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GENE-ENVIRONMENT INTERACTIONS BETWEEN STRESS AND 5-HTTLPR IN DEPRESSION: A META-ANALYTIC UPDATE

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Abstract

Background: Meta-analyses have yielded contradictory findings concerning the role of 5-HTTLPR in interaction with stress (GxE) in depression. The current meta-analysis investigates if these contradictory findings are a result of differences between studies in methodological approaches towards the assessment of stress and depression.

Methods: After performing a systematic database search (February to December 2016), first, a meta-analysis was used to investigate the total effect size and publication bias. Second, stratified meta-analyses were used to investigate the potential moderating influence of different methodological approaches on heterogeneity of study findings. Third, a meta-regression was used to investigate the combined influence of the methodological approaches on the overall effect size.

Results: Results showed a small but significant effect of 5-HTTLPR in interaction with stress in the prediction of depression (OR[95%CI] = 1.18[1.09; 1.28], n = 48 effect sizes from 51 studies, totaling 51,449 participants). There was no evidence of publication bias. Heterogeneity of effect sizes was a result of outliers and not due to different methodological approaches towards the assessment of stress and depression. Yet, there was some evidence that studies adopting a categorical and interview approach to the assessment of stress report higher GxE effects, but further replication of this finding is needed.

Limitations: A large amount of heterogeneity (i.e., 46%) was not explained by the methodological factors included in the study and there was a low response rate of invited studies.

Conclusions: The current meta-analysis provides new evidence for the robustness of the interaction between stress and 5-HTTLPR in depression.

1. INTRODUCTION

Current theories of depression emphasize the interplay between environmental and biological factors in explaining vulnerability for this disabling disorder (Heim and Binder, 2012; Lesch, 2004; Lohoff, 2010). Much of this work has focused on the role of the serotonin-transporter-linked polymorphic region (5-HTTLPR), following the seminal work of Caspi and colleagues (Caspi et al., 2003). These authors were the first to report that the impact of life stress on depression was moderated by a polymorphism of the 5-HTT gene. Specifically, associations between stressful life events and depression were more pronounced among individuals with one or two copies of the short allele of 5-HTTLPR. However, meta-analyses of subsequent studies have yielded contradictory conclusions concerning the role of an interaction between stress and 5-HTTLPR (GxE) in depression (Karg et al., 2011; Risch et al., 2009).

Various methodological factors that might account for these diverging findings have remained unexamined to date. First, extant research differs with regard to whether it adopts a categorical or a dimensional approach to depression and stress. Yet, with the exception of melancholic depression (Ambrosini et al., 2002; Haslam and Beck, 1994), taxometric studies suggest that depression is dimensionally distributed (Ruscio and Ruscio, 2000; Slade and Andrews, 2005). Similarly, both human and animal studies suggest that the underlying biological mechanisms involved in depression are dimensionally distributed (Charney and Manji, 2004; Nestler et al., 2002). Yet, many studies on GxE have adopted a categorical approach to assessing depression, which may moreover have resulted in a considerable loss of statistical power (Fraley and Spieker, 2003; Hankin et al., 2005). With regard to stress, there is an ongoing debate concerning the impact of stress on the risk for depression (Kessler, 1997; Tennant, 2002). Whereas some studies suggest a categorical threshold model, with the risk for depression increasing only after a certain stress threshold has been reached, other studies suggest a continuous effects model, arguing that the risk for depression simply increases as the number of stressful life events increases (Appleyard et al., 2005; Mitchell et al., 2015). Yet, no study to date has

addressed the potential influence of a categorical versus dimensional approach to the assessment of depression and stress on interactions between 5-HTTLPR and stress in the prediction of depression.

Second, it remains equally unclear whether the way depression is assessed (i.e., by self-report questionnaires or interviews) influences findings concerning GxE in depression. Although studies suggest moderate to high agreement between both types of assessment (Eaton et al., 2000; Stuart et al., 2014), interview-based measures of depression are often considered the "gold standard" because self-report questionnaires may be particularly prone to reporting bias (Enns et al., 2000; Hunt et al., 2003; Joiner et al., 2005; Logan et al., 2008). Similarly, in the domain of stress research, interview-based measures of stress are typically considered to be superior to self-report measures, as these latter measures would conflate stressful events and depressed mood (Hammen, 2005; Uher and McGuffin, 2008, 2010). Studies in this area, however, have yielded conflicting findings, with some studies suggesting that both measurement approaches lead to similar conclusions (Duggal et al., 2000; Lewinsohn et al., 2003), while other studies suggest that findings of an association between 5-HTTLPR and depression may be stronger using interview-based measures of stress (Karg et al., 2011; Uher and McGuffin, 2010). Clearly, a formal meta-analytic test of the role of type of assessment is needed.

A third possible reason for the diverging results of meta-analyses of GxE effects in the prediction of depression may be related to the timing of stress. Although stressful life events occurring during adulthood have been shown to be related to the onset of depression (Kendler et al., 1999; Tennant, 2002), the relationship between early stress and depression might be stronger because of early sensitization effects (Anda et al., 2006; Hammen et al., 2000; Lupien et al., 2009; McLaughlin et al., 2010). To date, however, it is unknown whether the interaction effect between stress and 5-HTLLPR in depression differs as a function of the timing of adversity.

The Present Study

Given the rapid growth of research in this area, the first aim of this study is to provide an updated meta-analysis of the interaction effects of 5-HTTLPR and stress in the prediction of depression. This update is urgently needed as the largest meta-analysis of GxE effect sizes in depression included only 14 studies (Risch et al., 2009). Also, we address potential publication bias in studies in this area (Kaufman et al., 2010).

Second, using stratified meta-analyses, we investigated the influence of dimensional versus categorical assessment of depression and stress, self-report versus interview-based assessment of depression and stress, and the timing of stress (i.e., early life stress versus stress in adulthood) as potential moderators of the interaction between 5-HTTLPR and stress in the prediction of depression.

Finally, we investigate the relative contribution of these potential moderators and their interactions on the magnitude of effect sizes within a meta-regression framework (van Houwelingen et al., 2002).

METHOD

Studies

From February 2016 to December 2016 potential studies were identified through a systematic search in databases (PubMed, SpingerLink, ScienceDirect, and Wiley Online Library using (combinations of) the following search terms with Boolean operators: "depression", "depressive symptoms", "gene-environment interactions", "interaction", "stress", "trauma", "5-HTTLPR". In addition, reference lists of relevant meta-analyses and studies were hand searched for additional studies. Inclusion criteria were (a) full-text paper published in English; (b) human participants; (c) a candidate gene approach with identification of 5-HTTLPR; (d) environmental factors that are stressful for the individual, with the exclusion of residency and physical illness or accidents (e.g., hip fracture); (e) a depression related outcome factor (depression diagnoses / symptoms), excluding measures of negative emotionality, bipolar disorder, broader symptom clusters such as internalizing symptoms or

anxious depression, and antidepressant treatment response. This led to the inclusion of 106 studies. Authors of studies containing insufficient data to calculate an effect size (see below) were contacted and asked to provide either the study data or to directly provide the needed additional data. Up to three consecutive e-mails (1 per month) were sent to multiple authors of the same study in case of non-response. The final number of included studies was 51. See Fig. A.1 in Appendices for the PRISMA flow diagram.

Data extraction

We extracted the following information from each identified study: (a) in case of categorical depression outcome, the regression coefficient and standardized error of the interaction term from a logistic regression or (b) in case of a continuous depression outcome, the difference in explained variance (R^2) after inserting the interaction term in a hierarchical regression analysis or the partial eta squared (η^2) belonging to the interaction term in an analysis of variance. All models included both main and interaction effects of the environmental stress factor and 5-HTTLPR (coded as LL-allele versus SS+SL-alleles). Moreover, we requested that results were restricted to biallelic coded 5-HTTLPR and were controlled for gender (Sjöberg et al., 2006), ethnicity (Scheid et al., 2011), and twin status, although this was not always applicable or possible. When a study was longitudinal, we requested data for each time point. See Table A.1 in Appendices for details of studies and statistical analysis per study.

Statistical analysis

All effect sizes were transformed to log Odds Ratios (ORs; Cohen, 1988; Cooper et al., 2009; Lipsey and Wilson, 2001) using the statistical software R (R Development Core Team, 2014) and the packages "compute.es" (Del Re, 2013). By transforming different types of effect sizes into readily interpretable Odds Ratios, this meta-analysis included all studies simultaneously and different types of studies (e.g., continuous versus dichotomous depression outcome) could be directly compared in terms

of effect sizes[1]. The meta-analysis was performed using the R package "meta" (Schwarzer, 2016). We applied the inverse variance method for the meta-analysis. Heterogeneity tests were performed using I^2,(Higgins et al., 2003) describing the percentage of variation across studies that is due to the heterogeneity and is not spurious (with $I^2 = 25\%$ = low, $I^2 = 50\%$ = moderate, $I^2 = 75\%$ = high heterogeneity), and a test of the significance of the heterogeneity based on the Q statistic (Cochran, 1950). Sensitivity analyses were performed to investigate the effect of leaving a study out on the overall effect size. We only discuss results of the random effects models, although for transparency, results of the fixed effects model of the overall meta-analysis are also presented in the figure. For estimation of the between-study variance, the adjustment of the weights in the random-effects meta-analysis, and for the meta-regression, the Tau^2 estimate was used (DerSimonian and Laird, 1986).

For the overall meta-analysis, all available effect sizes were averaged per study (averaging also between effect sizes of studies that included the same sample), resulting in 48 effect sizes from 51 studies. We also inspected publication bias using a funnel plot. For the stratified analyses, effect sizes from identical samples were allowed if they were not present in the same subgroup. For the random-effects meta-regression, available effect sizes were selected from the previous stratified analyses, regression predictors were the potential moderators and a control variable was included identifying effect sizes from the same sample to control for their interdependence (continuously coded: unique samples coded '0', studies with same sample '1', next set of studies with same sample '2', etc.). Cochran (1954) Q_E-test for residual heterogeneity was performed after introducing the predictors.

RESULTS

Overall meta-analysis

There was a small, but significant, GxE effect of 5-HTTLPR (OR[95%CI] = 1.18[1.09; 1.28], n = 51 studies yielding 48 effect sizes, totaling 51,449 participants; Figure 1). There was significant

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[1] A forest plot using the Cohen's d effect size for all studies with a dimensional (continuous) depression score is available in Fig. A. 2 in Appendices.

moderate to high heterogeneity between studies ($I^2 = 52.4\%$, $Q = 98.64$, $p < .0001$). A sensitivity

analysis showed no effect on the significance of the overall OR if one of the studies was omitted

(Table A.2 in Appendices), not even if we omitted the two studies with the largest positive effect size,

the study of Brown et al. (2013) and the study of Mehta et al. (2012) (overall OR[95% CI] = 1.13

[1.07; 1.19]). However, the I^2 heterogeneity index decreased to 21.0% and became non-significant ($p =$

.106) if the study of Mehta et al. (2012) was omitted (OR[95% CI] = 1.14 [1.07; 1.20]; Table A.2 in

Appendices). There was no evidence for publication bias (Figure 2).

Stratified meta-analyses

None of the examined moderators had a significant influence on the heterogeneity of effect sizes

of the GxE effect in separate stratified meta-analyses ($Q_{between} = 1.13$, $p = .289$, for categorical versus

dimensional assessment of depression; $Q_{between} = 1.86$, $p = .173$, for interview-based versus self-report

assessment of depression; $Q_{between} = 1.52$, $p = .218$, for categorical versus dimensional assessment of

stress; $Q_{between} = 0.73$, $p = .392$, for interview-based versus self-report assessment of stress; $Q_{between} =$

1.00, $p = .316$, for early- versus late-life stress; see Text A.1 in Appendices). Heterogeneity varied

widely in all of these analyses ($14.7\% < I^2 < 87.1\%$) but was mainly driven by specific studies with high

ORs. After excluding just one outlier per moderator subgroup during sensitivity analyses, I^2 decreased

to $0\% \leq I^2 < 23.9\%$, with non-significant low heterogeneity in all subgroups. The one exception was the

subgroup of studies using an interview to assess stress, which continued to show significant moderate

to high and high heterogeneity $60.8\% < I^2 < 89.0\%$ during sensitivity analysis (See Text A.1 in

Appendices for details).

Meta-regression

The combined set of predictors explained $R^2 = 41.88\%$ of heterogeneity with an I^2 residual

heterogeneity of 15.78%, which was non-significant ($Q_E = 56.99$, df = 48, $p = .175$, n = 41 studies

with non-missing information for predictors, yielding 57 effect sizes, see Table 1). Two significant

main effects emerged: categorical versus dimensional assessment of stress and interview versus self-

report assessment of depression, suggesting that studies adopting a categorical assessment of stress and interview assessment of depression were associated with higher effect sizes. Moreover, there was an interaction effect between categorical versus dimensional assessment of stress and interview versus self-report assessment of stress, with significantly higher ORs in studies using interviews to assess stress being observed only in studies that also adopted a categorical assessment of stress. The ORs in studies using a self-report questionnaire to assess stress, regardless of whether these studies adopted a categorical or dimensional approach, were similar. At the same time, it must be noted that the group of studies using both a categorical and interview approach to the assessment of stress, included only 3 effect sizes derived from two studies (Brown et al., 2013; Harkness et al., 2015). _ENREF_49 If we dropped non-significant predictors (categorical/dimensional depression and early-/late-life stress) in the meta-regression, additional studies could be included that were initially excluded in the meta-regression because they contained missing values for some of the predictors (n = 47 studies with in total 65 effect sizes, Table A.3 in Appendices). Results of these analyses were similar for the interaction effect, with higher ORs in studies using categorical and interview assessment of stress, reported in 4 studies yielding 5 effect sizes (Figure 3; Brown et al., 2013; Grabe et al., 2012b; Harkness et al., 2015; Mehta et al., 2012)[2]. In this step, the main effect observed for the studies adopting an interview versus self-report assessment of depression became non-significant. The remaining significant predictors (interview/self-report stress, categorical/dimensional stress, and their interaction) continued to predict a large amount of heterogeneity (explained R^2 = 13.97%), although the residual heterogeneity remained significant in this case (I^2 = 46.03%, Q_E = 113.02, df = 61, $p <$ .0001, n = 48 studies with in total 66 effect sizes). However, the interaction effect between assessment type of stress (categorical versus continuous) and assessment method of stress (interview-based versus questionnaire-based) was reduced to b = 0.18, SE = 0.14, p = .200 (95%CI of b = [-0.10 ; 0.46]) if both Brown et al. (2013) and Mehta et al. (2012) (the two studies with the highest effect sizes) were excluded. It should be noted that the estimation of this (non-significant) interaction effect was then

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[2] The interaction effect also remained when only one total effect size from the study of Brown et al. (2013) was used.

based on only 2 remaining studies in the group of studies adopting both a categorical and interview assessment of stress (i.e., Grabe et al., 2012b; Harkness et al., 2015).

DISCUSSION

This study provides an updated meta-analysis of the interaction between 5-HTTLPR and stress in the prediction of depression. It also investigated whether different methodological approaches towards the assessment of stress and depression influenced GxE effects. Results showed that the overall effect size across all included studies (n = 51, totaling n = 51,449 participants) was significant (OR[95%CI] = 1.18[1.09; 1.28]). The current findings therefore support a role of 5-HTTLPR in predicting depression in interaction with stress, even despite the fact that the risk for depression is likely to be influenced by multiple different (polymorphisms of) genes in multiple neuronal pathways (Peyrot et al., 2014). Yet, the obtained aggregated effect size was small.

These results parallel findings reported in a previous meta-analysis by Munafo and colleagues (Munafo et al., 2009) in a much smaller (n = 9) sample of studies (OR = 1.16, 95%CI = [0.89; 1.49]), and by Risch and colleagues (Risch et al., 2009) in a meta-analysis of 14 studies (OR = 1.01, 95%CI = [0.94; 1.10]). Yet, in both these latter meta-analyses, the obtained effect sizes were not significant. These differences could be due to the larger number of studies included in the present meta-analysis, which may have yielded a more reliable estimate of effects. Importantly, there was no evidence for publication bias, which addresses an often-heard criticism of research in this area (Kaufman et al., 2010).

Overall, there was very little evidence that the way depression and stress were assessed, or the timing of stress, influenced findings concerning interactions between 5HTTLPR and stress in the prediction of depression. Sensitivity analyses showed that heterogeneity between effect sizes of different studies in the overall meta-analysis and in the stratified meta-analyses, mostly resulted from individual studies. There was some evidence that studies using a categorical and interview approach to the assessment of stress yielded larger effect sizes. These findings are in line with suggestions that

interview-based approaches (Uher and McGuffin, 2008, 2010), which typically adopt a threshold model of stress (Monroe and Simons, 1991), are the most valid approach to assessing the effects of stress. However, this effect was driven by a small number of effect sizes and included effect sizes that were previously identified as outliers (Brown et al., 2013; Mehta et al., 2012). Future research is clearly needed in this area.

Limitations

Although the present study presents the largest meta-analysis of effect sizes of the interaction between stress and 5-HTTLPR in depression, results should be interpreted in the context of a number of limitations. First, we could not control for gender, ethnicity, and twin status or include the biallelic 5-HTTLPR in all studies (see Table A.1 in Appendices). Yet, in a post-hoc meta-regression, these covariates did not have an impact on GxE effect sizes in a combined analysis with all predictors (results not shown). Furthermore, we did not investigate possible other factors that may explain inconsistencies between GxE results (i.e., there was 46% unexplained heterogeneity), such as the influence of personality traits (Uher and McGuffin, 2008).

Second, although the 95%CI of the overall GxE effect was comparatively small, the majority of the individual studies showed a large 95%CI that included OR = 1. This particular finding raises the question of the quality of GxE studies in relation to other methodological factors that have not been investigated in the current study. For example, there are other classifications of the 5-HTTLPR polymorphism alleles possible (i.e., LL vs. SL vs. SS), including functional classifications (Scheid et al., 2011), which could result in different effect sizes compared to the effect sizes of the allelic classification adopted in the current meta-analysis (i.e., LL vs. SS+SL).

Third, the ratio of included studies to eligible studies was about 48%, with 19 authors who declined the invitation to provide data or perform additional analyses, and 28 authors not responding to requests for additional data or analyses. This raises the question whether including this missing data could lead to different conclusions. This also suggests problems with reporting standards in GxE

research for conducting meta-analyses. These concerns are somewhat mitigated by the absence of

publication bias in the current meta-analysis. Yet, future studies should clearly report all relevant data

for future meta-analyses.

Conclusion

The current meta-analysis found a small, but significant, effect of 5-HTTLPR in interaction with

stress in the prediction of depression. There was no evidence of publication bias. Heterogeneity of

effect sizes was mostly a result of outliers and not due to how stress and depression were assessed, nor

to the timing of stress. There was some evidence, however, that studies adopting an interview and

categorical approach to the assessment of stress reported higher effect sizes, although this effect was

driven by a small number of studies. The current meta-analysis contributes to ongoing efforts to

investigate apparently divergent findings in GxE studies of 5-HTTLPR, stress, and depression (Taylor

and Munafò, 2016). Future studies are needed to further disentangle the mechanisms involved in the

association between stress, 5-HTTLPR, and depression. Furthermore, given the small effect size, other

candidate genes (Aguilera et al., 2009), polygenic scores (Peyrot et al., 2014), and other novel

approaches are needed, and might provide more promising ways to assess GxE effects in depression.

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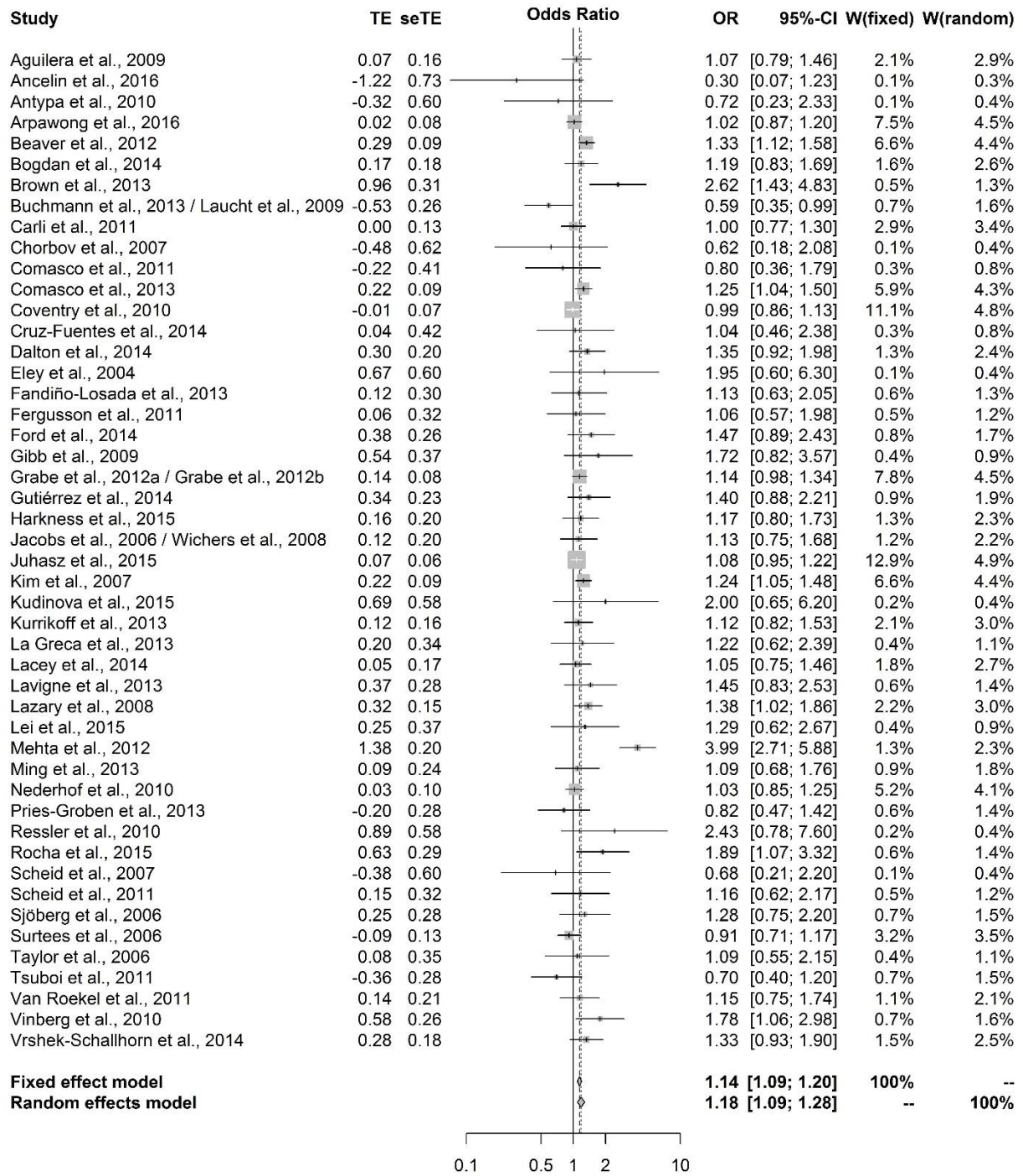
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Figure 1

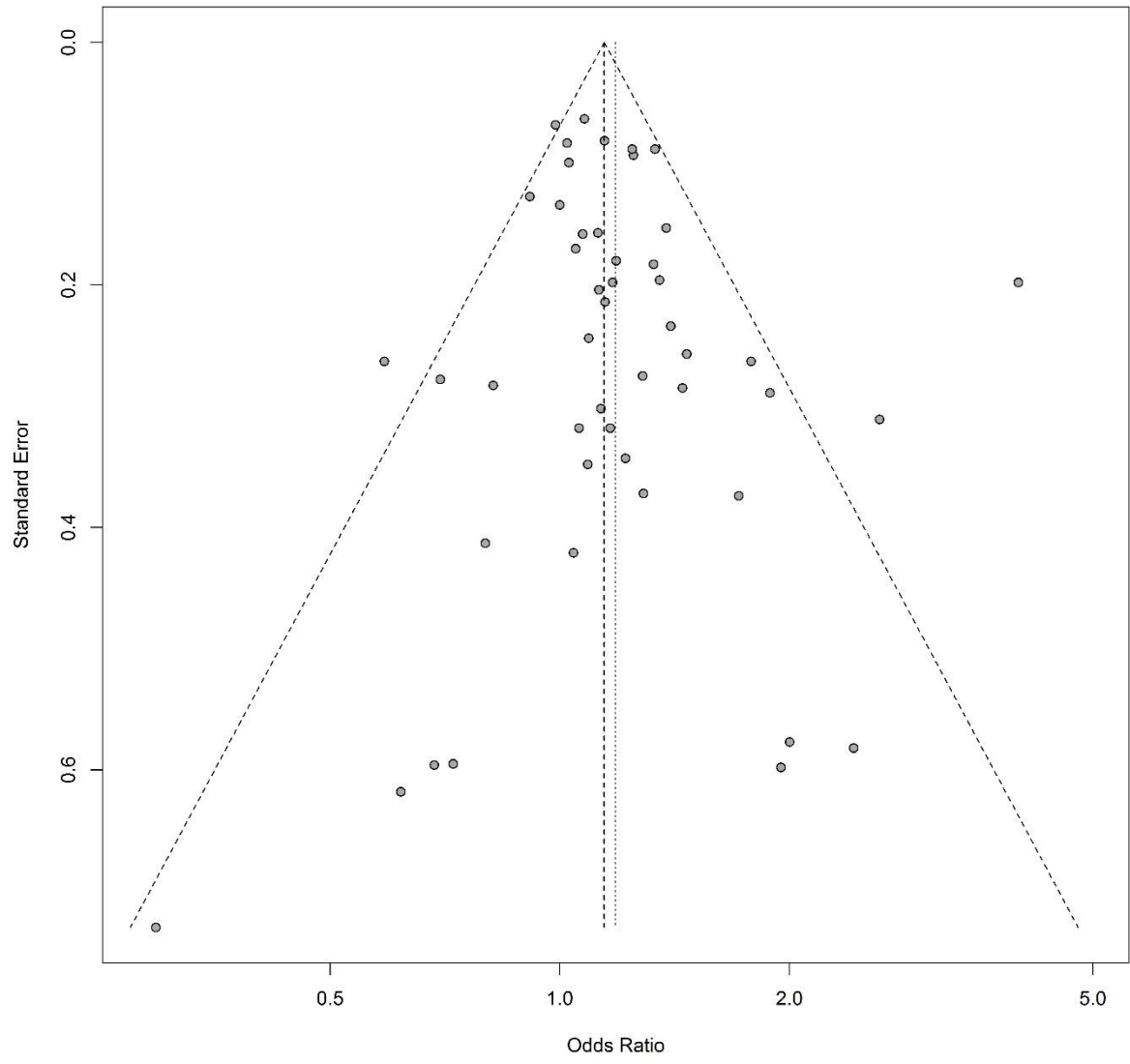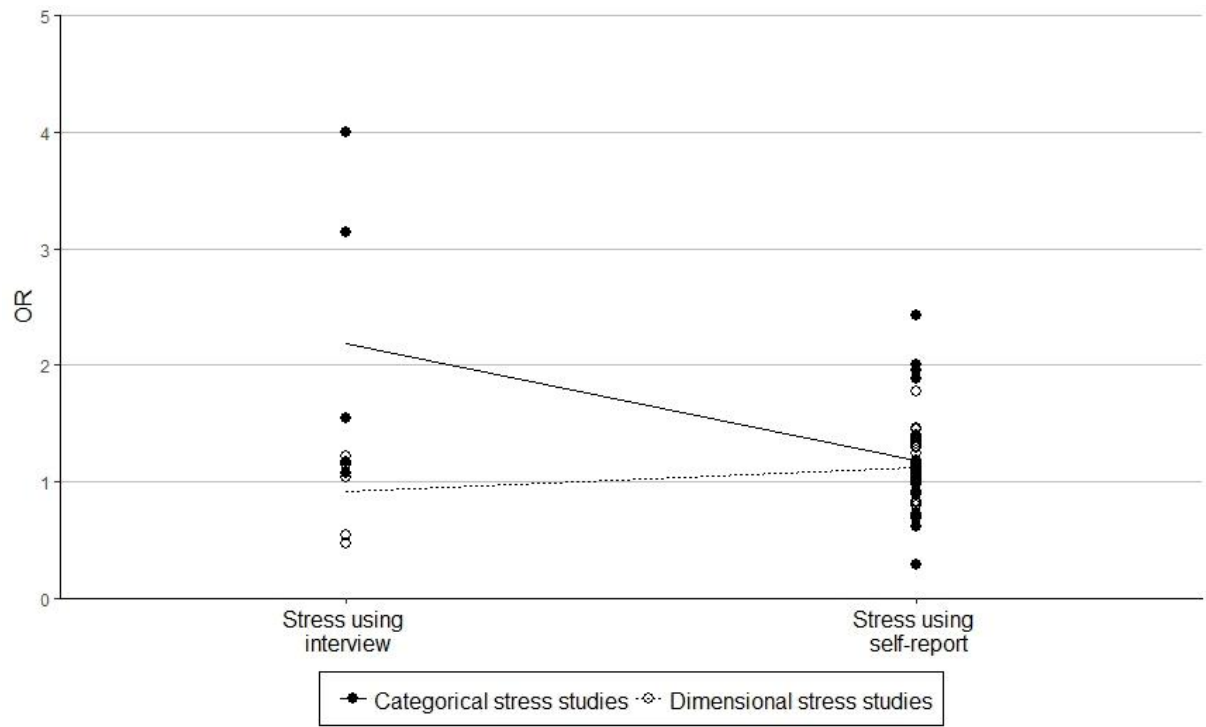| Study	TE	seTE	Odds Ratio	OR	95%-CI	W(fixed)	W(random)
Aguilera et al., 2009	0.07	0.16		1.07	[0.79; 1.46]	2.1%	2.9%
Ancelin et al., 2016	-1.22	0.73		0.30	[0.07; 1.23]	0.1%	0.3%
Antypa et al., 2010	-0.32	0.60		0.72	[0.23; 2.33]	0.1%	0.4%
Arpawong et al., 2016	0.02	0.08		1.02	[0.87; 1.20]	7.5%	4.5%
Beaver et al., 2012	0.29	0.09		1.33	[1.12; 1.58]	6.6%	4.4%
Bogdan et al., 2014	0.17	0.18		1.19	[0.83; 1.69]	1.6%	2.6%
Brown et al., 2013	0.96	0.31		2.62	[1.43; 4.83]	0.5%	1.3%
Buchmann et al., 2013 / Laucht et al., 2009	-0.53	0.26		0.59	[0.35; 0.99]	0.7%	1.6%
Carli et al., 2011	0.00	0.13		1.00	[0.77; 1.30]	2.9%	3.4%
Chorbov et al., 2007	-0.48	0.62		0.62	[0.18; 2.08]	0.1%	0.4%
Comasco et al., 2011	-0.22	0.41		0.80	[0.36; 1.79]	0.3%	0.8%
Comasco et al., 2013	0.22	0.09		1.25	[1.04; 1.50]	5.9%	4.3%
Coventry et al., 2010	-0.01	0.07		0.99	[0.86; 1.13]	11.1%	4.8%
Cruz-Fuentes et al., 2014	0.04	0.42		1.04	[0.46; 2.38]	0.3%	0.8%
Dalton et al., 2014	0.30	0.20		1.35	[0.92; 1.98]	1.3%	2.4%
Eley et al., 2004	0.67	0.60		1.95	[0.60; 6.30]	0.1%	0.4%
Fandiño-Losada et al., 2013	0.12	0.30		1.13	[0.63; 2.05]	0.6%	1.3%
Fergusson et al., 2011	0.06	0.32		1.06	[0.57; 1.98]	0.5%	1.2%
Ford et al., 2014	0.38	0.26		1.47	[0.89; 2.43]	0.8%	1.7%
Gibb et al., 2009	0.54	0.37		1.72	[0.82; 3.57]	0.4%	0.9%
Grabe et al., 2012a / Grabe et al., 2012b	0.14	0.08		1.14	[0.98; 1.34]	7.8%	4.5%
Gutiérrez et al., 2014	0.34	0.23		1.40	[0.88; 2.21]	0.9%	1.9%
Harkness et al., 2015	0.16	0.20		1.17	[0.80; 1.73]	1.3%	2.3%
Jacobs et al., 2006 / Wichers et al., 2008	0.12	0.20		1.13	[0.75; 1.68]	1.2%	2.2%
Juhasz et al., 2015	0.07	0.06		1.08	[0.95; 1.22]	12.9%	4.9%
Kim et al., 2007	0.22	0.09		1.24	[1.05; 1.48]	6.6%	4.4%
Kudinova et al., 2015	0.69	0.58		2.00	[0.65; 6.20]	0.2%	0.4%
Kurrikoff et al., 2013	0.12	0.16		1.12	[0.82; 1.53]	2.1%	3.0%
La Greca et al., 2013	0.20	0.34		1.22	[0.62; 2.39]	0.4%	1.1%
Lacey et al., 2014	0.05	0.17		1.05	[0.75; 1.46]	1.8%	2.7%
Lavigne et al., 2013	0.37	0.28		1.45	[0.83; 2.53]	0.6%	1.4%
Lazary et al., 2008	0.32	0.15		1.38	[1.02; 1.86]	2.2%	3.0%
Lei et al., 2015	0.25	0.37		1.29	[0.62; 2.67]	0.4%	0.9%
Mehta et al., 2012	1.38	0.20		3.99	[2.71; 5.88]	1.3%	2.3%
Ming et al., 2013	0.09	0.24		1.09	[0.68; 1.76]	0.9%	1.8%
Nederhof et al., 2010	0.03	0.10		1.03	[0.85; 1.25]	5.2%	4.1%
Pries-Groben et al., 2013	-0.20	0.28		0.82	[0.47; 1.42]	0.6%	1.4%
Ressler et al., 2010	0.89	0.58		2.43	[0.78; 7.60]	0.2%	0.4%
Rocha et al., 2015	0.63	0.29		1.89	[1.07; 3.32]	0.6%	1.4%
Scheid et al., 2007	-0.38	0.60		0.68	[0.21; 2.20]	0.1%	0.4%
Scheid et al., 2011	0.15	0.32		1.16	[0.62; 2.17]	0.5%	1.2%
Sjöberg et al., 2006	0.25	0.28		1.28	[0.75; 2.20]	0.7%	1.5%
Surtees et al., 2006	-0.09	0.13		0.91	[0.71; 1.17]	3.2%	3.5%
Taylor et al., 2006	0.08	0.35		1.09	[0.55; 2.15]	0.4%	1.1%
Tsuboi et al., 2011	-0.36	0.28		0.70	[0.40; 1.20]	0.7%	1.5%
Van Roekel et al., 2011	0.14	0.21		1.15	[0.75; 1.74]	1.1%	2.1%
Vinberg et al., 2010	0.58	0.26		1.78	[1.06; 2.98]	0.7%	1.6%
Vrshek-Schallhorn et al., 2014	0.28	0.18		1.33	[0.93; 1.90]	1.5%	2.5%
Fixed effect model				1.14	[1.09; 1.20]	100%	--
Random effects model				1.18	[1.09; 1.28]	--	100%

0.1   0.5 1   2   10

Figure 2

Figure 3

Table 1

Meta-regression estimates

Predictor		*b*	*SE*	*p*-value	95%CI of *b*
Intercept		0.49	0.16	.002	[0.18 ; 0.80]
Sample identification		-0.00	0.00	.515	[-0.01 ; 0.01]
Depression measurement					
Categorical/Dimensional	(a)	-0.02	0.09	.847	[-0.20 ; 0.17]
Interview/Self-report	(b)	-0.16	0.07	.029	[-0.31 ; -0.02]
(a)x(b) interaction		0.10	0.11	.342	[-0.11 ; 0.32]
Stress measurement					
Categorical/Dimensional	(c)	-0.50	0.18	.005	[-0.85 ; -0.15]
Interview/Self-report	(d)	-0.29	0.16	.071	[-0.61; 0.03]
(c)x(d) interaction		0.49	0.19	.009	[0.12 ; 0.85]
Early-life/Late-life stress		-0.01	0.05	.839	[-0.10 ; 0.08]

Note: *b* represents the change in log odds if subgroup changes from e.g. categorical depression measurement to dimensional depression measurement.