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

RUNNING HEAD: 5-HTTLPR AND MATERNAL BEHAVIOUR

Authors:

Rita Baiao[12], Pasco Fearon[3], Jay Belsky[4], Pedro Teixeira[5], Isabel Soares[1] & Ana Mesquita[1]

[1] CIPsi, School of Psychology, University of Minho;

[2] Neurosciences Building, Department of Psychiatry, University of Oxford

[3]Department of Clinical, Educational and Health Psychology, University College of London

[4] Department of Human Ecology, University of California, Davis

[5] School of Health Sciences, University of Minho

Correspondence concerning this article should be addressed to Ana Mesquita, School of Psychology, University of Minho, Campus de Gualtar, 4710-057 – Braga, Portugal. Phone: 00351 253 601 398. Email: ana.mesquita@psi.uminho.pt

Funding

This work was supported by the Fundação para a Ciência e a Tecnologia FCT (Portuguese Foundation for Science and Technology) [grant numbers SFRH/BD/96001/2013, PTDC/PSI-PCL/116897/2010 and IF/00750/2015]. The funder was not involved in conducting the research or preparation/submission of the manuscript.

ABSTRACT

Evidence documenting associations between 5-HTTLPR and parenting behaviour led to testing the hypothesis that this polymorphism moderates the effect of quality of the quality of environmental context on maternal sensitivity. Participants were 210 Portuguese mothers and their pre-school children, recruited from the community. An index reflecting the quality of the environmental context was 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 (GXE) 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 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 GXE findings.

Keywords: 5-HTTLPR, maternal sensitivity, quality of environmental context, family context, GXE interaction, differential susceptibility.

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 behavioural processes, this system has widespread effects on cognition and mood (cf. Homberg & Lesch, 2011), conceivably affecting parenting, the focus of this report. Serotonin may also be linked to parental behaviour 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, Riis, Knigge, Kjaer, & Warberg, 2003); and Lee, Garcia, Van de Kar, Hauger, and Coccaro, (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 & van IJzendoorn, 2008; Mileva-Seitz et al., 2011; Cents et al., 2014; Sturge-Apple, Cicchetti, Davies, & Suor, 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 behaviour. 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 & Landrø, 2014) and improved social cognition (Homberg & Lesch, 2011). Nonetheless, these, like many other genotype-phenotype associations, have

proven inconsistent across studies (e.g., Mesquita et al., 2015; Taylor et al., 2006; Wilhelm et al., 2006 for combined ss vs sL/LL genotypes; Brummett et al., 2008; Caspi et al., 2003; Gunthert et al., 2007 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 behaviour 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, Hammen and Lee (2016): Carriers of the *s*-allele exhibited less positive parenting when interacting with their 6- to 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 six-month olds (Mileva-Seitz et al., 2011). Results similar to these emerged when Cents and associates (2014) examined effects of *5-HTTLPR* on sensitivity 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 two-year old children (Sturge-Apple et al., 2012).

Regarding genotype-phenotype inconsistency of the kind just outlined, Caspi and associates (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 reported experiencing 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 behaviour. 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 & Pluess, 2009; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 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 (Brummett et al., 2008; Caspi et al., 2003; Taylor et al., 2006; Wilhelm et al., 2006; Zalsman et al., 2006), anxiety (Gunthert et al., 2007), and ADHD (Retz et al., 2008). Indeed, all these studies found that *s*-carriers (i.e., either *ss* or *sL*) 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; Morgan et al., 2016; Sturge-Apple et al., 2012), 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 associates (2011; Belsky et al., 2012; Belsky & 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, while 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 on Figure 1, 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).

In the present study we evaluated whether mothers carrying the ss vs. sL/LL genotypes were differentially affected by the quality of environmental context, while considering both strong and weak versions of the differential-susceptibility and diathesis-stress models of person-X-environment interaction. 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 have investigated 5-HTTLPR moderation of environmental influences (e.g. Bakermans-Kranenburg & van IJzendoorn, 2008; Hayden et al., 2007; Mesquita et al., 2015; Taylor et al., 2006; Wilhelm et al., 2006; Young et al., 2007), and also in meta-analytic work (Crawford, Lewis, Lewis, & Munafò, 2013). With regard 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 proceed this way for two reasons. First, the environmental context indicators we composited are associated with parenting (Belsky, 1984; Belsky & Jaffee, 2007); 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, Li & Whipple, 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 20-48 years (M = 33.36, SD = 5.60); 23.3% had less than nine years of education. Children's ages ranged from 40-77 months (M = 58.26, SD = 7.63); 114 (54.3%) were girls. The study was approved by the XXX National Committee for Data Protection (Authorisation number: 2496/2012) and the Ethical Committee of the University of XXX (Authorisation 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, Edmonds, Davagnino, and Briggs-Gowan (2013), we assessed presence vs. absence of nine sociodemographic and psychosocial factors, including (1) teenage pregnancy (9, 4.3%); (2) single parenthood (37, 17.6%); (3) (low) parental educational level (i.e., one of the parents had under nine 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%); (9) and 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* (BSI; Derogatis, 1982;

Portuguese version, Canavarro, 1999), based on a 5-point scale (0 ="not at all" to 4="extremely"), in terms of the presence of various symptoms experienced in the past week (Chronbach alpha = .96). A binary variable (presence/absence of Maternal Psychopathology) was computed based on the Portuguese normative mean and standard deviation for the Positive Symptoms Distress Index; a score greater than 1.96 qualified as evidence of maternal psychopathology. The nine factors were analysed 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 (PCR). The amplification products were separated on a 3% agarose gel and visualized using Gel Doc EZ system (Bio-Rad, 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 behaviour

Mother-child interaction was videotaped in a quiet room (at the family home or at the preschool) across three 5-minute episodes involving (a) child play with a challenging toy under mother's guidance; (b) 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 (c) 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 behaviour observed across all three videotaped episodes — using Ainsworth, Bell and Stayton's (1974) 9-point, maternal sensitivity scale; higher scores reflect greater sensitivity. Inter-rater reliability proved high (sensitivity: ICC = .93, n = 87; M = 4.53; SD = 1.70, range 1-8).

Statistical analysis

The statistical analysis proceeded in two stages. First we evaluate 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):

$$Y: \begin{cases} D = 0 : Y = B0 + B1\ (X - C) + E \\ D = 1 : Y = B0 + B3\ (X - C) + E \end{cases}$$

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 two versions (strong and weak) of the differential susceptibility and diathesis-stress models (see Figure 1).

---------- Figure 1 ----------

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 Akaik 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, see Belsky, Pluess and Widaman (2013) and Widaman et al. (2012).

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.

---------- Table 1 ----------

Weak and strong versions of differential-susceptibility and diathesis-stress models were simultaneously tested. Inspection of Table 2 indicates, upon considering both R2 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) (R2 = .152, F(3,204)=8.728, p <.001; AIC = 841,467, BIC = 846.890). Despite the non-significant difference between Models B and D (F(2,205)= 0.16, p = .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 favour of the model with the more negative BIC value – in this case, the weak differential susceptibility model.

---------- Table 2 ----------

The graphic depiction of findings in Figure 2 also proves highly consistent with the weak differential susceptibility model in that (a) mothers of both genetic subgroups evinced greater sensitivity under more positive environmental conditions and less sensitivity under more negative environmental conditions, though (b) 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.

---------- Figure 2 ----------

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 gene-X-environment (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 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 favour 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, Belsky, & Bakermans-Kranenburg, 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 (Morgan et al. 2016, Sturge-Apple et al. 2012), 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 gene-X-environment 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 (Bolder et al., 2019). Therefore, even if this study's focus is not maternal behaviour per se, it does raise the possibility of false positives on previous candidate gene and G-X-E 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 (Cassidy et al., 2011; Klein Velderman, Bakermans-Kranenburg, Juffer, & Van IJzendoorn, 2006). 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 & van IJzendoorn, 2015). Further investigation on this subject would provide insights into “what works for whom”, better matching intervention to mother–infant dyads (Belsky & van IJzendoorn, 2015).

Also, research on mechanisms underlying differential susceptibility is clearly called for (Moore & 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 & Lesch, 2011) and amygdala activation (Furman, Hamilton, Joormann & Gotlib, 2011).

Acknowledgments

The authors would like to thank all students and researchers involved in data collection, and specially the children, parents, and all school staff who participated in the study.

REFERENCES

Ainsworth, M., Bell, S., & Stayton, D. (1974). Infant-mother attachment and social development: ‘‘socialization’’ as a product of reciprocal responsiveness to signals. In M. Richards (Ed.), *The Integration of a Child into a Social World* (pp. 99-135). London: Cambridge University Press.

Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2008). Oxytocin receptor (OXTR) and serotonin transporter (5-HTT) genes associated with observed parenting. *Social Cognitive and Affective Neuroscience, 3*, 128–134. doi: 10.1093/scan/nsn004

Bakermans-Kranenburg, M. J. & van IJzendoorn, M. H. (2015). The Hidden Efficacy of Interventions: Gene × Environment Experiments from a Differential Susceptibility Perspective. *Annual Review of Psychology, 66*, 381-409. Doi: 10.1146/annurev-psych-010814-015407

Belsky, J. (1984). The determinants of parenting: A process model. *Child Development*, *55*, 83–96.

Belsky, J. & van IJzendoorn, M.H. (2015). What works for whom? Genetic moderation of intervention efficacy. *Development and Psychopathology, 27*, 1-6. doi: 10.1017/S0954579414001254

Belsky, J. & Jaffee, S.R. (2006). The multiple determinants of parenting. In: Cicchetti D, Cohen DJ, editors. *Developmental Psychopathology, Vol 3: Risk, Disorder, and Adaptation*, 38–85. Hoboken, NJ: Wiley.

Belsky, J, Jonassaint, C., Pluess, M., Stanton, M., Brummett, B. & Williams, R. (2009). Vulnerability genes or plasticity genes?. *Molecular Psychiatry*, *14*, 746–754. doi: 10.1038/mp.2009.44

Belsky, J. & Pluess, M. (2009). Beyond Diathesis Stress: Differential Susceptibility to Environmental Influences. *Psychological Bulletin*, *135*, 6, 885–908. doi: 10.1037/a0017376

Belsky, J. & Widaman, K. (2018). Integrating Exploratory and Competitive-confirmatory Approaches to Testing Person-X-Environment Interactions. *Journal of Child Psychology and Psychiatry*, 59(3), 296–298. doi: 10.1111/jcpp.12824

Bolt, D. M. (2005). Limited- and full-information estimation of item response theory models. In A. Maydeu-Olivares & J. J. McArdle (Eds.), *Contemporary psychometrics*, pp. 27–71. Erlbaum, Mahwah, NJ.

Border, R., Johnson, E. C., Evans, L. M., Smolen, A., Berley, N., Sullivan, P. F., & Keller, M. C. (2019). No support for historical candidate gene or candidate gene-by-interaction hypotheses for major depression across multiple large samples. *American Journal of Psychiatry, 176*, 5, 376-387.

Brummett, B. H., Boyle, S. H., Siegker, I. C., Kuhn, C. M., Ashley-Koch, A., Jonassaint, C. R. … Williams, R. B. (2008). Effects of Environmental Stress and Gender on Associations among Symptoms of Depression and the Serotonin Transporter Gene Linked Polymorphic Region (5-HTTLPR). *Behavior Genetics*, *38,* 34–43. doi: 10.1007/s10519-015-9740-8

Canavarro, M. C. (1999). Inventário de Sintomas Psicopatológicos: BSI. In M. R. Simões, M. Gonçalves, & L. S. Almeida (Eds.), *Testes e provas psicológicas em Portugal*, vol. II, pp. 87-109. Braga: SHO/APPORT.

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., … Poulton, R. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science*, *301,* 386–389. doi: 10.1126/science.1083968

Cassidy, J., Woodhouse, S.S., Sherman, L.J., Stupica, B., & Lejuez, C.W. (2011). Enhancing infant attachment security: An examination of treatment efficacy and differential susceptibility. *Development and Psychopathology*, *23*(1), 131–148. doi: 10.1017/S0954579410000696

Cents, R. A., Kok, R., Tiemeier, H., Lucassen, N., Székely, E., Bakermans-Kranenburg, M.J. … Lambregtse-van den Berg, M.P. (2014). Variations in maternal 5-HTTLPR affect observed sensitive parenting. *Journal of Child Psychology* and *Psychiatry and Allied Disciplines*, *55*(9), 1025–1032. doi: 10.1111/jcpp.12205

Fox, E., Ridgewell, A., & Ashwin, C. (2009) Looking on the bright side: biased attention and the human serotonin transporter gene. *Proc Roy Soc B Biol Sci, 276*, 1747–1751. doi: 10.1098/rspb.2008.1788

Ellis, B. J., Boyce, W. T., Belsky, J., Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2011). Differential susceptibility to the environment: an evolutionary–neurodevelopmental theory. *Development and Psychopathology*, *23*(1), 7-28. doi: 10.1017/S0954579410000611

Evans, G.W., Li, D., & Whipple, S.S. (2013). Cumulative risk and child development. *Psychological Bulletin, 139*, 1342-1396. doi: 10.1037/a0031808

Furman, D. J., Hamilton, J. P., Joormann, J., & Gotlib, I. H. (2011). Altered timing of amygdala activation during sad mood elaboration as a function of 5-HTTLPR.

Social Cognitive and Affective Neuroscience, *6* (3), 270-276. doi: 10.1093/scan/nsq029

Gunthert, K. C., Conner, T. S., Armeli, S., Tennen, H., Covault, J., & Kranzler, H. R. (2007). Serotonin transporter gene polymorphism (5- HTTLPR) and anxiety reactivity in daily life: A daily process approach to gene–environment interaction. *Psychosomatic Medicine*, *69*, 762– 768. doi: 10.1097/PSY.0b013e318157ad42

Hayden, E.P., Dougherty, L.R., Maloney, B., Durbin, C.E., Olino, T.M., Nurnberger, J.I. … Klein, D.N. (2007). Temperamental fearfulness in childhood and the serotonin transporter promoter region polymorphism: a multimethod association study. *Psychiatric Genetics*, *17*, 135–42. doi: 10.1097/YPG.0b013e3280147847

Homberg J. R., & Lesch K. P. (2011). Looking on the bright side of serotonin transporter gene variation. *Biological Psychiatry, 69*, 513–519. doi: 10.1016/j.biopsych.2010.09.024

Jonassen, R. & Landrø, N.I. (2014). Serotonin transporter polymorphisms (5-HTTLPR) in emotion processing: implications from current neurobiology. *Progress in Neurobiology, 117*, 41–53. doi: 10.1016/j.pneurobio.2014.02.003

Jorgensen, H., Riis, M., Knigge, U., Kjaer, A., Warberg, J. (2003). Serotonin receptors involved in vasopressin and oxytocin secretion. *Journal of Neuroendocrinology, 15*, 242–9. doi: 10.1046/j.1365-2826.2003.00978

Klahr, A. M., & Burt, S. A. (2014). Elucidating the etiology of individual differences in parenting: A meta-analysis of behavioral genetic research. *Psychological Bulletin, 140,* 544 –586. doi: 10.1037/a0034205

Klein Velderman, M., Bakermans-Kranenburg, M. J., Juffer, F., & van IJzendoorn, M. H., (2006). Effects of attachment-based interventions on maternal sensitivity and infant attachment: Differential susceptibility of highly reactive infants. *Journal of Family Psychology, 20*, 266–274. doi: 10.1037/0893-3200.20.2.266

Lee, R., Garcia, F., Van de Kar, L.D., Hauger, R.D., & Coccaro, E.F. (2003). Plasma oxytocin in response to pharmaco-challenge to D-fenfluramine and placebo in healthy men. *Psychiatry Research, 118*, 129–36. doi: 10.1016/S0165-1781(03)00070-2

Lesch, K. P., Bengel, D., Heils, A., Sabol, S. Z., Greenberg, B. D., Petri, S., ... & Murphy, D. L. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science, 274*(5292), 1527-1531. doi: 10.1126/science.274.5292.1527

Mesquita, A. R., Belsky, J., Li, Z., Baptista, J., Carvalho-Correia, E., Maciel, P. & Soares, I. (2015). Institutionalization and indiscriminate social behavior: Differential-susceptibility versus diathesis-stress models for the 5-HTTLPR and BDNF genotypes. *Physiology & Behavior, 152,* 85–91. doi: 10.1016/j.physbeh.2015.09.015

Mileva-Seitz, V., Kennedy, J., Atkinson, L., Steiner, M., Levitan, R., Matthews, S. G., … Fleming, A. S. (2011). Serotonin transporter allelic variation in mothers predicts maternal sensitivity, behavior and attitudes toward 6-month-old infants. *Genes, Brain and Behavior, 10*, 325–333. doi: 10.1111/j.1601-183X.2010.00671.x

Moore, S. R., & Depue, R. A. (2016). Neurobehavioral foundation of environmental reactivity. *Psychological Bulletin, 142* (2), 107-164. doi: 10.1037/bul0000028

Morgan, J. E, Hammen, C. & Lee, S.S. (2016). Parental Serotonin Transporter Polymorphism (5-HTTLPR) Moderates Associations of Stress and Child Behavior With Parenting Behavior, *Journal of Clinical Child & Adolescent Psychology*, *00*, 1–12. doi: 10.1080/15374416.2016.1152550

Raftery, A. E. (1995). Bayesian Model Selection in Social Research. *Sociological Methodology*, *25*, 111-163. doi: 10.2307/271063

Retz, W., Freitag, C. M., Retz-Junginger, P., Wenzler, D., Schneider, M., Kissling, C., … Rösler, M. (2008). A functional serotonin transporter promoter gene polymorphism increases ADHD symptoms in delinquents: Interaction with adverse childhood environment. *Psychiatry Research, 158*, 123–131. doi: 10.1016/j.psychres.2007.05.004

Sturge-Apple, M. L., Cicchetti, D., Davies, P. T., & Suor, J. H. (2012). Differential susceptibility in spillover between interparental conflict and maternal parenting practices: Evidence for OXTR and 5-HTT genes. *Journal of Family Psychology, 26*(3), 431-442. doi: 10.1037/a0028302

Roiser, M.U., Clark, L. & Sahakian, B.J. (2007). The effects of acute tryptophan epletion and serotonin transporter polymorphism on emotional processing in memory and attention. *Int J Neuropsychopharmacol, 10*, 449–461. doi: 10.1017/S146114570600705X

Taylor, S. E., Way, B. M., Welch, W. T., Hilmert, C. J., Lehman, B. J., & Eisenberger, N. I. (2006). Early family environment, current adversity, the serotonin transporter promoter polymorphism, and depressive symptomatology. *Biological Psychiatry, 60*, 671–676. doi: 10.1016/j.biopsych.2006.04.019

van IJzendoorn, M. H., Belsky, J., & Bakermans-Kranenburg, M. J. (2012). Serotonin transporter genotype 5HTTLPR as a marker of differential susceptibility? A meta-analysis of child and adolescent gene-by-environment studies. *Transl Psychiatry*, *2*, e147. doi: 10.1038/tp.2012.73

Weitzman, C., Edmonds, D., Davagnino, J., & Briggs-Gowan, M. J. (2013). Young child socioemotional/behavioral problems and cumulative psychosocial risk. *Infant Mental Health Journal*, *35*(1), 1–9. doi: 10.1002/imhj.21421

Widaman, K. F., Helm, J. L., Castro-Schilo, L., Pluess, M., Stallings, M. C., & Belsky, J. (2012). Distinguishing ordinal and disordinal interactions. *Psychological Methods, 17,* 615–622. doi: 10.1037/a0030003

Wilhelm, K., Mitchell, P. B., Niven, H., Finch, A., Wedgwood, L., Scimone, A., … Schofield, P. R. (2006). Life events, first depression onset and the serotonin transporter gene. *British Journal of Psychiatry, 188,* 210–215. doi: 10.1192/bjp.bp.105.009522

Young, K.A., Holcomb, L.A., Bonkale, W.L., Hicks, P.B., Yazdani, U., & German, D.C. (2007). 5HTTLPR Polymorphism and Enlargement of the Pulvinar: Unlocking the Backdoor to the Limbic System. *Biological Psychiatry*, *61*, 813–8. doi: 10.1016/j.biopsych.2006.08.047

Zalsman, G., Huang, Y. Y., Oquendo, M. A., Burke, A. K., Hu, X. Z., Brent, D. A. … Mann, J. J. (2006). Association of a triallelic serotonin transporter gene promoter region (5-HTTLPR) polymorphism with stressful life events and severity of depression. *American Journal of Psychiatry*, *163*, 1588–1593. doi: 10.1176/ajp.2006.163.9.1588

FIGURES

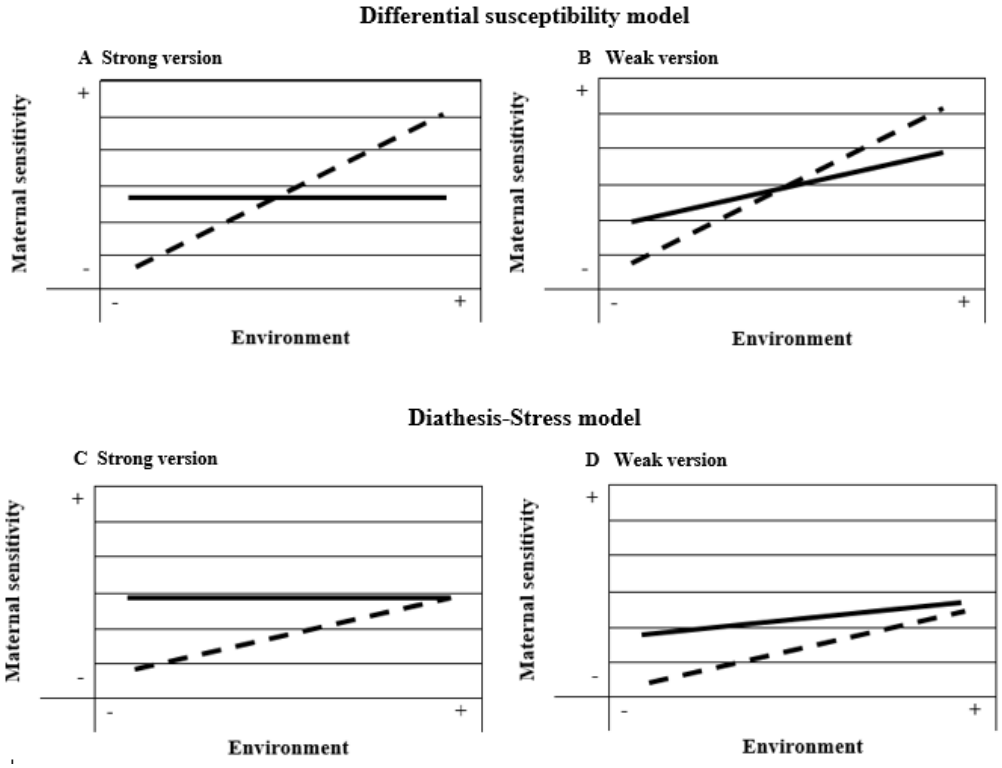

Figure 1. Graphical display of strong and weak versions of differential susceptibility (A and B) and diathesis-stress (C and D) models. The x-axis represents variation in the quality of environmental context, from negative to positive; the y-axis represents the maternal sensitivity scores, from negative to positive. The lines depict the two genotypes (*ss vs. sL/LL*).

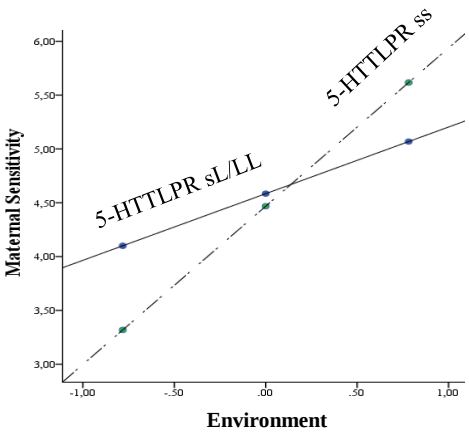

Figure 2. Plot of the interaction between the *5-HTTLPR* genotype (*LL/sL vs. ss*) and quality of environmental context on the explanation of maternal sensitivity.

TABLES

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***	**95% CI**	
			B	***SE***			**Lower**	**Upper**
1								
5-HTTLPR (*SS*)	.130 (.122)	15.411 (2,206)	-.120	.172	-.698	.486	-.458	.219
Environmental context			.452	.083	5.439	<.001	-.616	-.288
2								
5-HTTLPR (*SS*)	.152 (.140)	12.272 (3,205)	-.070	.171	-.408	.684	-.407	.268
Environmental context			-.365	.090	-4.030	<.001	-.543	-.186
GXE			-.501	.217	-2.311	.022	-.929	-.074

Note. *N* = 210

Table 2. Results for alternate regression models for maternal sensitivity

	Re-parameterized regression equation			
	Differential susceptibility		Diathesis-Stress	
Parameter	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 (-)	.484 (0.12)	0 (-)	.550 (0.00)
C	.116 (.00)	.175 (0.45)	10.0 (0.00)	10.0 (0.00)
B_3	1.149 (.27)	1.149 (0.26)	.445 (0.15)	.800 (0.21)
R^2	.085	.152	.044	.141
F	8.014	8.728	7.625	8.559
df	2,205	3,204	1,206	2,205
p	< .001	< .001	< .001	< .001
F vs. a	-	1.88	1.16	-
df	-	1,206	1,206	-
p	-	.17	.28	-
F vs. b	1.88	-	3.06	0.16
df	1,206	-	1,206	2,205
p	.17	-	.08	.85
AIC	910.341	841.467	930.018	853.513
BIC	916.427	846.890	935.008	859.053

Note. 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 versus Model a and Model b, respectively.

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