Letter to the editor: Bias in the measurement of bias. Letter regarding 'Citation bias and selective focus on positive findings in the literature on the serotonin transporter gene (5-HTTLPR), life stress and depression'

By: Suzanne Vrshek-Schallhorn, Vaibhav Sapuram, Bradley M. Avery

Vrshek-Schallhorn, S., Sapuram, V., Avery, B.M. (2017). Letter to the editor: Bias in the measurement of bias. Letter regarding 'Citation bias and selective focus on positive findings in the literature on the serotonin transporter gene (5-HTTLPR), life stress and depression'. Psychological Medicine, 47(1), 187-192.

Abstract:

de Vries et al. (2016) argue that discussion of the 5-HTTLPR-stress gene-environment interaction (G × E) (Caspi et al. 2003) is more positive than merited because authors often cast negative results as positive in abstracts, and negative papers with positive focus are differentially cited. These bold claims deserve careful scrutiny. Four methodological choices we highlight bias their primary results; the vast majority of papers disclose mixed and negative results in their abstracts (Table 1). Further, even if positive focus was prevalent, it could not bias meta-analytic results. The field can best move forward by ameliorating environmental measurement.

Keywords: measurement | serotonin | life stress | bias | serotonin transporter | psychiatry | stress | depression

Article:

de Vries et al. (2016) argue that discussion of the 5-HTTLPR-stress gene-environment interaction (G × E) (Caspi et al. 2003) is more positive than merited because authors often cast negative results as positive in abstracts, and negative papers with positive focus are differentially cited. These bold claims deserve careful scrutiny. Four methodological choices we highlight bias their primary results; the vast majority of papers disclose mixed and negative results in their abstracts (Table 1). Further, even if positive focus was prevalent, it could not bias meta-analytic results. The field can best move forward by ameliorating environmental measurement.

Methodological concerns

de Vries et al. (2016) coded papers' full results sections as positive or negative, then compared this with abstract conclusion sentences' positivity. Four choices that lead to errant conclusions contrast decisions reflecting care not to bias results - selecting the smallest p value when both traditional and triallelic results were available, and when both adjusted and unadjusted results were available. Similarly, sensitivity analyses using the lowest p value should address several issues, but still provide 'positive focus' results that contradict disclosures we extracted from abstracts. We focus our comments on their primary approach, which informs their conclusions.

Averaging p values

When papers included multiple G × E p values, the authors averaged them in their primary analyses, an approach biased toward negative conclusions. For a hypothetical paper with three findings at the $p = 0.001$ level and one finding at the $p = 0.300$ level, the average of the four is non-significant by traditional standards, $p = 0.076$. But who would conclude such a paper was negative overall? Although the most inclusive 5-HTTLPR and life stress G × E meta-analysis took a similar approach (Sharpley et al. 2014), a bias for negative conclusions could be entirely appropriate for a meta-analysis that ultimately has positive conclusions. However, the negative bias favors the perspective of de Vries et al. (2016).

Dichotomizing averaged p values

The authors imposed a false negative/positive dichotomy on averaged p values. For example, Jenness et al. (2011) reported a significant interaction for 5-HTTLPR with family chronic stress ($p = 0.02$) but not with recent stressful life events ($p = 0.88$), leading to a negative classification by de Vries et al. (2016) (average $p = 0.46$). Despite disclosure of mixed findings in their abstract (Table 1), de Vries et al. (2016) labeled their work as having partially positive focus relative to 'negative' findings. An alternative if imperfect approach is to classify papers across at least three categories (positive, negative and mixed), then evaluate abstracts for fidelity to actual findings.

Unbiased or atheoretical?

The primary approach assumes each of the averaged p values are equally valid, an approach which runs roughshod over theory. Several papers specifically hypothesized that one of their tests was more valid than another - sensitivity testing that refines G × E research and ought to be highly cited - accordingly presented the results of both approaches, and found support for their hypothesis. Uher et al. (2011) found support for Brown & Harris's (2008) hypothesis that the childhood adversity G × E predicts persisting depression, $p = 0.003$, but not single-episode depression, $p = 0.231$ (a finding replicated elsewhere; Brown et al. 2013). These results transparently appear in their abstract (Table 1), yet the faulty assumption that these tests are equally valid leads de Vries et al. (2016) to classify Uher et al.'s (2011) and Brown et al.'s (2013) papers as negative with positive focus. Although sensitivity analyses selecting the lowest p value ought to allow for theory to favor a particular test, we identified abstract sentences disclosing results for more papers than these analyses suggest.

Table 1. Transparent sentences from abstracts of papers that de Vries et al. (2016) classified as having (partially) positive focus

First author (year)	Quote from abstract results disclosing results
Brown (2013)	'The short alleles of 5-HTTLPR moderated the relationship between childhood maltreatment and chronic depression in adulthood, reflected in a significant gene-environment interaction (RD = 0.226, 95% CI: 0.076-0.376, p = 0.0032). 5-HTTLPR did not moderate the effects of either childhood maltreatment or severe life events on new depressive onsets'
Cichetti (2007)	None
Cichetti (2011)a	None. Test of G × G × Eb
Eley (2004)	'In addition, there was a trend for an effect of 5HTTLPR, which was significant in female subjects. Furthermore, there was a significant genotype-environmental risk interaction for 5HTTLPR in female subjects only....'
Goldman (2010)	'Although the gene-environment (G × E) interaction with recent major life events is not significant, our results suggest that trauma has a worse effect on depressive symptoms for those with S/S or S/L genotype than for those who do not carry the S allele ($p < 0.05$)'
Grabe (2012)a	'Tobit regression analyses revealed a three-way-interaction between the three genotypes of 5-HTTLPR and the BDNF genotypes and overall childhood abuse for the BDI-II score ($p = 0.02$). ... The s/s genotype of the 5-HTTLPR exerted its negative impact on mental health after childhood abuse only in the presence of the BDNF Val/Val genotype but not in the presence of the BDNF Met allele. In contrast, the l allele of the 5-HTTLPR also emerged as a genetic risk factor for depression in carriers of one or two Met alleles'
Hankin (2011)	'Lagged hierarchical linear modeling analyses showed 5-HTTLPR interacted with idiographic stressors (increases relative to the child's own average level over time), but not nomothetic stressors (higher stress exposure relative to the sample), to predict prospective elevations in depressive, but not anxious, symptoms'
Jenness (2011)	'A significant G × E showed that chronic family stress predicted prospective increases in depressive symptoms over 6 months among youth possessing the high-risk S allele. This G × E was not found for episodic stressors occurring in the last 6 months. ... This is the first study to show that chronic family stress, but not episodic stressors, when ascertained by rigorous stress interview, interacts with 5-HTTLPR to prospectively predict depressive symptoms among children and adolescents'
Mitchell (2011)a	None. Test of (G + G) x Eb
Quinn (2012)	'The results support a role for genetic factors in the development of non-melancholia. The lack of findings in melancholia indicates that other mechanisms may underlie the subtype'
Ritchie (2009)	'Interactions were observed between the 5-HTTLPR long (L) allele, poverty, and excessive sharing of parental problems'
Scheid (2007)	'The relationship between exposure to abuse and elevated depressive symptoms was more pronounced in the s/s group (OR 24.5) than in the s/l group (OR 3.0) and the l/l group (OR 7.7), but this significant interaction was detected only after excluding 73 (13%) women with recent use of psychotropic medications'
Scheid (2011)	'The relation between stressful life events and "elevated" depressive symptoms was stronger in S/S compared with LA/LA genotype (interaction $p = 0.11$). Of the six subconstructs, only abuse showed a statistically significant gene-environment interaction'
Sjöberg (2006)	'First, boys and girls carrying the short 5-HTTLPR allele react to different kinds of environmental factors. Whereas males were affected by living in public housing rather than in own owned homes and by living with separated parents, females were affected by traumatic conflicts within the family. Second, the responses of males and females carrying the short 5-HTTLPR allele to environmental stress factors go in opposite directions'

(*Table 1. continued)*

Stefanis (2011)a	'Homozygous for the 5-HTTLPR S allele reported significantly higher scores for paranoid ideation as compared with L-allele carriers. Slight effects on other subscales were observed, but were not significant after correction for multiple testing. ... In particular, variation within this gene may confer risk for paranoid/defensive reactions under conditions of environmental stress associated with military induction'
Sugden (2010)	None
Uher (2011)	'In both cohorts, statistical tests of gene-environment interactions showed positive results for persistent depression but not single-episode depression. Individuals with two short 5-HTTLPR alleles and childhood maltreatment had elevated risk of persistent but not single-episode depression'
Wichers (2008)a	None. Test of G × G × Eb
Wilhelm (2006)	None
Wilhelm (2012)	'The 5-HTTLPR low-expression genotype group (S or LG allele carriers) had significantly higher psychological distress (K10) scores (n = 234, p = 0.047). Subsequent analysis revealed that the effect of genotype was related to anxiety symptoms rather than depression symptoms. Furthermore, the main effect of genotype was not observed when the modification of the SNP polymorphism was not taken into account' [Exposure only design]
Zalsman (2006)	None
Zhang (2009a)	'In addition, the individuals carrying the L/L genotype of 5-HTTLPR could be susceptible to MDD when exposed to negative life events and MDD in the Chinese population'

5-HTTLPR, Serotonin transporter gene; RD, risk difference; CI, confidence interval; BDNF, brain-derived neurotrophic factor; OR, odds ratio; SNP, single nucleotide polymorphism; MDD, major depressive disorder; G × E, gene-environment interaction.

a. The primary focus of the paper was something other than 5-HTTLPR G × E for depression.

b. We debated whether to expect papers with a focus other than the 5-HTTLPR G × E (but which included it as an ancillary test) to report on this G × E in their abstracts. These include tests of G × G × E effects and one additive (G + G) × E test. To be conservative, we report results both ways. In each noted case, a paper tests a more complex effect but does not fully characterize the ancillary 5-HTTLPR G × E in the abstract.

Evaluation of abstract conclusion sentences not full abstracts

To determine whether abstracts had overly positive focus, the authors rated the conclusion sentence(s), not the full abstract. Such a selective approach disregards an abstract's 'gestalt' without any rationale for doing so. Where is the evidence that researchers cite papers based on abstract conclusion sentences? In contrast to the authors' assertions, we were able to identify very clear acknowledgement of mixed results in all but seven of the 22 abstracts characterized as having (partially) positive focus (Table 1).

Results of alternative rating approach

To estimate these decisions' impact on the positive focus ratings of de Vries et al. (2016), we rated the 38 'negative' papers. Two raters examined results, assigning negative, or mixed classifications, and examined the full abstract to determine whether negative or mixed results were not disclosed (ratings appear in online Supplementary Table S1). We extracted sentences demonstrating disclosure (Table 1). We deemed it unfair to papers with a primary focus other than the 5-HTTLPR G × E (e.g. focus on a G × G × E), but which included it as an ancillary test, to expect they report G × E results in their abstract; to be conservative, we present results both ways. Group discussion adjudicated non-matching ratings. Of these 38 'negative' studies, we characterized them as 58% (n

= 22) negative and 42% (n = 16) mixed. We assigned (partially) positive focus ratings to four to seven of the 22 articles that de Vries et al. (2016) characterized as having (partially) positive focus (depending on treatment of papers with a focus other than the 5-HTTLPR G × E). We conclude that the ratings of de Vries et al. (2016), which form the basis for evaluation of citation bias, are fundamentally flawed.

Sensitivity analyses using the lowest p value still do not square with evidence that authors disclosed results (Table 1): these indicate 12 have (partially) positive focus relative to our four to seven. Moreover, the authors suggested that sensitivity analyses did not markedly influence their findings (for citation bias), but their effect size of (partially) positive focus drops by 26% relative to their negative ratings (22/38 to 12/28) and by 45% relative to the population of 73 studies. Their procedures have a marked impact on estimating the prevalence of positive focus. We observe that this is not reported in their abstract.

Biased conclusions

A conclusion the authors draw in their own abstract is noteworthy: 'discussion of the 5-HTTLPR-stress interaction is more positive than warranted'. How positive should the discussion be? Clearly, this is controversial. On the one hand, there have been two negative meta-analyses that included a small number of reports to use homogeneous designs (k = 5 and 14, respectively; Munafò et al. 2009; Risch et al. 2009), many G × E investigations are under-powered (Duncan & Keller, 2011), and we observed some questionable research practices as we read. On the other hand, inclusive meta-analyses from Karg et al. (2011) (k = 54) and Sharpley et al. (2014) (k = 81) both reach positive conclusions, with Sharpley et al. (2014) showing that the meta-analytic effect emerges across four separate design subtypes. Karg et al. (2011) show that differences between the negative meta-analyses and theirs are due to paper selection, not meta-analytic technique. Papers selected for their statistically homogeneous designs tend to have methodological flaws including retrospective lifetime stress and depression assessment (Moffitt & Caspi, 2014) leading to confounding (Uher & McGuffin, 2010). Moreover, Karg et al. (2011) show that reports with more robust measures of stress (interview and objective measures) possess a more robust meta-analytic effect, so much that others observe an almost 1:1 relationship between stress measurement quality and likelihood of at least partial G × E effect replication (Uher & McGuffin, 2010). Neither positive focus nor citation bias influences this evidence. There is at least a reasonable basis for concluding that this is a legitimate G × E effect. Thus, when papers characterize the results of the 5-HTTLPR G × E literature positively and cite positive studies, how is this 'more positive than warranted?'

Where to go from here?

There is a much larger problem - and opportunity for progress - in G × E depression research. The unique environment contributes roughly 60% of risk to depression (Sullivan et al. 2000), but in G × E research we often fail to invest in environmental measurement. Many G × E researchers measure the environment with insufficiently valid measures (for discussion, see Monroe & Reid, 2008; Uher & McGuffin, 2010; Karg et al. 2011; Sharpley et al. 2014). But in addition, we must all more carefully conceptualize the 'candidate environment'.

Recent work supports that chronic stress and major severity interpersonal stress were consistent unique predictors of depressive episode onset across two samples of emerging adults, whereas minor stressors were never unique predictors and non-interpersonal stressors were rarely

so (Vrshek-Schallhorn et al. 2015). Early evidence indicates that these distinctions matter for G × E tests: Whereas no G × E effect emerged for minor events, consistent with expectations, an overall G × E effect between 5-HTTLPR and major events was accounted for exclusively by major interpersonal events and not non-interpersonal ones (Vrshek-Schallhorn et al. 2014). All forms and severities of stress are not created equal. As G × E research moves beyond 5-HTTLPR, we hope the field will work toward large-scale G × E research with valid, thoughtfully conceptualized environmental measures.

Conclusions

Although positive focus sometimes occurs in G × E research, as we expect it unfortunately does throughout science, through their methodological choices, the paper of de Vries et al. (2016) exemplifies bias. Four choices including classifying abstracts by only their conclusion sentence bias the primary results. Sensitivity tests do not overcome these issues. Ultimately, depression-genetics research enterprise aims to enhance prediction and intervention for depression. It is time we all renewed our 'positive focus' on that goal.

Supplementary material

The supplementary material for this article can be found at http://dx.doi.org/10.1017/S0033291716002178

Acknowledgements

The authors thank Drs Paul Silvia and Thomas Kwapil who provided comments on an earlier version.

Declaration of Interest

None.

References

Brown GW , Ban M , Craig TK , Harris TO , Herbert J , Uher R (2013). Serotonin transporter length polymorphism, childhood maltreatment, and chronic depression: a specific gene-environment interaction . Depression and Anxiety 30 , 5 -13 .10.1002/da.21982

Brown GW , Harris TO (2008). Depression and the serotonin transporter 5-HTTLPR polymorphism: a review and a hypothesis concerning gene-environment interaction . Journal of Affective Disorders 111 , 1 -12 .10.1016/j.jad.2008.04.009

Caspi A , Sugden K , Moffitt TE , Taylor A , Craig IW , Harrington H , McClay J , Mill J , Martin J , Braithwaite A , Poulton R (2003). Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene . Science 301 , 386 -389 .10.1126/science.1083968

Cicchetti D , Rogosch FA , Oshri A (2011). Interactive effects of corticotropin releasing hormone receptor 1, serotonin transporter linked polymorphic region, and child maltreatment on diurnal cortisol regulation and internalizing symptomatology . Development and Psychopathology 23 , 1125 -1138 .10.1017/S0954579411000599 S0954579411000599

Cicchetti D , Rogosch FA , Sturge-Apple ML (2007). Interactions of child maltreatment and serotonin transporter and monoamine oxidase A polymorphisms: Depressive symptomatology among adolescents from low socioeconomic status backgrounds . Development and Psychopathology 19 , 1161 -1180 .S0954579407000600

de Vries YA , Roest AM , Frantzen M , Munafò MR , Bastiaansen JA (2016). Citation bias and selective focus on positive findings in the literature on the serotonin transporter gene (5-HTTLPR), life stress and depression. Psychological Medicine . Published online 12 August 2016. doi:10.1017/S0033291716000805.

Duncan LE , Keller MC (2011). A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry . American Journal of Psychiatry 168 , 1041 -1049 .10.1176/appi.ajp.2011.11020191

Eley T , Sugden K , Corsico A , Gregory A , Sham P , McGuffin P , Plomin R , Craig I (2004). Gene-environment interaction analysis of serotonin system markers with adolescent depression . Molecular Psychiatry 9 , 908 -915 .10.1038/sj.mp.4001546

Goldman N , Glei DA , Lin YH , Weinstein M (2010). The serotonin transporter polymorphism (5â[euro]HTTLPR): allelic variation and links with depressive symptoms . Depression and Anxiety 27 , 260 -269 .10.1002/da.20660

Grabe HJ , Schwahn C , Mahler J , Appel K , Schulz A , Spitzer C , Fenske K , Barnow S , Freyberger HJ , Teumer A , Petersmann A , Biffar R , Rosskopf D , John U , Völzke H (2012). Genetic epistasis between the brain-derived neurotrophic factor Val66Met polymorphism and the 5-HTT promoter polymorphism moderates the susceptibility to depressive disorders after childhood abuse . Progress in Neuro-Psychopharmacology and Biological Psychiatry 36 , 264 -270 .10.1016/j.pnpbp.2011.09.010

Hankin BL , Jenness J , Abela JR , Smolen A (2011). Interaction of 5-HTTLPR and idiographic stressors predicts prospective depressive symptoms specifically among youth in a multiwave design . Journal of Clinical Child and Adolescent Psychology 40 , 572 -585 .10.1080/15374416.2011.581613

Jenness JL , Hankin BL , Abela JR , Young JF , Smolen A (2011). Chronic family stress interacts with 5-HTTLPR to predict prospective depressive symptoms among youth . Depression and Anxiety 28 , 1074 -1080 .10.1002/da.20904

Karg K , Burmeister M , Shedden K , Sen S (2011). The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: evidence of genetic moderation . Archives of General Psychiatry 68 , 444 -454 .10.1001/archgenpsychiatry.2010.189

Mitchell C , Notterman D , Brooks-Gunn J , Hobcraft J , Garfinkel I , Jaeger K , Kotenko I , McLanahan S (2011). Role of mother's genes and environment in postpartum depression . Proceedings of the National Academy of Sciences 108 , 8189 -8193 .10.1073/pnas.1014129108

Moffitt TE , Caspi A (2014). Bias in a protocol for a meta-analysis of 5-HTTLPR, stress, and depression . BMC Psychiatry 14 , 179 .10.1186/1471-244X-14-179

Monroe S , Reid M (2008). Gene-environment interactions in depression research: genetic polymorphisms and life-stress polyprocedures . Psychological Science 19 , 947 -956 .10.1111/j.1467-9280.2008.02181.x

Munafò M , Durrant C , Lewis G , Flint J (2009). Gene x environment interactions at the serotonin transporter locus . Biological Psychiatry 65 , 211 -219 .10.1016/j.biopsych.2008.06.009

Quinn CR , Dobson-Stone C , Outhred T , Harris A , Kemp AH (2012). The contribution of BDNF and 5-HTT polymorphisms and early life stress to the heterogeneity of major depressive disorder: a preliminary study . Australian and New Zealand Journal of Psychiatry 46 , 55 -63 .10.1177/0004867411430878

Risch N , Herrell R , Lehner T , Liang K , Eaves L , Hoh J , Griem A , Kovacs M , Ott J , Merikangas K (2009). Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis . Journal of the American Medical Association 301 , 2462 -2471 .10.1001/jama.2009.878

Ritchie K , Jaussent I , Stewart R , Dupuy A-M , Courtet P , Ancelin M-L , Malafosse A (2009). Association of adverse childhood environment and 5-HTTLPR genotype with late-life depression . Journal of Clinical Psychiatry 70 , 1281 -1288 .10.4088/JCP.08m04510

Scheid J , Holzman C , Jones N , Friderici K , Nummy K , Symonds L , Sikorskii A , Regier M , Fisher R (2007). Depressive symptoms in midâ[euro]pregnancy, lifetime stressors and the 5â[euro]HTTLPR genotype . Genes, Brain and Behavior 6 , 453 -464 .10.1111/j.1601-183X.2006.00272.x

Scheid JM , Holzman CB , Jones N , Friderici KH , Jernigan KA , Symonds LL , Sikorskii A , Fisher R (2011). Life stressors and 5-HTTLPR interaction in relation to mid-pregnancy depressive symptoms among African-American women . Psychiatric Genetics 21 , 271 -280 .10.1097/YPG.0b013e32834603e8

Sharpley CF , Palanisamy SK , Glyde NS , Dillingham PW , Agnew LL (2014). An update on the interaction between the serotonin transporter promoter variant (5-HTTLPR), stress and depression, plus an exploration of non-confirming findings . Behavioural Brain Research 273 , 89 -105 .10.1016/j.bbr.2014.07.030

Sjöberg RL , Nilsson KW , Nordquist N , Öhrvik J , Leppert J , Lindström L , Oreland L (2006). Development of depression: sex and the interaction between environment and a promoter polymorphism of the serotonin transporter gene . International Journal of Neuropsychopharmacology 9 , 443 -449 .10.1017/S1461145705005936

Stefanis N , Mandelli L , Hatzimanolis A , Zaninotto L , Smyrnis N , Avramopoulos D , Evdokimidis I , Serretti A (2011). Serotonin transporter gene variants and prediction of stressâ[euro]induced risk for psychological distress . Genes, Brain and Behavior 10 , 536 -541 .10.1111/j.1601-183X.2011.00690.x

Sugden K , Arseneault L , Harrington H , Moffitt TE , Williams B , Caspi A (2010). Serotonin transporter gene moderates the development of emotional problems among children following bullying victimization . Journal of the American Academy of Child and Adolescent Psychiatry 49 , 830 -840 .10.1016/j.jaac.2010.01.024

Sullivan P , Neale M , Kendler K (2000). Genetic epidemiology of major depression: review and meta-analysis . American Journal of Psychiatry 157 , 1552 -1562 .10.1176/appi.ajp.157.10.1552

Uher R , Caspi A , Houts R , Sugden K , Williams B , Poulton R , Moffitt TE (2011). Serotonin transporter gene moderates childhood maltreatment's effects on persistent but not single-episode depression: replications and implications for resolving inconsistent results . Journal of Affective Disorders 135 , 56 -65 .10.1016/j.jad.2011.03.010

Uher R , McGuffin P (2010). The moderation by the serotonin transporter gene of environmental adversity in the etiology of depression: 2009 update . Molecular Psychiatry 15 , 18 -22 .10.1038/mp.2009.123

Vrshek-Schallhorn S , Mineka S , Zinbarg R , Craske M , Griffith J , Sutton J , Redei E , Wolitzky-Taylor K , Hammen C , Adam EK (2014). Refining the candidate environment: interpersonal stress, the serotonin transporter polymorphism, and gene-environment interactions in major depression . Clinical Psychological Science 2 , 235 -248 .10.1177/2167702613499329

Vrshek-Schallhorn S , Stroud CB , Mineka S , Hammen C , Zinbarg RE , Wolitzky-Taylor K , Craske MG (2015). Chronic and episodic interpersonal stress as statistically unique predictors of depression in two samples of emerging adults . Journal of Abnormal Psychology 124 , 776 -790 .10.1037/abn0000098

Wichers M , Kenis G , Jacobs N , Mengelers R , Derom C , Vlietinck R , van Os J (2008). The BDNF Val(66)Met x 5-HTTLPR x child adversity interaction and depressive symptoms: an attempt at replication . American Journal of Medical Genetics Part B 147 , 120 -123 .

Wilhelm K , Gillis I , Reddy J , Mitchell PB , Campbell L , Dobson-Stone C , Pierce KD , Schofield PR (2012). Association between serotonin transporter promoter polymorphisms and psychological distress in a diabetic population . Psychiatry Research 200 , 343 -348 .10.1016/j.psychres.2012.07.008

Wilhelm K , Mitchell PB , Niven H , Finch A , Wedgwood L , Scimone A , Blair IP , Parker G , Schofield PR (2006). Life events, first depression onset and the serotonin transporter gene . British Journal of Psychiatry 188 , 210 -215 .10.1192/bjp.bp.105.009522

Zalsman G , Huang Y-y , Oquendo MA , Burke AK , Hu X-z , Brent DA , Ellis SP , Goldman D , Mann JJ (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 .10.1176/ajp.2006.163.9.1588

Zhang K , Xu Q , Xu Y , Yang H , Luo J , Sun Y , Sun N , Wang S , Shen Y (2009 a). The combined effects of the 5-HTTLPR and 5-HTR1A genes modulates the relationship between negative life events and major depressive disorder in a Chinese population . Journal of Affective Disorders 114 , 224 -231 .10.1016/j.jad.2008.07.012