

Online article and related content current as of November 5, 2009.

# **Gene-Environment Interactions and Depression**

Karestan C. Koenen; Sandro Galea

JAMA. 2009;302(17):1859-1862 (doi:10.1001/jama.2009.1575)

http://jama.ama-assn.org/cgi/content/full/302/17/1859

Correction	Contact me if this article is corrected. Contact me when this article is cited.
Topic collections	Occupational and Environmental Medicine; Psychiatry; Depression; Stress; Psychiatry, Other; Statistics and Research Methods; Genetics; Genetic Disorders Contact me when new articles are published in these topic areas.

Subscribe http://jama.com/subscribe

Permissions permissions@ama-assn.org http://pubs.ama-assn.org/misc/permissions.dtl Email Alerts http://jamaarchives.com/alerts

Reprints/E-prints reprints@ama-assn.org

## **Gene-Environment Interactions and Depression**

To the Editor: In their meta-analysis, Dr Risch and colleagues<sup>1</sup> concluded that the study of gene-environment interaction in mental disorders should await the identification of "robust marginal gene associations." We believe that this conclusion extends well beyond the data, and an alternate explanation of their findings suggests other courses of action. The absence of replicable findings across studies that assessed both direct genotype-depression associations and gene-environment interactions may be explained by mismeasurement and undermeasurement of relevant environmental contexts.

Two compelling strands of evidence support this hypothesis. First, there is a sharp contrast in the consistency of success in studies that have sought genotype-phenotype associations in animals and in humans. For example, animal models of depression and anxiety disorders have consistently demonstrated genotype-phenotype associations.<sup>2</sup> By contrast, a recent genome-wide association study (GWAS) of depression found no significant associations.<sup>3</sup> One central difference between these 2 research approaches lies in control over potentially relevant environmental exposures. These exposures are effectively randomized in animal models, but such control is absent from observational human gene-hunting studies.

Second, outside the gene-environment literature reviewed by Risch et al,<sup>1</sup> the evidence for environmental modification of genetic effects on human behavior is robust and increasing. The heritability of many phenotypes is modified by environmental factors such as socioeconomic status.<sup>4</sup> Genotype-phenotype associations are also modified by context familiarity in animal models<sup>2</sup> and features of social environments in human studies.<sup>5</sup> Unmeasured aspects of environmental context could contribute to nonreplication of gene-environment findings that at best limit the measurement of environment to life events.

Rather than conducting less research on how genotype and a range of environmental factors jointly produce mental disorders, what is needed is more and better-quality research. Unfortunately, to date GWAS of mental disorders have exclusively tested for genetic main effects, and geneenvironment interaction studies have focused on candidate genes and individual-level measures of environmental exposures. Genome-wide association studies of mental disorders may produce more robust findings if populations were sampled conditional on exposure to a range of plausible environmental risk factors. Gene-environment interaction studies would benefit from moving away from focus on single candidate genes and toward considering multiple levels of environmental exposures. Studies that integrate state-of-the-science methods of measurement of both genetic and environmental factors will provide a more comprehensive test of the role of geneenvironment interaction in mental disorders than a metaanalysis of a single gene–environmental risk factor disorder association.

Karestan C. Koenen, PhD kkoenen@hsph.harvard.edu Department of Society, Human Development, and Health Harvard School of Public Health Boston, Massachusetts Sandro Galea, MD, DrPH Department of Epidemiology School of Public Health University of Michigan Ann Arbor

Financial Disclosures: None reported.

**1.** Risch N, Herrell R, Lehner T, et al. Interaction between the serotonin transporter gene (*5-HTTLPR*), stressful life events, and risk of depression: a meta-analysis. *JAMA*. 2009;301(23):2462-2471.

 Kalin NH, Shelton SE, Fox AS, Rogers J, Oakes TR, Davidson RJ. The serotonin transporter genotype is associated with intermediate brain phenotypes that depend on the context of eliciting stressor. *Mol Psychiatry*. 2008;13(11):1021-1027.

**3.** Muglia P, Tozzi F, Galwey NW, et al. Genome-wide association study of recurrent major depressive disorder in two European case-control cohorts [published online December 23, 2008]. *Mol Psychiatry*. doi: 10.1038/mp.2008 .131.

**4.** Plomin R, DeFries JC, McClearn GE, McGuffin P. *Behavioral Genetics.* 5th ed. New York, NY: Worth Publishers; 2008.

**5.** Koenen KC, Aiello AE, Bakshis E, et al. Modification of the association between serotonin transporter genotype and risk of posttraumatic stress disorder in adults by county-level social environment. *Am J Epidemiol*. 2009;169(6):704-711.

To the Editor: We have some concerns with the metaanalysis by Dr Risch and colleagues,<sup>1</sup> which examined the role of *5-HTTLPR* in moderating the relationship between stress and depression. We agree with the authors that blanket acceptance of a robust and universal interaction between *5-HTTLPR* and stress is unwarranted, and it is premature to translate this into clinical and forensic settings. However, the authors concluded that the original finding

**GUIDELINES FOR LETTERS.** Letters discussing a recent *JAMA* article will have the best chance of acceptance if they are received within 4 weeks of the article's publication date. Letters may have no more than 3 authors. They should not exceed 400 words of text and 5 references. Letters reporting original research should not exceed 600 words and 6 references. They may have no more than 5 authors. All letters should include a word count. Letters must not duplicate other material published or submitted for publication. Letters will be published at the discretion of the editors and are subject to editing and abridgment. A signed statement for authorship criteria and responsibility, financial disclosure, copyright transfer, and acknowledgment is required for publication. Letters not meeting these specifications are generally not considered. Before submitting a Research Letter, please review the Instructions for Authors (http://jama.com/instructions). Letters should be submitted via the *JAMA* online submission and review system at http:// manuscripts.jama.com (note: do not include "www" before the URL). For technical assistance, please contact jama-letters@jama-archives.org.

Letters Section Editor: Robert M. Golub, MD, Senior Editor.

©2009 American Medical Association. All rights reserved.

(Reprinted) JAMA, November 4, 2009–Vol 302, No. 17 1859

## LETTERS

was not confirmed, despite numerous independent positive reports in the literature. Other conclusions should be considered.

First, the studies included in the meta-analysis had notable heterogeneity in measurement of both environment (life events) and outcome (depression). Numerous sources of error measurement, such as recall bias, vaguely worded questions or anchors, and rater bias, can reduce the precision of measurement. Approximately 73% of the participants in this meta-analysis came from cross-sectional/ retrospective studies, often using brief assessments, phone assessments, or both. Examples of studies that can measure environmental stressors with high precision include prospective studies of depression after quantifiable events (eg, job loss, pregnancy, hip fracture, heart disease, cytokine exposure),<sup>2-4</sup> and such studies were excluded from this metaanalysis. A reasonable conclusion is that the authors showed that the likelihood of finding a gene-environment interaction is influenced by study design and that more effort needs to be put into prospective high-precision measurement of both environment and outcome.

Second, many factors may alter or mitigate the geneenvironment interaction. These include age, the timing of stressor (recent stresses vs remote life events), ethnicity, antidepressant medication use, and social supports. It is difficult to interpret the null finding of a meta-analysis that combined all such factors.

Many but not all prospective studies have replicated increased depression incidence in individuals under stress who have the S/S genotype. Rather than conclude that there is no evidence for this, continued prospective research with a greater emphasis on precision and confounding variables is needed. There are preclinical data from animal models, neuroimaging, physiology, and epigenetics,<sup>5</sup> and evidence exists for potential interactions with other genes and other polymorphisms in the serotonin transporter. This accumulating body of evidence may be useful in interpreting past association studies (assessing the mixture of positive and null results) and carefully designing future prospective studies.

Francis E. Lotrich, MD, PhD lotrichfe@upmc.edu University of Pittsburgh Medical Center Pittsburgh, Pennsylvania Eric Lenze, MD Washington University St Louis, Missouri

Financial Disclosures: None reported

1. Risch N, Herrell R, Lehner T, et al. Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. JAMA. 2009;301(23):2462-2471.

**2.** Lotrich FE, Ferrell RE, Rabinovitz M, Pollock BG. Risk for depression during interferon-alpha treatment is affected by the serotonin transporter polymorphism. *Biol Psychiatry*. 2009;65(4):344-348.

**3.** Otte C, McCaffery J, Ali S, Whooley MA. Association of a serotonin transporter polymorphism (5-HTTLPR) with depression, perceived stress, and norepinephrine in patients with coronary disease: the Heart and Soul Study. *Am J Psychiatry*. 2007;164(9):1379-1384.

4. Kendler KS, Kuhn JW, Vittum J, Prescott CA, Riley B. The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression: a replication. Arch Gen Psychiatry. 2005;62(5): 529-535.

5. Canli T, Lesch KP. Long story short: the serotonin transporter in emotion regulation and social cognition. *Nat Neurosci.* 2007;10(9):1103-1109.

To the Editor: In their meta-analysis, Dr Risch and colleagues<sup>1</sup> reported on gene-environment interactions in depressive disorders, focusing on the interaction between the serotonin transporter promoter polymorphism and life events. They stated that "the samples, study designs, measures, and analyses were highly divergent across studies, thereby limiting the comparability of the studies and their evidence regarding replication." However, the authors did not address 2 other problems arising from the methodology of their meta-analysis.

First, although some original studies used a nondichotomized dimensional outcome and thus reported additive interaction effects, the study by Risch and colleagues<sup>1</sup> applied a multiplicative or log-additive model to estimate the interaction effects for a dichotomized outcome in all studies. Thus, studies that previously reported significant gene-environment interaction effects with a dimensional outcome measure in an additive model, such as the study by Grabe et al,<sup>2</sup> lost this effect in a multiplicative model with an arbitrary dichotomization of the outcome. Moreover, for a dichotomized outcome the absence of an interaction in the multiplicative model implies the presence of an interaction in the additive model when both environmental and genetic factors have effects.<sup>3</sup> Therefore, it may have been misleading to apply the same multiplicative model to all studies included in the meta-analysis.

Second, even for a dichotomized outcome an additive measure of an interaction effect is available (relative risk excess due to interaction).<sup>3,4</sup> For a dichotomous outcome, the additive measure, not the multiplicative measure, allows a causal interpretation of the results.<sup>3</sup> Recently proposed versions of the additive measure allow differentiating detailed types of gene-environment interactions on a dichotomous outcome (or outcomes that can be recoded as dichotomous outcome).<sup>3</sup> Among the interaction types, synergism is of great interest because it suggests joint work of the genetic and the environment factors on the outcome. The synergistic action can be identified by applying the corresponding modified measure for an additive interaction effect on a dichotomized outcome.<sup>3</sup>

We recommend the use of additive models for future geneenvironment interaction studies. The use of dichotomized outcomes will additionally allow for the calculation of the relative risk excess due to interaction based on  $4 \times 2$  tables, which should constitute the fundamental core of the statistical analysis of gene-environment interactions.<sup>3-5</sup>

Christian Schwahn, PhD schwahn@uni-greifswald.de Institute of Epidemiology and Social Medicine

1860 JAMA, November 4, 2009-Vol 302, No. 17 (Reprinted)

©2009 American Medical Association. All rights reserved.

#### Hans Jörgen Grabe, MD Department of Psychiatry and Psychotherapy University of Greifswald Greifswald, Germany

Financial Disclosures: Dr Grabe reported receiving research support from the German Research Foundation and the German Federal Ministry of Education and Research; speakers' honoraria from Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Novartis, Eisai, Wyeth, AstraZeneca, Pfizer; and travel funds from Janssen-Cilag, Eli Lilly, Novartis, AstraZeneca, and the SALUS Institute for Trend Research and Therapy Evaluation in Mental Health. Dr Schwahn reported no disclosures.

 Risch N, Herrell R, Lehner T, et al. Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. JAMA. 2009;301(23):2462-2471.

**2.** Grabe HJ, Lange M, Wolff B, et al. Mental and physical distress is modulated by a polymorphism in the 5-HT transporter gene interacting with social stressors and chronic disease burden. *Mol Psychiatry*. 2005;10(2):220-224.

3. Greenland S, Lash TL, Rothman KJ. Concepts of interaction. In: Rothman KJ, Greenland S, Lash TL, eds. *Modern Epidemiology*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008:71-83.

**4.** Grabe HJ, Spitzer C, Schwahn C, et al. Serotonin transporter gene (SLC6A4) promoter polymorphisms and the susceptibility to posttraumatic stress disorder in the general population. *Am J Psychiatry*. 2009;166(8):926-933.

**5.** Botto LD, Khoury MJ. Commentary: facing the challenge of geneenvironment interaction: the two-by-four table and beyond. *Am J Epidemiol*. 2001; 153(10):1016-1020.

To the Editor: Dr Risch and colleagues<sup>1</sup> concluded that the results of a study<sup>2</sup> showing that the serotonin transporter gene (*5-HTTLPR*) genotype moderates the effect of stressful life events on the risk of depression could not be replicated in a meta-analysis of 14 studies. The authors pointed out the importance of replication studies before new findings are translated into clinical and health practices. We believe that it is also important to note that editorial practices of scientific journals may contribute to the lack of attention received by studies that fail to replicate original findings.

The original study<sup>2</sup> was published in 2003 in *Science*, a prominent journal with a very high impact factor that year.<sup>3</sup> In the year following its publication, it was cited 110 times in sources indexed in the Web of Science citation report.<sup>4</sup> In 2005, the first study that failed to replicate the original finding<sup>5</sup> in a sample of 1091 participants was published in *Psychological Medicine*, a specialized journal with a relatively low impact factor. That study was cited 24 times in the following year.

We believe that unless editors actively encourage the submission of null findings, replication studies, and contradictory results alike, the premature uncritical adoption of new findings will continue to influence the way resources are allocated in research and clinical practice settings. Studies that do not replicate an important finding and that meet high methodological standards should be considered for publication by influential journals at the same level as the respective original reports. This will encourage researchers to conduct replication studies and to make primary data easily accessible.

Nina Rieckmann, PhD nina.rieckmann@charite.de Berlin School of Public Health Michael A. Rapp, MD, PhD Department of Psychiatry Jacqueline Müller-Nordhorn, MD, DPH Berlin School of Public Health Charité University Medical Center Berlin, Germany

Financial Disclosures: Dr Rieckmann reported serving as a consultant on contract N01-HC-25197 from the National Heart, Lung, and Blood Institute. Dr Rapp reported receiving research funding from the German Federal Ministry of Health, the German Federal Ministry of Education and Research, the National Institute of Aging, and NARSAD, and receiving speaker honoraria from Janssen Cilag, Pfizer, GlaxoWellcome, and Servier. No other disclosures were reported.

 Risch N, Herrell R, Lehner T, et al. Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. JAMA. 2009;301(23):2462-2471.

**2.** Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science*. 2003;301(5631):386-389.

3. ISI Web of Knowledge journal citation reports [restricted license access]. http: //admin-apps.isiknowledge.com/JCR/JCR . Accessed July 1, 2009.

 ISI Web of Knowledge cited reference search [restricted license access]. http: //apps.isiknowledge.com/WOS\_CitedReferenceSearch\_input.do?product=WOS &SID=S2M5DKKj8LLpjoLiiac&search\_mode=CitedReferenceSearch. Accessed July 1, 2009.

**5.** Gillespie NA, Whitfield JB, Williams B, Heath AC, Martin NG. The relationship between stressful life events, the serotonin transporter (5-HTTLPR) genotype and major depression. *Psychol Med.* 2005;35(1):101-111.

In Reply: We agree with Drs Koenen and Galea and Drs Lotrich and Lenze regarding the importance of consistent environmental measures in studies of gene-environment interaction. However, it is also important to acknowledge the myriad ways an environmental exposure is defined and potentially adjusted to identify an interaction effect in geneenvironment interaction studies when assessing statistical significance. For example, Lotrich and Lenze are critical of our meta-analysis for excluding studies with single heterogeneous life stressors such as job loss, pregnancy, hip fracture, or heart disease. However, exposure to a single life event was not significantly associated with depression in the original study of Caspi et al,<sup>1</sup> in which (as shown in Figure 1 of that article) an interaction with the 5-HTTLPR genotype occurred only among persons with 3 or more stressful life events.

Lotrich and Lenze also fault our analysis for failing to examine the effects of study design (prospective vs retrospective) and potential factors that may confound the association between a stressful life event and depression, such as ethnicity, age, antidepressant medication, and social supports. Our analysis found a consistent effect of stressful life events on depression (10 of 14 studies) irrespective of the method for assessing life events, and the geneenvironment interaction results did not differ by sample size, prospective vs retrospective design, or control for age and ethnicity. The gene-environment interaction effect was no stronger for those studies with vs those without a main effect of stressful life events.

There also appears to be confusion regarding heterogeneity of results among studies and between what constitutes "positive reports" vs "replications." Although we noted significant heterogeneity in the main effect of stressful life events, we found no between-study heterogeneity in the gene-

©2009 American Medical Association. All rights reserved.

(Reprinted) JAMA, November 4, 2009-Vol 302, No. 17 1861

## LETTERS

environment interaction results. While we agree that there have been positive reports, we disagree that these have been replications. Many studies that had reported positive findings were not replications, mostly because the interaction effects occurred in a direction opposite to that first reported<sup>1</sup> or the key study variables had not been assessed in a comparable way. For example, Drs Schwann and Grabe suggest that our interpretation of their study results<sup>2</sup> differed from theirs because of our use of a multiplicative rather than additive model of interaction and dichotomization of their continuous depression scale. Our gene-environment interaction results were in the same direction as their published findings,<sup>2</sup> even though we used the same multiplicative model as in the study by Caspi et al.<sup>1</sup> Furthermore, as Schwann and Grabe point out, the model of interaction is only important when "both environmental and genetic factors have effects." While our meta-analysis yielded strong support for the environmental effect of life events on depression, the most consistent finding across all studies included in our analysis was the lack of effect of 5-HTTLPR on depression. In addition, we also reanalyzed the data submitted to us for meta-analysis by Grabe et al using their continuous depression scale and found no evidence of interaction, using an additive or any other model.

Cited evidence from animal and human experimental studies of stress reactivity has no bearing on the results of our meta-analysis. While such data might provide an increased prior belief that an association should exist, only data from subsequent observational studies in humans can serve to assess the original study associations.

Finally, we agree with Dr Rieckmann and colleagues, who highlight the importance of publication bias and negative reports in adjudging the full spectrum of evidence for replication.

Kathleen Ries Merikangas, PhD kathleen.merikangas@nih.gov Thomas Lehner, PhD Genetic Epidemiology Research Branch National Institute of Mental Health Bethesda, Maryland Neil J. Risch, PhD Institute for Human Genetics University of California at San Francisco

#### Financial Disclosures: None reported

**1.** Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science*. 2003;301(5631):386-389.

2. Grabe HJ, Lange M, Wolff B, et al. Mental and physical distress is modulated by a polymorphism in the 5-HT transporter gene interacting with social stressors and chronic disease burden. *Mol Psychiatry*. 2005;10(2):220-224.

### Postherpetic Neuralgia in Herpes Zoster

To the Editor: In his Clinical Crossroads article discussing herpes zoster, Dr Whitley<sup>1</sup> stated that our Cochrane review<sup>2</sup> reported no benefit of valacyclovir for prevention of postherpetic neuralgia (PHN) at 4 or 6 months after rash onset. However, this is not accurate; our review did not include any trials of valacyclovir.

In addition, Whitley stated that "[p]revention of PHN is a major concern because antiviral drugs alone do not reliably prevent this complication." Although the results of randomized controlled trials and meta-analyses showing that antiviral drugs reduce the risk of developing PHN can be challenged, the overall findings support the use of antiviral therapy for herpes zoster to reduce the duration or incidence of prolonged pain.3 Cut points used to define PHN have ranged from 1 to 6 months after onset of zoster<sup>2,4</sup>; using a definition of PHN as pain present for more than 30 days after the onset of rash caused by herpes zoster, our review<sup>2</sup> indicates that antiviral drugs significantly reduce the incidence of PHN. We also note that recent evidence-based recommendations for the management of patients with herpes zoster recommend using antiviral therapy to decrease the incidence of PHN.3

Muke Zhou, MD Dong Zhou, MD Li He, MD heli2003new@126.com Department of Neurology West China Hospital Chengdu, China

Financial Disclosures: None reported.

1. Whitley RJ. A 70-year-old woman with shingles: review of herpes zoster. JAMA. 2009;302(1):73-80.

2. Li Q, Chen N, Yang J, et al. Antiviral treatment for preventing postherpetic neuralgia. *Cochrane Database Syst Rev.* 2009;15(2):CD006866.

3. Dworkin RH, Johnson RW, Breuer J, et al. Recommendations for the management of herpes zoster. *Clin Infect Dis.* 2007;44(suppl 1):S1-S26.

 Gnann JW Jr, Whitley RJ. Clinical practice: herpes zoster. N Engl J Med. 2002; 347(5):340-346.

**In Reply**: Dr Zhou and colleagues address several points regarding my Clinical Crossroads article. They are correct in noting an inaccuracy in the article regarding their Cochrane review. The sentence in question should have read, "A Cochrane review of antiviral treatment for preventing PHN reported no benefit of acyclovir for reducing the incidence of PHN; there was insufficient evidence to determine the efficacy of other antivirals." A correction appears in this issue of *JAMA*.

I stand by my statement that "[p]revention of PHN is a major concern because antiviral drugs alone do not reliably prevent this complication." The US Food and Drug Administration (FDA), using the definition of PHN cited by Zhou et al, concluded that although treatment may decrease the median duration of pain (as a continuum), the data from well-controlled clinical trials did not provide evidence of reduction of PHN for any of the licensed drugs: acyclovir,<sup>1</sup> valacyclovir,<sup>2</sup> or famciclovir.<sup>3</sup> The FDA refused to grant this indication based on its analyses and input from advisory committees.

1862 JAMA, November 4, 2009-Vol 302, No. 17 (Reprinted)

©2009 American Medical Association. All rights reserved.