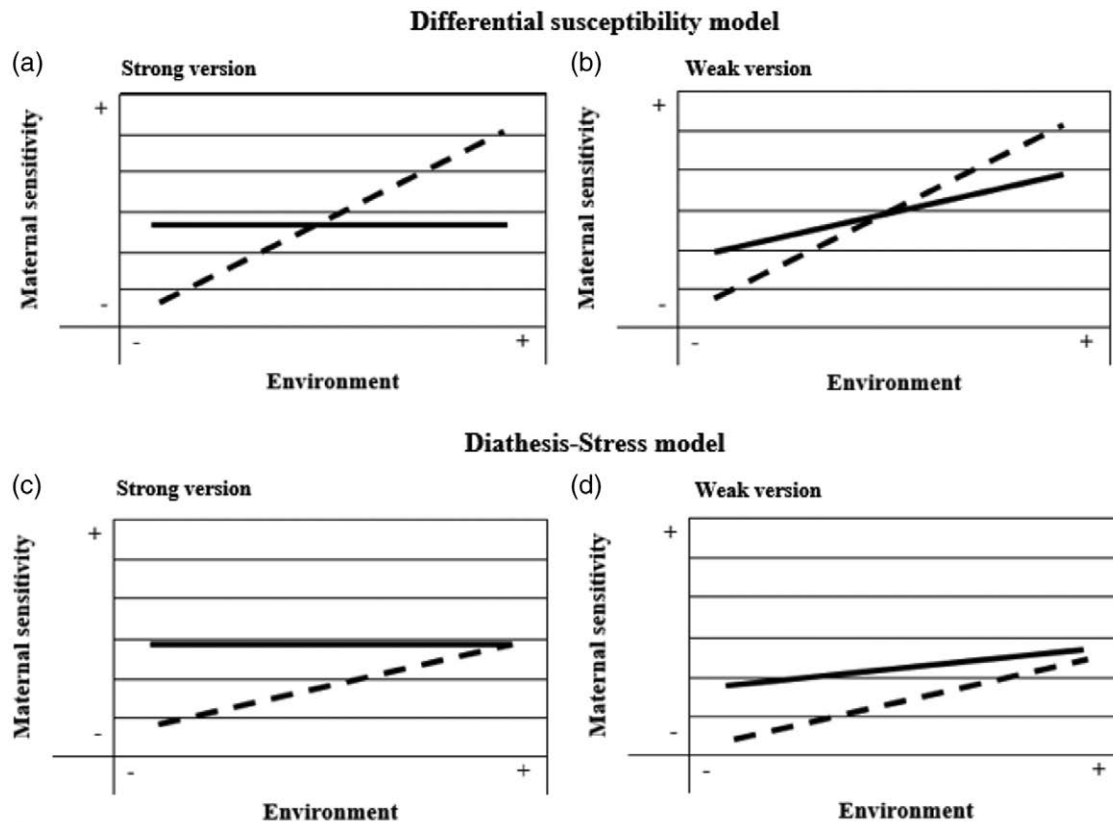
and prevailing diathesis-stress model of person-X-environment interaction. Whereas the differential-susceptibility model stipulates that susceptible individuals will be more affected than others by both positive and negative contextual conditions, the diathesis-stress model only postulates that some ‘vulnerable’ individuals will be more susceptible to the negative effects of adversity than will others (i.e. there will be no difference between more and less ‘vulnerable’ individuals under benign or supportive conditions). In fact, it was the failure of investigations to formally evaluate how well GXE findings fit competing models of person-X-environment interaction that led Widaman and colleagues (Widaman *et al.*, 2011; Belsky *et al.*, 2012; Belsky and Widaman, 2018) to develop the competitive, model-testing approach that is employed in the GXE research reported herein.

Thus, in the present inquiry examining the interaction of *5-HTTLPR* and family contextual conditions in predicting observed parenting, we formally test alternative models of person-X-environment interaction by directly contrasting the differential-susceptibility and diathesis-stress models, whereas evaluating weak vs. strong versions of each. Strong versions posit that only one genotypic subgroup is affected by the contextual condition under investigation (i.e. a zero correlation between context and outcome for the non-susceptible allelic subgroup); the weak version, in contrast, posits that the two genotypic groups are affected by the environment, but one more strongly than the other. As displayed in Fig. 1, in this case the strong version assumes that the non-susceptible/non-vulnerable group (*sL/LL*) would not be influenced by the quality of environmental context. Conversely, the weak version allows that the family environment may impact the non-susceptible/non-vulnerable group, but to a lesser extent than the susceptible/vulnerable group (*ss*).

It was predicted that the parenting of mothers homozygous for the *s*-allele would be more strongly affected by the quality of environmental context—in a differential-susceptibility-related manner—though no hypothesis was advanced as to whether the strong or weak version of the model would be supported.

Although some authors have distinguished between *s*-carriers (*ss/sL*) and *L* homozygotes, we compared *s* homozygotes and *L*-carriers (*LL/Ls*) in our analysis. We have done so because the *ss* genotype is believed to be the most affected in terms of the serotonin transporter activity, as the *s*-allele is associated with lower levels of transcription (Lesch *et al.*, 1996). This parametrization has been used in previous research that has investigated *5-HTTLPR* moderation of environmental influences (e.g. Taylor *et al.*, 2006; Wilhelm *et al.*, 2006; Hayden *et al.*, 2007; Young *et al.*, 2007; Bakermans-Kranenburg and van IJzendoorn, 2008; Mesquita *et al.*, 2015), and also in meta-analytic work (Crawford *et al.*, 2013). With regard

Fig. 1



Graphical display of strong and weak versions of differential susceptibility (a and b) and diathesis-stress (c and d) models. The x-axis represents variation in the quality of environmental context, from negative to positive; the y-axis represents the maternal sensitivity scores, from negative to positive. The lines depict the two genotypes (*ss* vs. *sL/LL*).

to environmental influences, we considered, in aggregate, nine well-established family risk factors (including teenage pregnancy, single parenthood, economic disadvantage, lack of social support) to create a composite index of quality of environmental context (as detailed in the Methods section). We proceeded this way for two reasons. First, the environmental context indicators we composited are associated with parenting (Belsky, 1984; Belsky and Jaffee, 2006); and second, composite measures of risk and support, including just the relative absence of risk, prove more powerful than single risk-support indicators when predicting many phenotypes (Evans *et al.*, 2013).

Methods

Participants

The sample consists of 210 Caucasian mothers and their preschool children. Recruitment took place in preschools with children from families that varied in terms of psychosocial risk. Mother's age ranged from 20 to 48 years ($M = 33.36$, $SD = 5.60$); 23.3% had less than 9 years of education. Children's ages ranged from 40 to 77 months ($M = 58.26$, $SD = 7.63$); 114 (54.3%) were girls. The study

was approved by the Portuguese Committee for Data Protection (Authorization number: 2496/2012) and the Ethical Committee of the University of Minho, Portugal (Authorization number: SECVS 027/2016). Informed consent was obtained from mothers.

Measures

Quality of environmental context composite

To create a summary measure reflecting the developmental supportiveness, or lack thereof, of the environmental context, multiple measurements were composited. Following Weitzman *et al.* (2013), we assessed presence vs. absence of nine sociodemographic and psychosocial factors, including (1) teenage pregnancy (nine, 4.3%); (2) single parenthood (37, 17.6%); (3) (low) parental educational level (i.e. one of the parents had under 9 years of education) (88, 41.9%); (4) parental unemployment (i.e. one of the parents was unemployed at the time of the study) (74, 35.2%); (5) economic difficulties (89, 42.4%); (6) absence of social support (18, 8.6%); (7) family conflict (64, 30.5%); (8) maternal psychopathology (see below) (47, 22.0%); and (9) chronic health conditions in the

family living with the child (128, 59.8%). To assess presence/absence of (8) maternal psychopathology, mothers completed the 53-item of the Brief Symptom Inventory (Derogatis and Spencer, 1982; Portuguese version, Canavarro, 1999), based on a five-point scale (0 = 'not at all' to 4 = 'extremely'), in terms of the presence of various symptoms experienced in the past week (Chronbach alpha = 0.96). A binary variable (presence/absence of Maternal Psychopathology) was computed based on the Portuguese normative mean and SD for the Positive Symptoms Distress Index; a score greater than 1.96 qualified as evidence of maternal psychopathology. The nine factors were analyzed with Item Response Theory (Bolt, 2005). A standardized score of the quality of environmental context was calculated by summing and reversing those considered 'negative', with higher scores reflecting better environmental context quality. Thus, higher scores reflect a more developmentally supportive environmental context ($M = 2.11$; $SD = 1.45$, range 0–6).

Genetic assessment

Mother's saliva was collected using OraGene OG-500 (DNA Genotek, Inc., Ottawa, Ontario, Canada) and stored at room temperature. Genomic DNA was isolated as instructed by the manufacturers, using the standard protocol from PrepIT L2P (DNA Genotek), and sample concentrations were assessed using Nanodrop technology. The *5-HTTLPR* allelic assay was performed by polymerase chain reaction. The amplification products were separated on a 3% agarose gel and visualized using Gel Doc EZ system (Bio-Rad, Hercules, California, USA), in order to identify the short (*s*) and long (*L*) alleles. Results were also validated using Sanger Sequencing of representative samples of each genotype (*ss*, *sL* and *LL*). The genotypes were in Hardy–Weinberg Equilibrium ($\chi^2(1) = 1.178$, $P = 0.278$). The majority of the participants were heterozygous (*sL*) ($n = 111$, 52.9%), followed by homozygous for the long allele (*LL*) ($n = 63$, 30%). Short allele (*s*) frequency was 0.44. Primary statistical analysis contrasted the *ss*-genotype with *LL/sL* genotypes.

Maternal behavior

Mother-child interaction was videotaped in a quiet room (at the family home or at the preschool) across three 5-minute episodes involving (1) child play with a challenging toy under mother's guidance; (2) maternal completion of a sham questionnaire while the child had only an uninteresting toy to play with, after being instructed not to touch more interesting, but difficult-to-reach toys; and (3) mother and child engage in free play for half the period followed by mother-directed child clean-up.

Mother's ability to accurately perceive the child's signals and to respond to them promptly, contingently and appropriately was rated based on behavior observed across all three videotaped episodes, using Ainsworth *et al.*'s (1974) nine-point, maternal sensitivity scale; higher scores reflect greater sensitivity. Inter-rater reliability

proved high (sensitivity: Intraclass correlation = 0.93, $n = 87$; $M = 4.53$; $SD = 1.70$, range 1–8).

Statistical analysis

The statistical analysis proceeded in two stages. First, we evaluated in a traditional regression analysis whether the GXE effect involving *5-HTTLPR* and environmental context predicted parenting; following Belsky and Widaman (2018), this was done not to see whether the interaction was significant, but whether the *F* value was sufficiently large—greater than 1.0—to permit formal, competitive model testing.

After establishing that the *F* ratio of the GXE effect exceeded 1.0, we proceeded to the second stage in which we evaluated competing models of person-X-environment interaction. To test whether *ss* carriers were vulnerable (diathesis-stress) or susceptible for better and for worse (differential susceptibility) to the quality of the environmental context, a reparametrized equation was used, following Widaman *et al.* (2012):

$$Y: \begin{cases} D = 0 : Y = B_0 + B_1 (X - C) + E \\ D = 1 : Y = B_0 + B_3 (X - C) + E \end{cases}$$

Where variable *D* are the genotypes (0 = *sL/LL*; 1 = *ss*), B_0 is the intercept, B_1 the slope for *sL/LL* genotype, B_3 the slope for *ss* genotype and *C* is the cross over point between the two slopes. The magnitude of the crossover point (*C*) distinguishes a diathesis-stress from a differential susceptibility model: if the magnitude of *C* is zero, then the two lines meet at the left of the graph without crossing-over, and the *ss* genotype cannot have a better outcome than the *sL/LL* genotype—which would be in accordance to diathesis-stress model. If the magnitude of *C* is not zero, then the two lines cross over in the middle of the graph and the *ss* genotype can have a better outcome than *sL/LL* genotype—which would be in accordance to the differential susceptibility model. Using this comparative approach, we simultaneously tested for the two versions (strong and weak) of the differential susceptibility and diathesis-stress models.

Following Widaman *et al.* (2012), the four possible models were tested and compared with each other in terms of fit to the data based on explained variance (R^2) and Akaike and Bayesian criteria (AIC and BIC, respectively). Models that fit the data better should explain more variance (higher R^2), and those with lower values of AIC and BIC are preferred as showing better fit to the data. For detailed statistical procedures please refer to Widaman *et al.*, (2012) and Belsky *et al.*, (2013).

Results

Table 1 presents the prediction model for maternal sensitivity including maternal *5-HTTLPR* and family context

as predictors (independently and in interaction). As displayed, the F value of the GXE interaction term greatly exceeded 1.0 ($F_{(3,205)} = 12\,272$), thereby allowing us to test competing GXE models.

Weak and strong versions of differential-susceptibility and diathesis-stress models were simultaneously tested. Inspection of Table 2 indicates, upon considering both R^2 and AIC and BIC criteria, that the best fitting model (i.e. the one explaining more of the variance and having lower values of AIC and BIC) proved to be the weak version of differential susceptibility (i.e. model B) ($R^2 = 0.152$, $F_{(3,204)} = 8.728$, $P < 0.001$; AIC = 841 467, BIC = 846 890). Despite the non-significant difference between models B and D ($F_{(2205)} = 0.16$, $P = 0.85$), the actual difference in BIC between model B and the three other ones is higher than 10, which, according to Raftery (1995), is considered 'very strong' evidence in favor of the model with the more negative BIC value—in this case, the weak differential susceptibility model.

The graphic depiction of findings in Fig. 2 also proves highly consistent with the weak differential susceptibility model in that (1) mothers of both genetic subgroups evinced greater sensitivity under more positive environmental conditions and less sensitivity under more negative environmental conditions, though (2) the strength of this for-better-and-for-worse pattern of association was greater for mothers homozygous for the s allele than for those who were L carriers.

Discussion

The aim of this study was to determine whether—and how—the serotonin-transporter gene, *5-HTTLPR*, moderated the effect of quality of environmental context on parenting, thereby extending research on the determinants of parenting and on GXE interaction. We first ascertained the GXE interaction in the prediction of maternal sensitivity. Then our competitive model-testing analysis designed to contrast diathesis-stress and differential-susceptibility models of person-X-environment interaction

Table 1 Prediction model for maternal sensitivity, considering maternal 5-HTTLPR and quality of environmental context

Model; predictors	R^2 (R^2_{adj})	F (df)	Unstandard. coefficient		t	P value	95% CI	
			B	SE			Lower	Upper
1								
5-HTTLPR (SS)	0.130 (0.122)	15.411 (2206)	-0.120	0.172	-0.698	0.486	-0.458	0.219
Environmental context			0.452	0.083	5.439	<0.001	-0.616	-0.288
2								
5-HTTLPR (SS)	0.152 (0.140)	12.272 (3205)	-0.070	0.171	-0.408	0.684	-0.407	0.268
Environmental context			-0.365	0.090	-4.030	<0.001	-0.543	-0.186
GXE			-0.501	0.217	-2.311	0.022	-0.929	-0.074

$N = 210$.

CI, confidence interval; GXE, gene-X-environment.

Table 2 Results for alternate regression models for maternal sensitivity

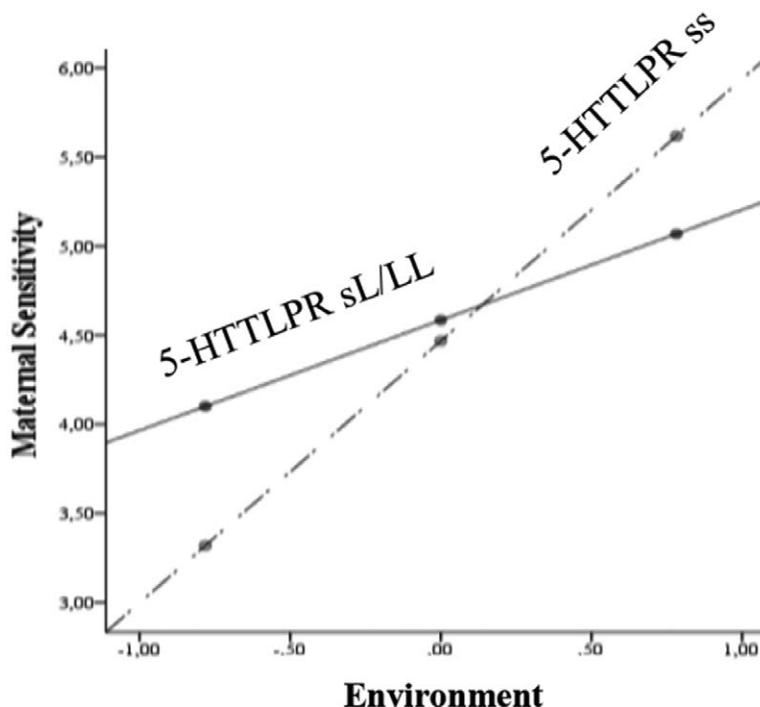
Parameter	Re-parameterized regression equation			
	Differential susceptibility		Diathesis-stress	
	Model A: strong	Model B: weak	Model C: strong	Model D: weak
B_0	4.601 (0.12)	4.669 (0.29)	4.683 (0.12)	5.517 (0.16)
B_1	0 (-)	0.484 (0.12)	0 (-)	0.550 (0.00)
C	0.116 (0.00)	0.175 (0.45)	10.0 (0.00)	10.0 (0.00)
B_2	1.149 (0.27)	1.149 (0.26)	0.445 (0.15)	0.800 (0.21)
R^2	0.085	0.152	0.044	0.141
F	8.014	8.728	7.625	8.559
df	2205	3204	1206	2205
P	<0.001	<0.001	<0.001	<0.001
F vs. a	-	1.88	1.16	-
df	-	1206	1206	-
P	-	0.17	0.28	-
F vs. b	1.88	-	3.06	0.16
df	1206	-	1206	2205
P	0.17	-	0.08	0.85
AIC	910 341	841 467	930 018	853 513
BIC	916 427	846 890	935 008	859 053

Tabled values are parameter estimates, with their standard errors in parentheses.

F vs. a and F vs. b stand for F tests of the difference in R^2 for a given model vs. model b, respectively.

AIC, Akaike information criterion; BIC, Bayesian information criterion; C, cross-over point.

Fig. 2



Plot of the interaction between the *5-HTTLPR* genotype (*LL/sL* vs. *ss*) and quality of environmental context on the explanation of maternal sensitivity.

indicated that the weak differential-susceptibility model fitted the data best. Thus, even though both mothers homozygous for the *s* allele and those carrying the *L* allele proved more sensitive in parenting when the environmental context was supportive and less sensitive when such context posed risk, this context-parenting association proved stronger in the case of *ss* mothers than those carrying *L* alleles. It must be acknowledged, however, that despite meeting some statistical criteria—namely, explaining more of the variance, having lower values of AIC, and, particularly, having a difference in BIC which was enough to be considered ‘very strong’ evidence in favor of the model (Raftery, 1995)—this best-fitting model did not prove significantly different from the weak diathesis-stress one. Thus, there is a clear need to replicate these results, ideally using larger samples or employing meta-analysis to multiple samples.

Given the fact that different allelic subgroups have been tested in previous GXE literature involving *5-HTTLPR*, we reran the analysis in order to contrast the presence vs. absence of the *s*-allele (i.e. *sL/ss* vs. *LL*); proceeding in this alternative GXE manner yielded results consistent with those already reported. Notable, then, is that the results presented herein are generally in line with those of a meta-analysis showing that *5HTTLPR* is a genetic marker of differential susceptibility in Caucasian children and adolescents (van IJzendoorn *et al.*, 2012).

Therefore, this study underlines the importance of considering both genetic and environmental sources of influence when investigating the determinants of parenting. Recall in this regard how inconsistent genotype-phenotype results reviewed in the Introduction proved to be when *5-HTTLPR* was only directly related to parenting (i.e. as a main effect). The findings reported herein raise the possibility that one reason why the data proved so inconsistent across prior studies was because samples differed in fundamental ways in terms of family conditions that were not taken into account by considering GXE interaction.

Despite the strengths of this study, most notably its GXE focus on parenting and reliance on competitive model testing, this work has some limitations that should be highlighted. First, even if the sample size ($N = 210$) was in line with previous research on this topic reporting on GXE interactions (Sturge-Apple *et al.*, 2012; Morgan *et al.*, 2016), it is still modest. Second, as the study involved a community sample, and even if some degree of risk was captured, the number of families at very high risk was limited. A third limitation, involved the need to create a quality of environmental context composite and the resultant inability to decompose it in order to illuminate, perhaps, which components proved most predictive in a GXE analysis. A final limitation might be that the study was not designed to illuminate endophenotypic processes

that could explain why *ss* mothers appear more affected, for better and for worse, by environmental context when it comes to their parenting. Also, candidate gene and candidate GXE approaches have been the focus of much recent debate. In fact, a recent study on depression phenotypes conducted on large population-based and case-control samples found no support for previous depression-related candidate gene findings (Border *et al.*, 2019). Therefore, even if this study's focus is not maternal behavior per se, it does raise the possibility of false positives on previous candidate gene and GXE interaction findings, and the need for caution when considering this literature.

Future research could extend this study through the use of experiments. Do mothers with the *ss* genotype benefit more from parenting intervention than mothers carrying the *L* allele? Notably, previous experimental research has shown that putative 'risk' factors actually operate as 'opportunity' factors in that those carrying them benefit more from interventions than those not carrying them (Klein Velderman *et al.*, 2006; Cassidy *et al.*, 2011; Crawford *et al.*, 2013; Derogatis and Spencer, 1982). Indeed, a meta-analysis of such gene-X-intervention work revealed greater effects of a variety of experimental manipulations for hypothesized susceptible genotypes than nonsusceptible genotypes (Bakermans-Kranenburg and van IJzendoorn, 2015). Further investigation on this subject would provide insights into 'what works for whom', better matching intervention to mother-infant dyads (Belsky and van IJzendoorn, 2015).

Also, research on mechanisms underlying differential susceptibility is clearly called for (Moore and Dupre, 2016). Such work should consider in particular possible mechanisms by which the polymorphism comes to affect sensitivity to context and, thereby how family conditions come to influence parenting. Possible mechanisms include maternal cognitive functioning (cf. Homberg and Lesch, 2011) and amygdala activation (Furman *et al.*, 2011).

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Conflicts of interest

There are no conflicts of interest.

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