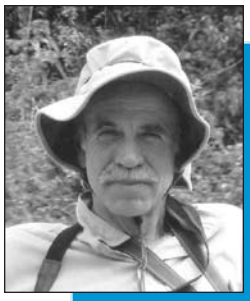
THE BIOLOGICAL ROOTS OF CHILD PSYCHIATRY

GxE Depression Hypothesis Challenged: Researchers Reply



Gene x environment interplay is central to our understanding of the mechanisms of development – the basic science of child and adolescent psychiatry.

Douglas A. Kramer, M.D., M.S.

In 2003, Terrie Moffitt and Avshalom Caspi published in the journal *Science* one of the landmark studies in our understanding of the interplay between the individual genome and the environment (GxE) with respect to that interplay and the risk of developing major depression.[1] The abstract from that report states, *"In a prospective-longitudinal study of a representative birth cohort, we tested why stressful experiences lead to depression in some people but not in others. A functional polymorphism in the promoter region of the serotonin transporter (5-HT T) gene was found to moderate the influence of stressful life events on depression. Individuals with one or two copies of the short allele of the 5-HT T promoter polymorphism exhibited more depressive symptoms, diagnosable depression, and suicidality in relation to stressful life events than individuals homozygous for the long allele. This epidemiological study thus provides evidence of a gene-by-environment interaction, in which an individual's response to environmental insults is moderated by his or her genetic makeup."*

Their collaboration on this and other GxE studies has been reported previously in this column, and elsewhere. Gene x environment interplay is central to our understanding of the mechanisms of development – the basic science of child and adolescent psychiatry. In June 2009, *JAMA* reported on a meta-analysis, the results of which appear to contradict the findings of Moffitt and Caspi with respect to this interplay and the risk of depression. Risch and colleagues conclude,[2] *"This meta-analysis yielded no evidence that the serotonin transporter genotype alone or in interaction with stressful life events is associated with an elevated risk of depression in men alone, women alone, or in both sexes combined."*

Journalists who contacted Drs. Moffitt and Caspi after the publication of the *JAMA* report were given the following information, reprinted here by permission. *The New York Times* reported the *JAMA* findings, but simply noted that Dr. Caspi recommended more research into GxE. For no reason that I can ascertain, a Google search turned up only a blog "intended primarily for other attorneys" that did quote their response. This almost universal lack of interest is baffling. *AACAP News* is the first print publication, and the first medical or scientific publication, to report the entire Moffitt/Caspi response:

Terrie Moffitt and Avshalom Caspi Reply to Risch et al. (June 2009)

"(1) The JAMA article ignores the wider body of scientific evidence. In the past six years, extensive research in experimental neuroscience using both animals and humans has validated the original report by showing that 5-HTTLPR short allele-carriers are excessively vulnerable to stress. Experimental studies that expose human participants to stressors in the laboratory show that individuals having the 5-HTTLPR short genotype have greater stress responses on measures of cognitive reactivity,[3] hormonal reactivity,[4] physiological reactivity,[5] and reactivity in the brain's emotion-circuitry.[6] This vulnerability of 5-HTTLPR short allele carriers has also been confirmed in animal research.[7] Further validation comes from studies which have shown that 5-HTTLPR short allele carriers are vulnerable not only to depression, but also to other mental-health problems caused by stress, including PTSD and anxiety.[8]

"(2) The selection of studies for meta-analysis clearly fails to represent the pool of papers in the literature. Four out of 17 positive replications were included (24%), but six out of nine published negative studies (67%) were also included, a bias that violates a basic requirement of the meta-analysis method to examine a representative sample of the existing literature. Further, the article opted not to analyze several well-designed studies of individuals exposed to stress. For example, studies of children who are victims of abuse,[9, 10] and patients suffering hip fractures, strokes and coronary heart disease[11] have reported positive findings for this GxE hypothesis. Several other positive replications from studies with very strong research designs were omitted from the meta-analysis as well.[12-14]

"(3) Within the smaller subset of studies in the meta-analysis, there is important heterogeneity. The article says this heterogeneity was not statistically significant enough to warrant further investigation. However, we have learned that the test fell just short of statistical significance. One obvious characteristic that varies widely across studies in the meta-analysis is measurement quality. As one example, meta-analysis gives more mathematical weight to studies with the largest samples. But in this case the big studies had to collect their data through telephone calls or self-completed postal questionnaires, which are known to be weak methods of measuring life events and

continued on page 284

depression. Not surprisingly, these big studies with weak measures tended not to find positive results, tilting the meta-analysis toward a null finding. In the existing literature of tests of this GxE hypothesis, 13 studies have replicated the finding, using measures collected in face-to-face clinical assessments, and nine studies failed to replicate the finding, using measures collected via phone or postal questionnaires. This clear methodological pattern, which had been reported online in 2007, was ignored in the meta-analysis.[15] This is one example of heterogeneity that could have been followed up in a meta-analysis. There may be others."

Conclusion

The report in *JAMA* provides an opportunity both to revisit the scientific foundation of GxE interplay, and to reconsider the role of meta-analyses in developing meaning and adding statistical power. Interestingly, the difficulties in finding such meaning from the majority of studies analyzed by Risch and colleagues had been anticipated earlier.[15] Meta-analyses provide unique challenges in the ongoing quest for scientific truth.

References

1. Caspi, A. et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301, 386-9 (2003).

2. Risch, N. et al. Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. JAMA 301, 2462-71 (2009).

3. Beevers, C. G., Gibb, B. E., McGeary, J. E. & Miller, I. W. Serotonin transporter genetic variation and biased attention for emotional word stimuli among psychiatric inpatients. J Abnorm Psychol 116, 208-12 (2007).

4. Gotlib, I. H., Joormann, J., Minor, K. L. & Hallmayer, J. HPA axis reactivity: a mechanism underlying the associations among 5-HTTLPR, stress, and depression. Biol Psychiatry 63, 847-51 (2008).

5. Lonsdorf, T. B. et al. Genetic gating of human fear learning and extinction: possible implications for gene-environment interaction in anxiety disorder. Psychol Sci 20, 198-206 (2009).

6. Hariri, A. R. et al. A susceptibility gene for affective disorders and the response of the human amygdala. Arch Gen Psychiatry 62, 146-52 (2005).

7. Kalin, N. H. et al. The serotonin transporter genotype is associated with intermediate brain phenotypes that depend on the context of eliciting stressor. Mol Psychiatry 13, 1021-7 (2008).

8. Kilpatrick, D. G. et al. The serotonin transporter genotype and social support and moderation of posttraumatic stress disorder and depression in hurricane-exposed adults. Am J Psychiatry 164, 1693-9 (2007).

9. Cicchetti, D., Rogosch, F. A. & Sturge-Apple, M. L. Interactions of child maltreatment and serotonin transporter and monoamine oxidase A polymorphisms: depressive symptomatology among adolescents from low socioeconomic status backgrounds. Dev Psychopathol 19, 1161-80 (2007).

10. Kaufman, J. et al. Social supports and serotonin transporter gene moderate depression in maltreated children. Proc Natl Acad Sci U S A 101, 17316-21 (2004).

11. Kohen, R. et al. Association of serotonin transporter gene polymorphisms with poststroke depression. Arch Gen Psychiatry 65, 1296-302 (2008).

12. Kendler, K. S., Kuhn, J. W., Vittum, J., Prescott, C. A. & 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 62, 529-35 (2005).

13. Drachmann Bukh, J. et al. Interaction between genetic polymorphisms and stressful life events in first episode depression. J Affect Disord (2009).

14. Lazary, J. et al. New evidence for the association of the serotonin transporter gene (SLC6A4) haplotypes, threatening life events, and depressive phenotype. Biol Psychiatry 64, 498-504 (2008).

15. Uher, R. & McGuffin, P. The moderation by the serotonin transporter gene of environmental adversity in the aetiology of mental illness: review and methodological analysis. Mol Psychiatry 13, 131-46 (2008).

Note: Due to *AACAP News* guidelines on the number of references, only examples of each point in the Moffitt/Caspi response have been cited rather than the complete reference list in their response. Please contact either Dr. Kramer or Dr. Moffitt for the full list of references – e-mail addresses below, or their Web site (also below). Dr. Moffitt's gracious assistance with this column is very much appreciated.

Drs. Moffitt and Caspi are Professors, Departments of Psychology and Neuroscience, Psychiatry and Behavioral Sciences, and the Institute for Genome Sciences and Policy, Duke University; Dr. Moffitt is Associate Director, Dunedin Multidisciplinary Health and Development Research Unit, New Zealand. She may be contacted at: terrie.moffitt@duke.edu. Additional information may be found at: www.moffittcaspi.com.

Dr. Kramer is in the Division of Child & Adolescent Psychiatry at the University of Wisconsin School of Medicine and Public Health. He is co-chair of the AACAP Family Committee. He may be contacted at: dakrame1@wisc.edu