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The Serotonin Transporter Promoter Variant (5-HTTLPR), Stress, and Depression Meta-Analysis Revisited: Evidence of Genetic Moderation

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Abstract

Context—The initial report of an interaction between a serotonin transporter promoter polymorphism (5-HTTLPR) and stress in the development of depression is perhaps the best-known and most cited finding in psychiatric genetics. Two recent meta-analyses explored the studies seeking to replicate this initial report and concluded that the evidence did not support the presence of the interaction. However, even the larger of the meta-analyses included only 14 of the 56 studies that have explored the relationship between 5-HTTLPR, stress and depression.

Objective—We sought to perform a meta-analysis including all relevant studies assessing whether 5-HTTLPR moderates the relationship between stress and depression.

Data Sources—We identified relevant articles from previous meta-analyses and reviews and a PubMed database search.

Study Selection—We excluded two studies presenting data that were included in other, larger, studies already included in our meta-analysis to avoid duplicate counting of subjects.

Data Extraction—In order to perform a more inclusive meta-analysis, we used the Liptak-Stouffer Z-score method to combine findings of primary studies at the significance test level rather than raw data level.

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Study concept and design: Sen, Karg, Burmeister
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Results—We included 54 studies and found strong evidence that 5-HTTLPR moderates the relationship between stress and depression, with the 5-HTTLPR s allele associated with an increased risk of developing depression under stress ($p<0.0001$). When restricting our analysis to the studies included in the previous meta-analyses, we found no evidence of association (Munafo studies $p=0.16$; Risch studies $p=0.11$). This suggests that the difference in results between previous meta-analyses and ours was not due to the difference in meta-analytic technique but instead to the expanded set of studies included in this analysis.

Conclusions—Contrary to the results of the smaller earlier meta-analyses, we find strong evidence that 5-HTTLPR moderates the relationship between stress and depression in the studies published to date.

Keywords

Graduate; Medical; Education; Residency; Serotonin; Transporter

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The principal function of the serotonin transporter is to remove serotonin from the synapse, returning it to the presynaptic neuron where the neurotransmitter can be degraded or re-released at a later time. A polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) has been found to affect the transcription rate of the gene, with the short (s) allele transcriptionally less efficient that the alternate long (l) allele. In 2003, Caspi and colleagues examined the relationship between 5-HTTLPR, stress and depression using a prospective, longitudinal birth cohort and found that subjects carrying the less functional 5-HTTLPR s allele reported greater sensitivity to stress[1].

This study has been cited over 2000 times in the scientific literature and generated a great deal of excitement and controversy around the potential of gene × environment interaction studies[2]. To date, there have been 55 follow-up studies, exploring whether 5-HTTLPR moderates the relationship between stress and depression, with some studies supporting the association between the 5-HTTLPR s allele and greater stress sensitivity and others not. Two recent meta-analyses have assessed a subset of these studies and concluded that there is no evidence supporting the presence of genetic moderation[3, 4].

Since their publication, these meta-analyses have been criticized for only including a subset of the studies investigating the relationship between 5-HTTLPR stress and depression[5–9]. In fact, while 56 primary data studies have assessed whether 5-HTTLPR moderates the relationship between stress and depression, the Munafo and Risch meta-analyses included only 5 and 14 of those studies respectively[10–48]. Further, Uher and McGuffin have demonstrated that the larger, Risch meta-analysis included a significantly greater proportion of negative replication studies than positive replication studies[8].

There are multiple reasons that the studies included in the meta-analyses were limited. First, the primary study data needed for traditional meta-analysis was often not available, either in the original publications or in follow-up email inquiries to study authors. For instance, Munafo and colleagues reported that 15 studies met criteria for inclusion in their meta-analysis. However, they were only able to obtain the primary study data needed for inclusion for five of those studies. There is no evidence that the studies that were able to be included in the meta-analyses were of higher “quality” than those not included.

Another reason why many studies were not included in the Risch and Munafo meta-analysis is that both meta-analyses focused exclusively on studies that explored an interaction between 5-HTTLPR and stressful life events (SLEs) in the development of depression. The original Caspi article, however, not only reported an interaction between 5-HTTLPR and SLEs, but also an interaction between 5-HTTLPR and childhood maltreatment stress. Nine

studies have attempted to replicate this interaction with childhood maltreatment, but these studies were not included in the meta-analyses.

Some observers have noted that the SLE study design may have limited power to detect genetic moderation effects because they are susceptible to biases introduced by impaired recall of stressors by subjects and highly variable stressors between subjects[9, 45]. A newer class of studies has attempted to bypass these potential problems by focusing on specific populations that have experienced a substantial, specific stressor. These studies test whether 5-HTTLPR moderates the relationship between a specific stressor and depression. Eighteen studies have employed such specific stressor designs, but like the childhood maltreatment studies, these studies were excluded from the previous meta-analysis.

In this study, rather than focus on a limited of studies, we sought to perform a meta-analysis on the entire body of work assessing the relationship between 5-HTTLPR, stress and depression. Unfortunately, different types of studies have generally used different study designs to explore this question, rendering it very difficult to combine the studies into a single traditional meta-analysis. An approach useful in situations where equivalent raw data are not available across all studies, is to combine the studies at the level of significance tests [49]. The Liptak-Stouffer Z-score method is a well-validated method for combining p-values across studies that has been utilized widely across genomics and biostatistics [50–56]. In this study, we utilize the Liptak-Stouffer Z-score method to combine the results from studies investigating whether the 5-HTTLPR variant moderates the relationship between stress and depression.

Methods

Studies

Potential studies were identified from previous meta-analyses and review articles and through PubMed at the National Library of Medicine, using the search terms (depression OR depressed) AND (“serotonin transporter” OR 5-HTTLPR) AND (stress OR stressful OR maltreatment)[3, 4, 9]. We subsequently checked the reference sections of the identified publications and reviews found and contacted authors through email to identify additional studies in press or review. We considered all English language studies published by March 2010 assessing whether 5-HTTLPR moderates the relationship between either stressful life events, childhood maltreatment or specific stressors and depression. Two studies were excluded because their data was part of another, larger study included in the analysis[14, 57]. In total, data from 54 publications met inclusion criteria and were included in the analysis.

In addition to investigating all studies together, we also utilized a grouping method proposed in an earlier review to stratify studies by the type of stressor studied (Childhood Maltreatment, Specific Medical Conditions and Stressful Life Events) and assessed the presence of the association within each group[9]. When publications reported results for multiple types of stressors that matched different groups, we included the study in each relevant group[1, 46, 58–61].

Quality Assessment

We evaluated the methodological quality of the included studies by applying an 11-item quality checklist, derived from the STREGA and STROBE checklists [62, 63]. We extracted information relevant to methodological quality criteria (items 2–7, 10), and basic reporting standards (items 1, 8, 9, 11) from the Introduction, Methods, Results and Discussion sections of all included studies. Consistent with current guidelines, we did not weigh studies by quality scores or exclude studies with low quality studies [64]. Instead we report the quality data extracted, so that it is available for readers to evaluate (Supplemental Table 1) [64, 65].

Further, to assess whether our results were influenced by studies rated as lower quality through this measure, we repeated our overall meta-analysis with only studies with a quality score above the median [66].

P value extraction

Two investigators (KK and SS) independently extracted the relevant p value from each study. There were no cases of disagreement between the two investigators. When several p values were provided (due to the use of several depression scales or separate p values for different subsets of samples) we used a weighted mean p value for our analyses. For studies with non-significant results that did not provide exact probabilities, a p value of 1 (no association in either direction) was assumed. When an article reported analyses that matched different groups of our study, we incorporated the mean of the p value of each group into the overall analysis.

Statistical Analysis

The Liptak-Stouffer Z-score method was utilized to combine studies at the level of significance tests, weighted by study sample size. First, all extracted p-values were converted to one-tailed p-values, with p-values below 0.5 corresponding to greater s allele stress sensitivity and p-values above 0.5 corresponding to greater l allele stress sensitivity.

Next, these p-values were converted to Z-scores using a standard normal curve such that p-values below 0.5 were assigned positive Z-scores and p-values above 0.5 were assigned negative Z-scores. Subsequently these Z-scores were combined by calculating $Z_w = \frac{\sum_{i=1}^{k} w_i Z_i}{\sqrt{\sum_{i=1}^{k} w_i^2}}$, where the weighting factors w_i corresponds to the individual sample sizes, k corresponds to the number of total studies and Z_i corresponds to the individual study Z-scores. The outcome of this test, Z_w, follows a standard normal distribution and the corresponding probability can be obtained from a standard normal distribution table. We applied this procedure to the overall sample as well as to each of the three study groups.

To assess whether our results were substantially influenced by the presence of any individual study, we conducted a sensitivity analysis by systematically removing each study and recalculating the significance of the result. Further, to compare our method of combining studies at the significance test level with the method of combining studies at the raw data level utilized in the previous meta-analyses, we performed an analysis with only the studies included in the previous meta-analyses[4].

In order to account for the possibility that results of the meta-analysis were affected by publication bias, we calculated the number of unpublished studies that would have to exist to change the outcome of the Liptak-Stouffer test from significant to non-significant (Fail-safe N)[67]. The ratio between the Fail-safe N and the number of studies actually published gives an estimate for the likelihood that the significant meta-analytical result is due to publication bias.

Results

Our initial search identified 148 publications. Out of these studies, we identified 54 studies that included 40,749 subjects meeting criteria for inclusion (Table 1). We found strong evidence that 5-HTTLPR moderates the relationship between stress and depression, with the s allele associated with an increased risk of developing depression under stress (p=0.00002). The significance of the result was robust to sensitivity analysis, with the overall p values

remaining significant when each study was individually removed from the analysis (1.0E-6<p<0.00016). In addition, when we restricted our analysis to those studies with a study "quality" score above the median, the p value remained highly significant (3.2E-10, N=14).

In examining the three groups of stress studies separately, we found strong evidence for an association between the s allele and increased stress sensitivity in studies of childhood maltreatment (p=0.00007), in studies of specific medical conditions (p=0.0004), but only marginal evidence in the studies of stressful life events (p=0.033) (Table 2, 3 and 4 respectively). The removal of individual studies did not lead to changes in the significance of the outcome in studies of childhood maltreatment (7.4E-6<p<0.00014) or specific medical conditions (0.00017<p<0.0068). However, because the genetic effect in the set of stressful life events was barely below the significance threshold (p=0.033), the result was no longer significant after the exclusion of any one of several studies [1, 32, 35, 37, 68] (0.013<p<0.62).

When we restricted our analysis to the studies included in the two previous meta-analyses, we found no evidence of an association between 5-HTTLPR and stress sensitivity (Munafo studies p=0.16; Risch studies p=0.11).

One criticism of meta-analyses is that positive studies may be more likely to be published than negative studies and this sort of publication bias can create false positive results. We thus determine how many unpublished studies would need to exist to make the result of our overall analysis non-significant (p=0.05). We found that 729 unpublished or undiscovered studies with an average sample size (N = 755) and a non-significant result (p = 0.5) would need to exist. This corresponds to a fail-safe ratio of 14 studies not included in this meta-analysis for every included study.

Discussion

We found strong evidence that a serotonin transporter promoter polymorphism (5-HTTLPR) moderates the relationship between stress and depression, with the less functional short (s) allele associated with increased stress sensitivity. Our results differ from the results of the two other meta-analyses that have explored this specific association. To test whether this difference in results was due to the expanded set of studies that we included or the different meta-analytic technique utilized, we applied our meta-analytic technique to the sets of studies used in the previous meta-analyses. With these limited set of studies, our meta-analytic technique produced the same non-significant results as the previous meta-analyses, suggesting that the difference in results between meta-analyses was due to the different set of included studies.

The results of our secondary meta-analyses, where we stratified studies by stressor type, provide insight into how the inclusion of studies missing from previous studies resulted in an overall highly significant result in our meta-analysis. Both previous meta-analyses focused exclusively on stressful life events and reported no evidence that 5-HTTLPR moderates the relationship between SLEs and depression. Here, we were able to include 11 additional SLE studies, most of which were published too recently for inclusion in the previous meta-analyses. Still, we found only marginal evidence that 5-HTTLPR moderates the relationship between stressful life events and depression[6]. In contrast, we found robust evidence that 5-HTTLPR moderates the relationship between both childhood maltreatment and specific stressors and depression.

One important variable that may help to account for the different results in the different stressor groups is the variation in methods between the studies within each group[69]. Within

the childhood maltreatment and specific stressors groups, the methodological details of the primary studies were generally similar. In contrast, there is marked variation in methods between SLE studies. First the studies vary substantially in what was considered a stressful life event. In addition, the method through which stressful life events were measured varied substantially between studies in this group. Some studies measured stress through one-time self-report life events checklists while others employed repeated in-person interviews and life history calendars[1, 70]. It is noteworthy that almost all of the studies that failed to identify an effect of genetic moderation used self-report checklists (Table 1). In addition, some studies asked subjects about SLEs and depressive episodes that occurred decades earlier while others assessed SLEs and depressive episodes soon after they occurred[30, 71]. As a result, the extent to which recall bias affected the findings of these studies varied substantially between the studies. Given this marked variation in methods between SLE studies, it is not surprising that the results between studies have also varied. In contrast, the methods of childhood maltreatment and specific stressors have been more uniform and the results of the studies have been more consistent.

An additional reason for the difference between the meta-analyses of the different stressor subgroups may be the nature of the stressors studied. Most of the specific stressor studies focused on chronic stressors while the SLE studies focused on acute stressful life events. Interestingly, three studies have explicitly looked at both acute and chronic stressors in their cohorts and all three have found that the 5-HTTLPR moderating effects were stronger for chronic stressors [10, 16, 45]. Future primary studies that are able to systematically test genetic moderation effects on different types of stressors will be valuable in furthering our understanding of the specific characteristics of stressors that are moderated by 5-HTTLPR and other genetic loci important in stress response.

One criticism of the 5-HTTLPR-stress studies published to date is that investigators often performed multiple tests, using different subsets of their population or different stress or depression measures, but focus their paper on the tests that produced the most significant results and present their overall findings as a confirmation of the original hypothesis[4, 72]. For instance, different studies have found evidence of genetic moderation only in the female subset of their sample, only in the subset of their sample that was evaluated through an in-depth clinical interview or only when the analysis was restricted to chronic stressors[10, 73, 74]. As we discuss above, some of the variation in results with different population sub-samples or depression and stress measures may represent true and important heterogeneity in the 5-HTTLPR moderation effect. However another possible explanation for the variation in results within the same study is that some of these secondary findings are actually false positive results that resulted from uncorrected multiple testing. To guard against false positive from the primary studies causing a false positive in our meta-analysis, we did not rely on the statistical tests highlighted by authors. Instead, we calculated a weighted average of p values of the tests that were performed in a given study. When authors only reported the significance results for a subset of these tests, we assumed that $p = 1$ for the unreported tests. The fact that we confirmed the previous non-significant results when we applied our meta-analytic technique to the sets of studies included in the previous meta-analyses suggests that statistical bias from primary studies did not unduly affect our results.

While this meta-analysis focused specifically on observational studies specifically assessing whether 5-HTTLPR moderates the relationship between stress and depression, the results we found are consistent with a broad range of studies exploring the relationship between functional serotonin transporter genetic variation and stress in different ways. Experimental neuroscience studies have found consistent evidence that 5-HTTLPR s allele carriers demonstrate a more pronounced amygdala and HPA axis response to affective or threatening stimuli [75–77]. In addition, non-human primates studies that have found increased stress

sensitivity among individuals with a low functioning serotonin transporter allele[78, 79]. Together, these lines of evidence provide clear and converging evidence that 5-HTTLPR plays a role in moderating the response to stress. It is also clear from these studies however, that this variant explains only a small proportion of the genetic variance relevant to stress response. The successes and failures of the studies exploring the 5-HTTLPR variant included in this analysis should guide our future work as we try to develop a broader understanding of the genetic architecture that moderates the relationship between stress and depression.

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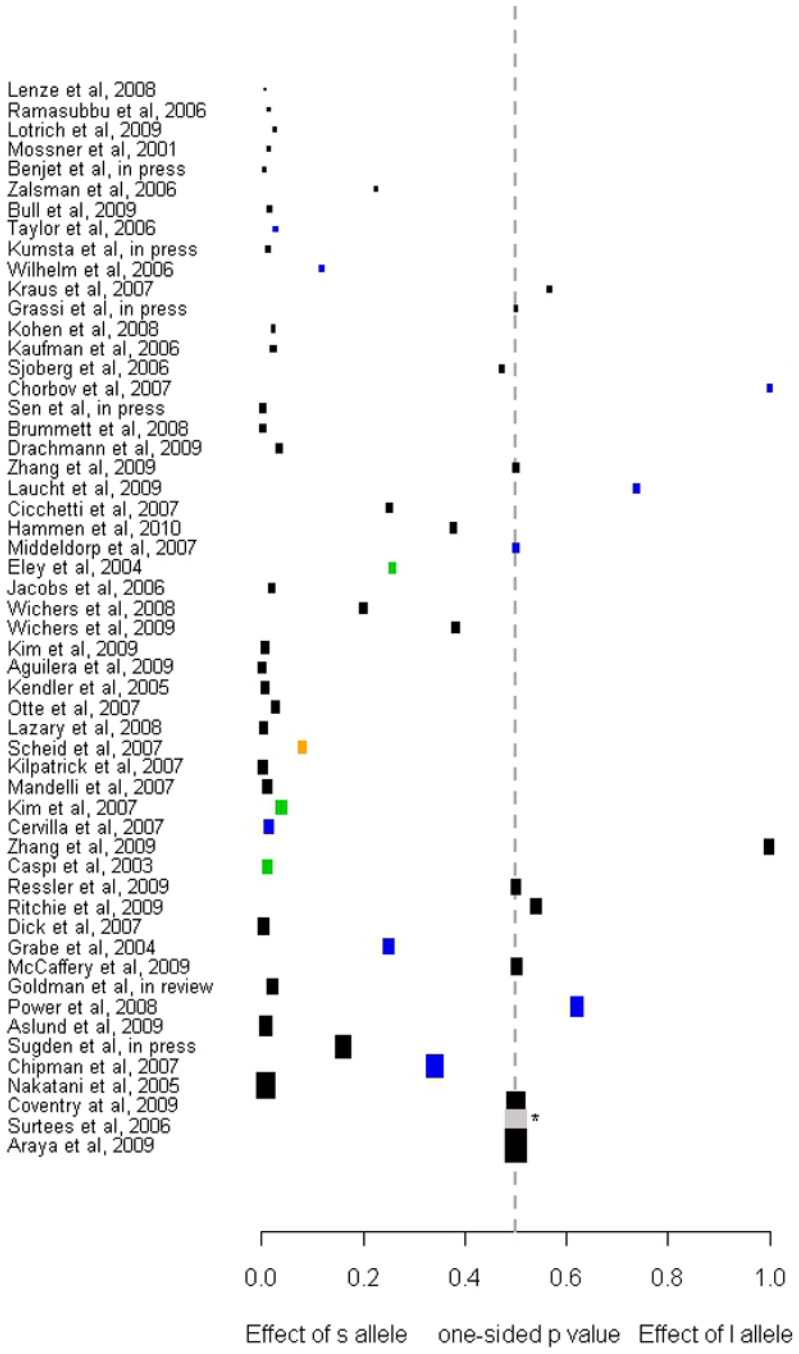

Figure 1. Forest plot for the 54 studies included in the meta-analysis

The boxes indicate the one-tailed p value for each study, with lower values corresponding to greater stress sensitivity of s allele carriers and higher values corresponding to greater stress sensitivity of l allele carriers. The size of the box indicates the relative sample size. The triangle indicates the result of our overall meta-analysis.

Labels: Magenta - study included only in the Munafo meta-analysis; Cyan - study included only in the Risch meta-analysis; Blue - study included both in the Munafo and the Risch meta-analysis.

* Risch et al included only a subset of this study (Gillespie et al, N=1091).

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Table 1

Description of 5-HTTLPR, Stress and Depression Studies Included in the Overall Meta-analysis

Study	No. of Participants	% Female	Mean Age	Study Design	Stressor	Depression Measure	Reported Findings*	Averaged one-tailed p value**	Fisher's p after study exclusion
Mossner et al, 2001	72	46	NA	Exposed only	Parkinson's Disease	Hamilton Depression Rating Scale	Positive	0.0125	1.90E-05
Caspi et al, 2003	845	48	26	Longitudinal	Child Maltreatment	Diagnosis of Depression	Positive	0.0100	4.20E-05
Eley et al, 2004	374	58	16	Case-Control	Adverse Family Environment	MFQ	Partially positive	0.2575	1.95E-05
Grabe et al, 2004	973	69	52	Cross-sectional	Number of Chronic Diseases	von Zerssen's Complaints Scale	Partially positive	0.2503	2.16E-05
Kendler et al, 2005	549	NA	35	Longitudinal	Stressful Life Events	Diagnosis of Depression	Positive	0.0070	3.27E-05
Nakatani et al, 2005	2509	25	64	Exposed only	Acute Myocardial Infarction	Zung Self-Rating Depression Scale	Positive	0.0075	1.62E-04
Jacobs et al, 2006	374	100	27	Longitudinal	Stressful Life Events	SCL-90	Positive	0.0200	2.51E-05
Kaufman et al, 2006	196	51	9	Cross-sectional	Child Abuse	MFQ	Partially positive	0.0225	2.12E-05
Ramasubbu et al, 2006	51	35	60	Exposed only	Stroke	Diagnosis of Depression	Positive	0.0130	1.86E-05
Sjoberg et al, 2006	198	63	17	Cross-sectional	Psychosocial Circumstances in Family	Depression Self-Rating Scale	Partially positive/ opposite	0.4721	1.76E-05
Surtees et al, 2006	4175	47	60	Cross-sectional	Childhood Adversities/Stressful Life Events	Diagnosis of Depression	Negative	0.5000	1.33E-06
Taylor et al, 2006	110	57	21	Cross-sectional	Childhood Adversities	BDI	Partially positive	0.0268	1.95E-05
Wilhelm et al, 2006	127	67	48	Longitudinal	Stressful Life Events	Diagnosis of Depression	Partially positive	0.1178	1.89E-05
Zalsman et al, 2006	79	68	38	Case-control	Stressful Life Events	Hamilton Depression Rating Scale	Partially positive	0.2233	1.81E-05
Cervilla et al, 2007	737	72	49	Case-control	Stressful Life Events	Diagnosis of Depression	Positive	0.0143	3.62E-05
Chipman et al, 2007	2094	52	23	Cross-sectional	Stressful Life Events	Goldman Depression Scale	Negative	0.3400	1.60E-05

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Study	No. of Participants	% Female	Mean Age	Study Design	Stressor	Depression Measure	Reported Findings*	Averaged one-tailed p value**	Fisher's p after study exclusion
Chorbov et al, 2007	236	100	22	Longitudinal	Traumatic Events	Diagnosis of Depression	Opposite	1.0000	1.10E-05
Cicchetti et al, 2007	339	46	17	Cross-sectional	Child Abuse	ASEBA	Partially positive	0.2518	1.94E-05
Dick et al, 2007	956	NA	NA	Family-based association study	Problems with work, relationship or health	Diagnosis of Depression	Positive	0.0040	5.37E-05
Kilpatrick et al, 2007	589	64	≥ 60 (77%)	Cross-sectional	Hurricane exposure + low social support 6 months before hurricane	Diagnosis of Depression	Positive	0.0015	3.94E-05
Kim et al, 2007	732	NA	≥65	Cross-sectional	Stressful Life Events	Diagnosis of Depression	Negative	0.0385	3.11E-05
Kraus et al, 2007	139	49	42	Exposed only	Interferon-α Treatment	Hospital Anxiety and Depression Scale	Negative	0.5650	1.73E-05
Mandelli et al, 2007	670	68	48	Case-only	Stressful Life Events	Diagnosis of Depression	Positive	0.0112	3.50E-05
Middeldorp et al, 2007	367	68	39	Longitudinal	Stressful Life Events	Anxiety-Depression Rating Scale	Negative	0.5000	1.73E-05
Otte et al, 2007	557	15	68	Exposed only	Coronary Disease	Diagnosis of Depression	Partially positive	0.0275	2.86E-05
Scheid et al, 2007	568	100	20–34	Cross-sectional	Stressful Life Events	CES-D	Negative	0.0800	2.50E-05
Brummett et al, 2008	288	75	58	Cross-sectional	Caregiving to patients with Altzheimer's disease/dementia	CES-D	Positive	0.0015	2.64E-05
Kohen et al, 2008	150	37	60	Exposed only	Stroke	Geriatric Depression Scale	Positive	0.0225	2.03E-05
Lazary et al, 2008	567	79	31	Cross-sectional	Stressful Life Events	Zung Self-Rating Depression Scale	Positive	0.0025	3.67E-05
Lenze et al, 2008	23	87	77	Exposed only	Hip Fracture	Diagnosis of Depression	Positive	0.0068	1.81E-05
Power et al, 2008	1421	NA	≥65	Cross-sectional	Stressful Life Events	MINI, CES-D	Negative	0.6200	1.10E-05
Wichers et al, 2008	394	100	18–64	Cross-sectional	Childhood Trauma	SCL-90; SCID Depressive Symptoms	Negative	0.2000	2.03E-05
Aguilera et al, 2009	534	55	23	Cross-sectional	Childhood Trauma	SCL-90-R	Positive	0.0001	4.63E-05
Araya et al, 2009	4334	NA	7	Longitudinal	Stressful Life Events	SDQ Emotional Symptom 5-item Subscale	Negative	0.5000	1.03E-06

Study	No. of Participants	% Female	Mean Age	Study Design	Stressor	Depression Measure	Reported Findings*	Averaged one-tailed p value**	Fisher's p after study exclusion
Aslund et al, 2009	1482	48	17–18	Cross-sectional	Quarrels or violence between parents; Physical or Psychological Matreatment	Depression Self-Rating Scale	Positive	0.0078	7.68E-05
Bull et al, 2009	98	36	46	Longitudinal	Interferon-α and Ribavirin Treatment	Zung Self-Rating Depression Scale/BDI	Positive	0.0150	1.95E-05
Coventry at al, 2009	3243	60	32	Longitudinal	Stressful Life Events	Diagnosis of Depression	Negative	0.5000	4.33E-06
Drachmann Bukh et al, 2009	290	66	39	Case-only	Stressful Life Events	Diagnosis of Depression	Negative	0.0350	2.25E-05
Kim et al, 2009	521	55	72	Longitudinal	Number of Chronic Health Problems	Diagnosis of Depression	Positive	0.0050	3.27E-05
Laucht et al, 2009	309	54	19	Cross-sectional	Stressful Life Events	Diagnosis of Depression, BDI	Partially negative/ opposite	0.7375	1.57E-05
Lotrich et al, 2009	71	27	48	Exposed only	Interferon-α Treatment	BDI	Positive	0.0250	1.88E-05
McCaffery et al, 2009	977	21	59	Exposed only	Established Cardiovascular Disease	BDI	Negative	0.5000	1.57E-05
Ressler et al, 2009	926	62	≥ 18	Cross-sectional	Childhood Trauma	Diagnosis of Depression (partially), BDI	Partially positive	0.5000	1.59E-05
Ritchie et al, 2009	942	58	65–92	Cross-sectional	Childhood Adversities	Diagnosis of Depression, CES-D, Treatment with Antidepressants	Partially opposite	0.5390	1.51E-05
Wichers et al, 2009	502	100	27	Longitudinal	Stressful Life Events	Diagnosis of Depression, SCL-90-R	Partially positive	0.3803	1.84E-05
Zhang et al, 2009	792	54	33	Case-control	Stressful Life Events	Diagnosis of Depression	Opposite	0.9975	5.24E-06
Zhang et al, 2009	306	38	NA	Exposed only	Parkinson's Disease	CES-D	Negative	0.5000	1.74E-05
Hammen et al, 2010	346	62	24	Longitudinal	Negative Acute Life Events, Chronic Family Stress at age 15	BDI	Partially positive	0.3763	1.86E-05
Benjet et al, in press	78	100	12	Cross-sectional	Relational Aggression	Children's Depression Inventory	Positive	0.0050	1.94E-05
Goldman et al, in press	984	45	66	Longitudinal	Stressful Life Events	CES-D	Partially positive	0.0203	4.19E-05
Grassi et al, in press	145	100	56	Exposed only	Breast Cancer	Hospital Anxiety and	Negative	0.5000	1.75E-05

Study	No. of Participants	% Female	Mean Age	Study Design	Stressor	Depression Measure	Reported Findings*	Averaged one-tailed p value**	Fisher's p after study exclusion
						Depression Scale			
Kumsta et al, in press	125	NA	11/15	Longitudinal	Institutionalization in Romanian orphanages at ages 6 – 42 months	CAPA, Rutter Child Scale, Strengths&Difficulties Questionnaire	Positive	0.0117	2.02E-05
Sen et al, in press	268	58	28	Longitudinal	Medical Internship	Patient Health Questionnaire (PHQ)	Positive	0.0020	2.54E-05
Sugden et al, in press	2017	51	12	Longitudinal	Bullying Victimization	ASEBA	Negative	0.1603	2.94E-05
Sum	40749								
Average (N)	755								**p=0.00002**

*"Positive" indicates a significant ($p<0.05$) interaction effect with the S allele, "Negative" indicates no interaction effect ($p>0.05$) and "Opposite" indicates a significant ($p<0.05$) interaction effect with the L allele.

**One-tailed p value with smaller values indicating greater stress sensitivity among S allele subjects

Table 2

Study	Total No. of Participants	1-tailed p	Fisher's p after study exclusion
Caspi et al, 2003	845	0.010	5.38E-04
Kaufman et al, 2006	196	0.023	1.17E-04
Wichers et al, 2008	394	0.200	9.71E-05
Aguilera et al, 2009	534	5.0E-05	8.31E-04
Aslund et al, 2009	1482	0.008	1.40E-03
Ressler et al, 2009	926	0.500	2.97E-05
Benjet et al, in press	78	0.005	9.27E-05
Kumsta et al, in press	125	0.012	1.03E-04
Sugden et al, in press	2017	0.160	7.42E-06
Sum	6936		
Average (N)	694		**p=0.00007**

Table 3

Study	Total No. of Participants	1-tailed p	Fisher's p after study exclusion
Grabe et al, 2004	973	0.250	0.00041
Nakatani et al, 2005	2509	0.008	0.00679
Ramasubbu et al, 2006	51	0.013	0.00041
Kraus et al, 2007	139	0.565	0.00035
Otte et al, 2007	557	0.028	0.00104
Kohen et al, 2008	150	0.023	0.00051
Lenze et al, 2008	23	0.007	0.00038
Bull et al, 2009	98	0.015	0.00046
Kim et al, 2009	521	0.005	0.00145
Lotrich et al, 2009	71	0.025	0.00042
McCaffery et al, 2009	977	0.500	0.00017
Zhang et al, 2009	306	0.500	0.00034
Grassi et al, in press	145	0.5	0.00035
Sum	6592		
Average (N)	471		**p=0.0004**

Table 4

Study	Total No. of Participants	1-tailed p	Fisher's p after study exclusion
Caspi et al, 2003	845	0.010	0.054
Eley et al, 2004	374	0.258	0.034
Kendler et al, 2005	549	0.007	0.047
Jacobs et al, 2006	374	0.020	0.040
Sjoberg et al, 2006	198	0.472	0.032
Surtees et al, 2006	4175	0.500	0.014
Taylor et al, 2006	110	0.028	0.034
Wilhelm et al, 2006	127	0.118	0.034
Zalsman et al, 2006	79	0.342	0.033
Cervilla et al, 2007	737	0.014	0.050
Chipman et al, 2007	2094	0.292	0.039
Chorbov et al, 2007	236	0.99995	0.025
Dick et al, 2007	956	0.004	0.062
Kim et al, 2007	732	0.039	0.046
Mandelli et al, 2007	670	0.011	0.049
Middeldorp et al, 2007	367	0.500	0.032
Scheid et al, 2007	568	0.080	0.040
Lazary et al, 2008	567	0.002	0.050
Power et al, 2008	1421	0.620	0.026
Araya et al, 2009	4334	0.500	0.013
Coventry et al, 2009	3243	0.500	0.021
Drachmann Bukh et al, 2009	290	0.035	0.037
Laucht et al, 2009	309	0.500	0.032
Ritchie et al, 2009	942	0.539	0.030
Wichers et al, 2009	502	0.380	0.033
Zhang et al, 2009	792	0.998	0.016
Hammen et al, 2010	346	0.376	0.034
Goldman et al, in press	984	0.020	0.055
Sum	26921		
Average (N)	961		**p=0.03**