ONLINE FIRST

The Serotonin Transporter Promoter Variant (5-HTTLPR), Stress, and Depression Meta-analysis Revisited

Evidence of Genetic Moderation

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Context: Two recent meta-analyses assessed the set of studies exploring the interaction between a serotonin transporter promoter polymorphism (5-HTTLPR) and stress in the development of depression 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 assessed the relationship between 5-HTTLPR, stress, and depression.

Objective: To perform a meta-analysis including all relevant studies exploring the interaction.

Data Sources: We identified studies published through November 2009 in PubMed.

Study Selection: We excluded 2 studies presenting data that were included in other larger studies.

Data Extraction: To perform a more inclusive meta-analysis, we used the Liptak-Stouffer *z* score method to combine findings of primary studies at the level of significance tests rather than the level of raw data.

Data Synthesis: 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 ($P=.00002$). When stratifying our analysis by the type of stressor studied, we found strong evidence for an association between the *s* allele and increased stress sensitivity in the childhood maltreatment ($P=.00007$) and the specific medical condition ($P=.0004$) groups of studies but only marginal evidence for an association in the stressful life events group ($P=.03$). When restricting our analysis to the studies included in the previous meta-analyses, we found no evidence of association (Munafò et al studies, $P=.16$; Risch et al studies, $P=.11$). This suggests that the difference in results between meta-analyses was due to the different set of included studies rather than the meta-analytic technique.

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

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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 rereleased 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 than the alternate long (*l*) allele. In 2003, Caspi and colleagues[1] used a prospective, longitudinal design to examine the relationship between 5-HTTLPR, stress, and depression in a large birth cohort and found a significant interaction between 5-HTTLPR and both stressful life events (SLEs) and childhood maltreatment in the development of depression. In this cohort, subjects carrying the less functional 5-HTTLPR *s* allele reported greater sensitivity to stress.

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The Caspi et al study has been cited more than 2000 times in the scientific literature and generated a great deal of excitement 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 the interaction.[3,4]

Since their publication, these meta-analyses have generated substantial debate and intense criticism. Some of the discussion has revived the long-standing debate about whether exploring epidemiological interaction effects, in general, will produce worthwhile results.[5,6] The criticism specific to this genetic association, however, has largely revolved around the fact that only a subset of the studies investigating the relationship between 5-HTTLPR, stress, and depression were included in the meta-analyses.[7-12] In fact, while 56 primary data studies have assessed whether 5-HTTLPR moderates the relationship between stress and depression, the Munafò et al[3] and Risch et al[4] meta-analyses included only 5 and 14 of those studies, respectively.[13-51] Further, Uher and McGuffin[11] have demonstrated that the larger Risch et al meta-analysis included a significantly greater proportion of negative replication studies than positive replication studies.

There are multiple reasons that the studies included in the meta-analyses were limited. First, the primary study data needed for traditional meta-analysis were often not available, either in the original publications or in follow-up e-mail inquiries to study authors. For instance, Munafò 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 5 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.

A second reason why many studies were not included in the Risch et al and Munafò et al meta-analyses is that both meta-analyses focused exclusively on studies that explored an interaction between 5-HTTLPR and SLEs in the development of depression. The original Caspi et al 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 a set of potential biases: (1) impaired recall of stressors by subjects, (2) highly variable stressors between subjects, and (3) the reduced statistical power inherent to tests of statistical interaction.[10,48] A newer class of studies has attempted to bypass these potential problems by focusing on specific populations that have experienced a substantial, specific stressor. Eighteen studies have used such a specific stressor design to assess whether 5-HTTLPR moderates the relationship between stress and depression, but like the childhood maltreatment studies, these studies were excluded from the previous meta-analysis.

In this investigation, rather than focus on a specific class 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, the different classes of studies 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.[52] The Liptak-Stouffer *z* score method is a well-validated method for combining *P* values across studies and has been used widely across genomics and biostatistics.[53-59] Herein, we use 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 maltreatment.[3,4,10] We subsequently checked the reference sections of the identified publications and contacted authors through e-mail to identify additional studies in press or review. We considered all English-language studies published by November 2009 assessing whether 5-HTTLPR moderates the relationship between stress and depression. Two studies were excluded because their data were part of another larger study included in the analysis.[12,60] In total, data from 54 publications met inclusion criteria and were included in the analysis.

To identify study design characteristics that might influence the ability to detect the interaction effect between 5-HTTLPR and life stress, we used 2 different grouping methods set out in a recent review article[10] and assessed the presence of the association within each group. First, we stratified studies by the type of stressor studied (childhood maltreatment, specific medical conditions, and SLEs). When publications reported results for multiple types of stressors that matched different groups, we included the study in each relevant group.[1,49,61-64] Second, we stratified studies by the method of stress assessment (objective, interview, and self-report questionnaire).

QUALITY ASSESSMENT

We evaluated the methodological quality of the included studies by applying an 11-item quality checklist, derived from the STREGA (Strengthening the Reporting of Genetic Association Studies) and STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklists.[65,66] Specifically, the quality criteria were (1) clear statement of objectives and hypothesis, (2) clear eligibility criteria for study participants, (3) clear definition of all variables, (4) replicability of statistical methods, (5) assessment of Hardy-Weinberg equilibrium, (6) assessment of ethnicity, (7) addressing the problem of mixed ethnicities statistically (if applicable), (8) sufficient descriptive data (age, sex, ethnicity), (9) statement of genotype frequencies, (10) sample in Hardy-Weinberg equilibrium, and (11) consideration of population stratification.

Consistent with current guidelines, we did not weigh studies by quality scores or exclude studies with low-quality studies. Instead, we report the quality data extracted, so that they

are available for readers to evaluate (eTable, http://www.archgenpsychiatry.com).[67,68] 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 higher than the median.[69]

P VALUE EXTRACTION

Two investigators (K.K. and S.S.) independently extracted the relevant *P* value from each study. There were no cases of disagreement between the 2 investigators. When several *P* values were provided (because of 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 nonsignificant 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 used to combine studies at the level of significance tests, weighted by study sample size. First, all extracted *P* values were converted to 1-tailed *P* values, with *P* values less than .50 corresponding to greater *s* allele stress sensitivity and *P* values more than .50 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 less than .50 were assigned positive *z* scores and *P* values more than .50 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 factor w_i corresponds to the individual study 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 used this procedure on the overall sample as well as on each of the individual study subgroups. 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 used in the previous meta-analyses, we performed an analysis with only the studies included in the previous meta-analyses.[3,4]

To assess the possibility that results of the meta-analysis were affected by publication bias, we calculated the fail-safe N for our overall analysis, the number of unpublished studies that would have to exist to change the outcome of the Liptak-Stouffer test from significant to nonsignificant. Because the commonly used analytic approximation[70] method of calculating the fail-safe N has been criticized for inadequate reliability and accuracy, we used a more rigorous, direct computational approach.[71] Specifically, we calculated the number of studies with a *P* value equal to .50 and a sample size of 755 (the average sample size in the studies we analyzed) that we would need to incorporate into the weighted Liptak-Stouffer analysis to obtain a nonsignificant outcome. The ratio between the fail-safe N and the number of studies actually published estimates the potential for publication bias to influence our results. We also considered the effect of false-positive findings due to small sample size by calculating the number of smallest studies that could be deleted before the analysis would reveal a nonsignificant result.

RESULTS

OVERALL META-ANALYSIS

Our initial search identified 148 publications. 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 ($P=.00002$) (**Figure**). 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 ($1.0\times10^{-6}<P<.00016$). When we restricted our analysis to those studies with a study "quality" score higher than the median, the *P* value remained significant (3.2×10^{-10}). Further, there was evidence for genetic moderation among both the group of studies that used categorical measures of depression ($P=.03$; n=17) and the group of studies that used continuous measures of depression ($P=.001$; n=23).

SUBGROUP STRATIFICATION

When stratifying our analysis by the type of stressor studied, we found strong evidence for an association between the *s* allele and increased stress sensitivity in the childhood maltreatment group ($P=.00007$) and the specific medical condition group ($P=.0004$) and marginal evidence for an association in the SLEs group ($P=.03$) (**Tables 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 ($7.4\times10^{-6}<P<.00014$) or specific medical conditions ($.00017<P<.0068$). However, the result among studies of SLEs became nonsignificant after the exclusion of any 1 of several studies[1,35,38,40,76] ($.013<P<.062$).

When stratifying our analysis by the stress assessment method, we found strong evidence for an association between the *s* allele and increased stress sensitivity among the objective measure group ($P=.000003$) and the interview assessment group ($P=.0002$) and marginal evidence in the self-report questionnaire group ($P=.042$). The removal of individual studies did not lead to changes in the significance of the outcome in studies assessing stress with objective measures ($8.7\times10^{-7}<P<.000029$) or with interview assessments ($4.0\times10^{-6}<P<.0014$). However, the result among studies assessing stress with self-report questionnaires became nonsignificant after the exclusion of several studies[23,25,35,38,40,73,76] ($.018<P<.093$).

Table 1. Description of 5-HTTLPR, Stress, and Depression Studies Included in the Overall Meta-Analysis

Source, Year	No. of Participants	Female, %	Mean Age, y	Study Design	Stressor	Stress Assessment Method	Depression Measure	Reported Findings[a]	Averaged 1-Tailed *P* Value[b]	Liptak-Stouffer *P* Value After Study Exclusion
Mössner et al,[51] 2001	72	46	NA	Exposed only	Parkinson disease	Objective	Hamilton Depression Rating Scale	Positive	.0125	1.90×10^{-5}
Caspi et al,[1] 2003	845	48	26	Longitudinal	Child maltreatment	Objective	Diagnosis of depression	Positive	.0100	4.20×10^{-5}
Eley et al,[72] 2004	374	58	16	Case-control	Adverse family environment	Self-report questionnaire	MFQ	Partially positive	.2575	1.95×10^{-5}
Grabe et al,[73] 2005	973	69	52	Cross-sectional	Number of chronic diseases	Self-report questionnaire	von Zerssen Complaints Scale	Partially positive	.2503	2.16×10^{-5}
Kendler et al,[19] 2005	549	NA	35	Longitudinal	Stressful life events	Interview	Diagnosis of depression	Positive	.0070	3.27×10^{-5}
Nakatani et al,[28] 2005	2509	25	64	Exposed only	Acute myocardial infarction	Objective	Zung Self-Rating Depression Scale	Positive	.0075	1.62×10^{-4}
Jacobs et al,[20] 2006	374	100	27	Longitudinal	Stressful life events	Self-report questionnaire	SCL-90	Positive	.0200	2.51×10^{-5}
Kaufman et al,[18] 2006	196	51	9	Cross-sectional	Child abuse	Objective	MFQ	Partially positive	.0225	2.12×10^{-5}
Ramasubbu et al,[30] 2006	51	35	60	Exposed only	Stroke	Objective	Diagnosis of depression	Positive	.0130	1.86×10^{-5}
Sjöberg et al,[21] 2006	198	63	17	Cross-sectional	Psychosocial circumstances in family	Interview	Depression Self-Rating Scale	Partially positive/ opposite	.4721	1.76×10^{-5}
Surtees et al,[74] 2006	4175	47	60	Cross-sectional	Childhood adversities/ stressful life events	Self-report questionnaire	Diagnosis of depression	Negative	.5000	1.33×10^{-6}
Taylor et al,[63] 2006	110	57	21	Cross-sectional	Childhood adversities	Self-report questionnaire	BDI	Partially positive	.0268	1.95×10^{-5}
Wilhelm et al,[75] 2006	127	67	48	Longitudinal	Stressful life events	Interview	Diagnosis of depression	Partially positive	.1178	1.89×10^{-5}
Zalsman et al,[64] 2006	79	68	38	Case-control	Stressful life events	Interview	Hamilton Depression Rating Scale	Partially positive	.2233	1.81×10^{-5}
Cervilla et al,[76] 2007	737	72	49	Case-control	Stressful life events	Self-report questionnaire	Diagnosis of depression	Positive	.0143	3.62×10^{-5}
Chipman et al,[61] 2007	2094	52	23	Cross-sectional	Stressful life events	Self-report questionnaire	Goldman Depression Scale	Negative	.3400	1.60×10^{-5}
Chorbov et al,[77] 2007	236	100	22	Longitudinal	Traumatic events	Self-report questionnaire	Diagnosis of depression	Opposite	1.0000	1.10×10^{-5}
Cicchetti et al,[22] 2007	339	46	17	Cross-sectional	Child abuse	Objective	ASEBA	Partially positive	.2518	1.94×10^{-5}
Dick et al,[35] 2007	956	NA	NA	Family-based association study	Problems with work, relationship, or health	Self-report questionnaire	Diagnosis of depression	Positive	.0040	5.37×10^{-5}
Kilpatrick et al,[14] 2007	589	64	≥60 (77%)	Cross-sectional	Hurricane exposure + low social support	Objective	Diagnosis of depression	Positive	.0015	3.94×10^{-5}
Kim et al,[78] 2007	732	NA	≥65	Cross-sectional	Stressful life events	Interview	Diagnosis of depression	Negative	0.0385	3.11×10^{-5}
Kraus et al,[36] 2007	139	49	42	Exposed only	Interferon alfa treatment	Objective	Hospital Anxiety and Depression Scale	Negative	.5650	1.73×10^{-5}
Mandelli et al,[15] 2007	670	68	48	Case-only	Stressful life events	Interview	Diagnosis of depression	Positive	.0112	3.50×10^{-5}
Middeldorp et al,[79] 2007	367	68	39	Longitudinal	Stressful life events	Self-report questionnaire	Anxiety-Depression Rating Scale	Negative	.5000	1.73×10^{-5}

(continued)

Table 1. Description of 5-HTTLPR, Stress, and Depression Studies Included in the Overall Meta-Analysis (continued)

Source, Year	No. of Participants	Female, %	Mean Age, y	Study Design	Stressor	Stress Assessment Method	Depression Measure	Reported Findings[a]	Averaged 1-Tailed *P* Value[b]	Liptak-Stouffer *P* Value After Study Exclusion
Otte et al,[29] 2007	557	15	68	Exposed only	Coronary disease	Objective	Diagnosis of depression	Partially positive	.0275	2.86×10^{-5}
Scheid et al,[16] 2007	568	100	20-34	Cross-sectional	Stressful life events	Self-report questionnaire	CES-D	Negative	.0800	2.50×10^{-5}
Brummett et al,[37] 2008	288	75	58	Cross-sectional	Alzheimer caregiving	Objective	CES-D	Positive	.0015	2.64×10^{-5}
Kohen et al,[26] 2008	150	37	60	Exposed only	Stroke	Objective	Geriatric Depression Scale	Positive	.0225	2.03×10^{-5}
Lazary et al,[38] 2008	567	79	31	Cross-sectional	Stressful life events	Self-report questionnaire	Zung Self-Rating Depression Scale	Positive	.0025	3.67×10^{-5}
Lenze et al,[27] 2005	23	87	77	Exposed only	Hip fracture	Objective	Diagnosis of depression	Positive	.0068	1.81×10^{-5}
Power et al,[80] 2010	1421	NA	≥65	Cross-sectional	Stressful life events	Self-report questionnaire	MINI, CES-D	Negative	.6200	1.10×10^{-5}
Wichers et al,[39] 2008	394	100	18-64	Cross-sectional	Childhood trauma	Self-report questionnaire	SCL-90; SCID depressive symptoms	Negative	.2000	2.03×10^{-5}
Aguilera et al,[23] 2009	534	55	23	Cross-sectional	Childhood trauma	Self-report questionnaire	SCL-90-R	Positive	.0001	4.63×10^{-5}
Araya et al,[34] 2009	4334	NA	7	Longitudinal	Stressful life events	Self-report questionnaire	SDQ emotional symptom 5-item subscale	Negative	.5000	1.03×10^{-6}
Aslund et al,[40] 2009	1482	48	17-18	Cross-sectional	Parental fighting and maltreatment	Self-report questionnaire	Depression Self-Rating Scale	Positive	.0078	7.68×10^{-5}
Bull et al,[41] 2009	98	36	46	Longitudinal	Interferon alfa and ribavirin treatment	Objective	Zung Self-Rating Depression Scale/BDI	Positive	.0150	1.95×10^{-5}
Coventry at al,[42] 2010	3243	60	32	Longitudinal	Stressful life events	Self-report questionnaire	Diagnosis of depression	Negative	.5000	4.33×10^{-6}
Bukh et al,[43] 2009	290	66	39	Case-only	Stressful life events	Interview	Diagnosis of depression	Negative	.0350	2.25×10^{-5}
Kim et al,[25] 2009	521	55	72	Longitudinal	No. of chronic health problems	Self-report questionnaire	Diagnosis of depression	Positive	.0050	3.27×10^{-5}
Laucht et al,[62] 2009	309	54	19	Cross-sectional	Stressful life events	Self-report questionnaire	Diagnosis of depression, BDI	Partially negative/ opposite	.7375	1.57×10^{-5}
Lotrich et al,[33] 2009	71	27	48	Exposed only	Interferon alfa treatment	Objective	BDI	Positive	.0250	1.88×10^{-5}
McCaffery et al,[44] 2009	977	21	59	Exposed only	Cardiovascular disease	Objective	BDI	Negative	.5000	1.57×10^{-5}
Ressler et al,[81] 2010	926	62	≥18	Cross-sectional	Childhood trauma	Self-report questionnaire	Diagnosis of depression (partially), BDI	Partially positive	.5000	1.59×10^{-5}
Ritchie et al,[82] 2009	942	58	65-92	Cross-sectional	Childhood adversities	Self-report questionnaire	Diagnosis of depression, CES-D, treatment with antidepressants	Partially opposite	.5390	1.51×10^{-5}

(continued)

STUDIES FROM PREVIOUS META-ANALYSES

When we restricted our analysis to the studies included in the 2 previous meta-analyses, we found no evidence of an association between 5-HTTLPR and stress sensitivity (Munafò et al studies, $P=.16$; Risch et al studies, $P=.11$).

PUBLICATION BIAS

To make the result of our overall analysis nonsignificant ($P=.05$), more than 729 unpublished or undiscovered studies with an average sample size (N=755) and a nonsignificant result ($P=.50$) would need to exist. This corresponds to a fail-safe ratio of 14 studies not in-

Table 1. Description of 5-HTTLPR, Stress, and Depression Studies Included in the Overall Meta-Analysis (continued)

Source, Year	No. of Participants	Female, %	Mean Age, y	Study Design	Stressor	Stress Assessment Method	Depression Measure	Reported Findings[a]	Averaged 1-Tailed *P* Value[b]	Liptak-Stouffer *P* Value After Study Exclusion
Wichers et al,[83] 2009	502	100	27	Longitudinal	Stressful life events	Self-report questionnaire	Diagnosis of depression, SCL-90-R	Partially positive	.3803	1.84×10^{-5}
Zhang et al,[45] 2009	792	54	33	Case-control	Stressful life events	Self-report questionnaire	Diagnosis of depression	Opposite	.9975	5.24×10^{-6}
Zhang et al,[84] 2009	306	38	NA	Exposed only	Parkinson disease	Objective	CES-D	Negative	.5000	1.74×10^{-5}
Hammen et al,[13] 2010	346	62	24	Longitudinal	Negative acute life events, chronic family stress	Interview	BDI	Partially positive	.3763	1.86×10^{-5}
Benjet et al,[46] 2010	78	100	12	Cross-sectional	Relational aggression	Self-report questionnaire	Children's Depression Inventory	Positive	.0050	1.94×10^{-5}
Goldman et al,[50] 2010	984	45	66	Longitudinal	Stressful life events	Interview	CES-D	Partially positive	.0203	4.19×10^{-5}
Grassi et al,[85] 2010	145	100	56	Exposed only	Breast cancer	Objective	Hospital Anxiety and Depression Scale	Negative	.5000	1.75×10^{-5}
Kumsta et al,[47] 2010	125	NA	11/15	Longitudinal	Institutionalization in Romanian orphanages	Objective	CAPA, Rutter Child Scale, SDQ	Positive	.0117	2.02×10^{-5}
Sen et al,[48] 2010	268	58	28	Longitudinal	Medical internship	Self-report questionnaire	PHQ	Positive	.0020	2.54×10^{-5}
Sugden et al,[49] 2010	2017	51	12	Longitudinal	Bullying victimization	Interview	ASEBA	Negative	.1603	2.94×10^{-5}
Total	**40 749**									
Average sample size	755									.00002

Abbreviations: ASEBA, Achenbach System of Empirically Based Assessment; BDI, Beck Depression Inventory; CAPA, Child and Adolescent Psychiatric Assessment; CES-D, Center for Epidemiologic Studies Depression Scale; MFQ, Mood and Feelings Questionnaire; MINI, Mini International Neuropsychiatric Interview; NA, not available; PHQ, Patient Health Questionnaire; SCID, Structured Clinical Interview for *DSM* Disorders; SCL-90, Symptom Checklist 90; SCL-90-R, Symptom Checklist 90 Revised; SDQ, Strengths and Difficulties Questionnaire.

[a] "Positive" indicates a significant ($P<.05$) interaction effect with the *s* allele, "Negative" indicates no interaction effect ($P>.05$), and "Opposite" indicates a significant ($P<.05$) interaction effect with the *l* allele.

[b] One-tailed *P* value, with smaller values indicating greater stress sensitivity among *s* allele subjects.

cluded in this meta-analysis for every included study. Additionally, we found that 45 of the 54 studies with the smallest sample sizes could be deleted before the outcome of the analysis would change to nonsignificant.

COMMENT

We found strong evidence that a serotonin transporter promoter polymorphism (5-HTTLPR) moderates the relationship between stress and depression, with the less functional *s* allele associated with increased stress sensitivity. This quantitative meta-analytic result is consistent with recent qualitative reviews on the same set of studies.[10,11] In addition, our results are consistent with a wide range of experimental neuroscience studies that have found increased stress reactivity among 5-HTTLPR *s* allele carriers.[87-89] Evidence from animal studies also supports that functional variation in the serotonin transporter (SERT) gene affects behavioral response to stress. Serotonin transporter knockout mice show increased hypothalamic-pituitary-adrenal axis activation in response to both physical and psychological stressors.[90,91] Developmentally, SERT knockout mice show impaired cortex-layer 4-barrel pattern formation and altered levels of a broad range of serotonin receptor subtypes, providing potential mechanisms through which SERT function may be affecting behavior.[92-94] Further, naturally occurring, low-functioning SERT gene variants in mice and nonhuman primates are associated with changes in central nervous system biochemistry as well as with behaviors linked to stress sensitivity.[95,96]

While our findings are consistent with this broad set of experimental neuroscience and animal studies, our findings are inconsistent with 2 other meta-analyses that have explored this association. The 2 most likely causes of the conflicting results between our meta-analysis and the previous meta-analyses are (1) the difference in meta-analytic technique used and (2) the different sets of included studies. To distinguish between these 2 possible causes, we applied our meta-analytic technique to the sets of studies used in the previous meta-analyses.[4] With these limited sets of studies, our meta-analytic technique produced the same nonsignificant result as the previous meta-analyses, suggesting that the difference in results be-

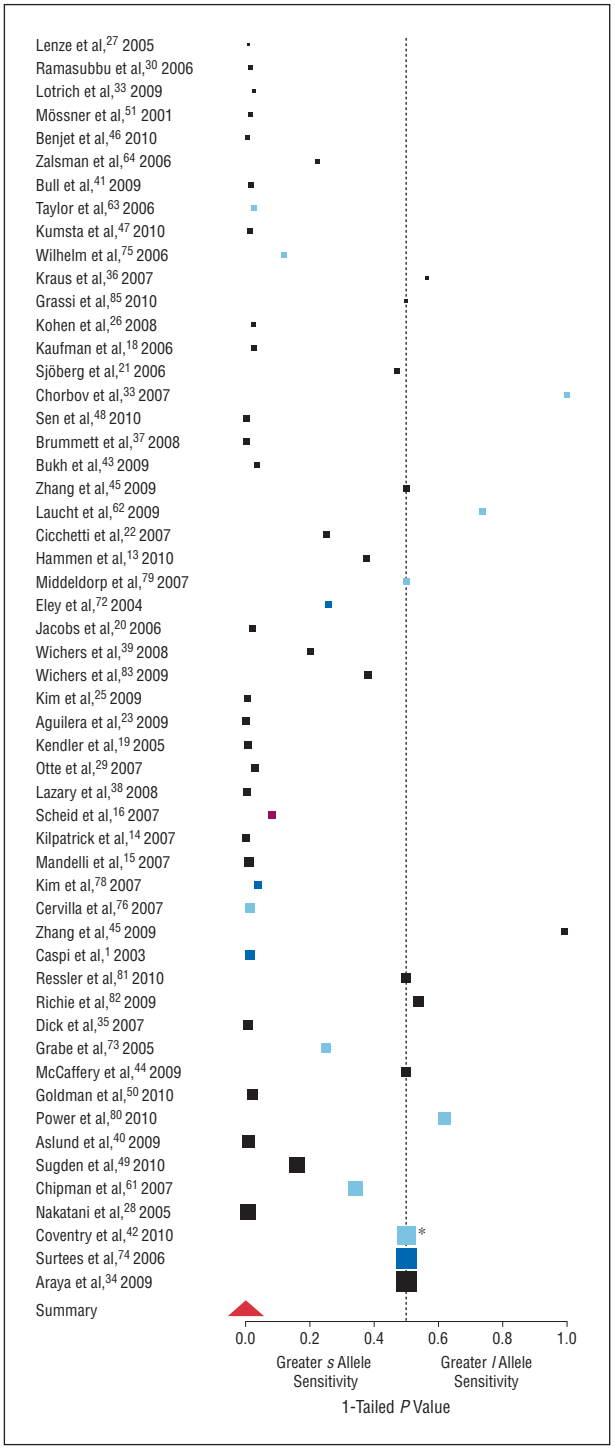

Figure. Forest plot for the 56 human observational studies assessing the relationship between 5-HTTLPR, stress, and depression. The boxes indicate the 1-tailed *P* value for each study, with lower values corresponding to greater stress sensitivity of *s* allele carriers and higher values, greater stress sensitivity of *l* allele carriers. The size of the box indicates the relative sample size. The triangle indicates the overall result of our meta-analysis. Purple indicates that the study was included only in the Munafò et al meta-analysis[3]; cyan, only in the Risch et al meta-analysis[4]; blue, both in the Munafò et al and the Risch et al meta-analyses; black, both in the Munafò et al and the Risch et al meta-analyses but the validity is questionable. *Participants were selected according to extremes of high and low neuroticism scores.[74] Because there is a strong positive correlation between depression and neuroticism, a large portion of variance in depression in such a sample will be explained by neuroticism alone.[86] The absence of individuals with intermediate neuroticism scores, for which the gene × environment effect may be strongest, might obscure any gene × environment interaction effect.

Table 2. Studies Included in the Childhood Maltreatment Group Meta-Analysis

Source, Year	Total No. of Participants	1-Tailed *P* Value	Fisher *P* Value After Study Exclusion
Caspi et al,[1] 2003	845	.010	5.38×10^{-4}
Kaufman et al,[18] 2006	196	.023	1.17×10^{-4}
Cicchetti et al,[22] 2007	339	.252	8.72×10^{-5}
Wichers et al,[39] 2008	394	.200	9.71×10^{-5}
Aguilera et al,[23] 2009	534	5.0×10^{-5}	8.31×10^{-4}
Aslund et al,[40] 2009	1482	.008	1.40×10^{-3}
Ressler et al,[81] 2010	926	.500	2.97×10^{-5}
Benjet et al,[46] 2010	78	.005	9.27×10^{-5}
Kumsta et al,[47] 2010	125	.012	1.03×10^{-4}
Sugden et al,[49] 2010	2017	.160	7.42×10^{-6}
Total	6936		
Average sample size	694		.00007

Table 3. Studies Included in the Specific Medical Condition Group Meta-Analysis

Source, Year	Total No. of Participants	1-Tailed *P* Value	Fisher *P* Value After Study Exclusion
Mössner et al,[51] 2001	72	.025	.00044
Grabe et al,[73] 2005	973	.250	.00041
Nakatani et al,[28] 2005	2509	.008	.00679
Ramasubbu et al,[30] 2006	51	.013	.00041
Kraus et al,[36] 2007	139	.565	.00035
Otte et al,[29] 2007	557	.028	.00104
Kohen et al,[26] 2008	150	.023	.00051
Lenze et al,[27] 2005	23	.007	.00038
Bull et al,[41] 2009	98	.015	.00046
Kim et al,[25] 2009	521	.005	.00145
Lotrich et al,[33] 2009	71	.025	.00042
McCaffery et al,[44] 2009	977	.500	.00017
Zhang et al,[84] 2009	306	.500	.00034
Grassi et al,[85] 2010	145	.500	.00035
Total	**6592**		
Average sample size	471		.0004

tween meta-analyses was due to the different set of included studies rather than the different meta-analytic technique.

The results of our secondary meta-analysis, where we stratified studies by stressor type, also support the hypothesis that the difference in results between our meta-analysis and the previous meta-analyses is due to the difference in the primary studies included. Both previous meta-analyses focused exclusively on SLEs and reported no evidence that 5-HTTLPR moderates the relationship between SLEs and depression. Herein, we were able to include 11 additional SLE studies not included in previous meta-analyses but still found only marginal evidence that 5-HTTLPR moderates the relationship between SLEs 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 variability between studies within each group.[86] Within

Table 4. Studies Included in the Stressful Life Events Group Meta-Analysis

Source, Year	Total No. of Participants	1-Tailed *P* Value	Fisher *P* Value After Study Exclusion
Caspi et al,[1] 2003	845	.010	.054
Eley et al,[72] 2004	374	.258	.034
Kendler et al,[19] 2005	549	.007	.047
Jacobs et al,[20] 2006	374	.020	.040
Sjöberg et al,[21] 2006	198	.472	.032
Surtees et al,[74] 2006	4175	.500	.014
Taylor et al,[63] 2006	110	.028	.034
Wilhelm et al,[75] 2006	127	.118	.034
Zalsman et al,[64] 2006	79	.342	.033
Cervilla et al,[76] 2007	737	.014	.050
Chipman et al,[61] 2007	2094	.292	.039
Chorbov et al,[77] 2007	236	.99995	.025
Dick et al,[35] 2007	956	.004	.062
Kim et al,[78] 2007	732	.039	.046
Mandelli et al,[15] 2007	670	.011	.049
Middeldorp et al,[79] 2007	367	.500	.032
Scheid et al,[16] 2007	568	.080	.040
Lazary et al,[38] 2008	567	.002	.050
Power et al,[80] 2010	1421	.620	.026
Araya et al,[34] 2009	4334	.500	.013
Coventry et al,[42] 2010	3243	.500	.021
Bukh et al,[43] 2009	290	.035	.037
Laucht et al,[62] 2009	309	.500	.032
Ritchie et al,[82] 2009	942	.539	.030
Wichers et al,[83] 2009	502	.380	.033
Zhang et al,[45] 2009	792	.998	.016
Hammen et al,[13] 2010	346	.376	.034
Goldman et al,[50] 2010	984	.020	.055
Total	**26 921**		
Average sample size	961		.03

the childhood maltreatment and specific stressors groups, the designs of the primary studies were generally similar. In contrast, there is marked variation in study design between SLE studies. Some studies asked subjects about SLEs and depressive episodes that occurred decades earlier while others assessed SLEs and depressive episodes soon after they occurred.[33,75] Further, SLE studies vary substantially in what they consider a life event. Another potential reason for the difference in stressor subgroup results is the nature of the stressors studied. Most of the specific stressor studies focused on chronic stressors while the SLE studies focused on acute SLEs. Interestingly, 3 studies have explicitly looked at both acute and chronic stressors in their cohorts and all 3 have found that the evidence for moderating effects was stronger for chronic stressors.[13,19,48]

In addition to the type of stressor studied, the stress assessment method used by investigators emerged as an important variable in our analysis. In particular, we found that the evidence of genetic moderation was stronger among studies that used objective measures or in-person interviews to assess stress than among studies that used self-report questionnaires.

There are limitations to our study, most of which follow from the meta-analytic technique that we used. Because we combined studies at the level of *P* values, errors or bias present in the statistical tests performed in the primary studies could potentially affect the results of this meta-analysis. We guarded against finding false-positive results due to this potential bias by using an average of reported *P* values when authors performed separate tests on different sample subgroups or multiple depression measures. Further, when authors performed multiple tests but only reported the significance results for a subset of these tests, we assumed that $P=1$ for the unreported tests. The fact that we found a nonsignificant result when we applied our meta-analytic technique to the set of studies included in a previous nonsignificant meta-analysis suggests that statistical bias from primary studies did not unduly affect our results. Another drawback of using this meta-analytic method is that we were unable to estimate the magnitude of the genetic effect and, in particular, how the interaction effect size compares with any genetic main effect.[17]

Against this background, the present study suggests that there is cumulative and replicable evidence that 5-HTTLPR moderates the relationship between stress and depression. Our findings, particularly the identification of important study characteristics that influence study outcome (stressor type and stress assessment method), can provide guidance for the design of future gene × environment interaction studies. While there is certainly variation between study results, there is hope that a new generation of studies purpose-built for testing this specific hypothesis will improve replicability and shed light on sources of inconsistency. In the meantime, the results of our inclusive analysis of studies in this controversial area underscore the importance of including all relevant studies in meta-analyses and highlight the utility of incorporating environmental exposures in genetic association studies.

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