

Environmental Risk Factors for Psychopathology

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ABSTRACT

In the past all psychopathologies were viewed as caused by the environment. Later on case-control and family-based studies of major psychiatric disorders found genetic associations, but in many cases these findings did not survive replications. A gene-environment approach gave new hope for possible associations. Gene environment correlations emphasized that the relationship are bidirectional. However, recent meta-analyses raised doubts about the consistency of these findings as well. The review summarizes the current view on the environmental factors in the major psychopathologies.

INTRODUCTION

The views about the role of environmental and genetic risk factors for psychopathology have changed over the years from “extreme environmentalism” through denial to the appearance of critiques of environmental risk mediation, and the concept of a single genetic cause, to the acceptance of the multi-factorial origin of psychopathology, which is the currently prevailing view (1). By agreeing with the multi-factorial origin, the importance of environmental influences was reaccepted without dismissing the genetic influences. The interest in gene-environment interaction was renewed.

Genes interact with environment at a few levels, and some authors emphasized the bilateral influence which was described as gene-environment *correlations* (1). Gene-environment correlations (rGE) refer to the genetic control of exposure to the environment (2). rGE are divided into “passive,” “active” and “evocative” (3). Gene-environment interactions (GXE) refer to genetic

differences in susceptibility to specific environmental risks. In other words, environmental pathogens cause disorder and genes influence susceptibility to pathogens (4). Therefore the relationship between genes and environment is bidirectional: organisms both impact on and are impacted by the environment (5-7). The study of endo-phenotypes instead of the external phenotypic “DSM disorder” may shed light on the difficulties in finding genetic associations in some cases (4).

Psychiatric illnesses are affected by both genetic and environmental factors. The aim of this review is to focus on the environmental effects on psychopathology.

While testing causal hypotheses for psychopathology by twin and adoption studies, a number of counter arguments to the theory of environmentally mediated risks have been raised. Among them were: Measurement issues concerning the possibility of bias resulting from retrospective recall and Bell’s (5) reexamination of socialization effects, where he argued that some of the effects reflected reverse causation, namely the effects of children on their environments rather than the effects on the children of experiences stemming from their upbringing (5).

Two challenges came from behavioral genetics:

1. Plomin and Daniels’ (8) study showing that siblings growing up in the same family tend to differ despite their common environment. Thus, a shared environment may affect children in different ways.
2. Three studies by Plomin, Bergeman and Rowe (9-11) showed that at least some, if not most, of the effects of risk environments were genetically mediated, rather than environmentally mediated (12).

Still, some studies have shown that rearing environments have important effects on psychopathology (13, 14). Also, the critique of Plomin (9), although presenting a serious challenge, did not minimize the importance of environmental mediation, but showed that there is a genetic mediation between environmental risk factors and psychopathology.

As studies continuously demonstrated genetic influences on most types of psychopathology, it became apparent that genetic influences are ubiquitous, with heritability for psychopathology ranging between 20-60%. However, it never reaches 100%. Therefore it points to the existence of non-genetic effects (15, 16).

Additional evidence for the existence of environmental effects can be found in the psychopathology in populations. Over the last half century, there has been a significant increase in the rates of crime and drug use among young people (17). This cannot be explained by changes in the gene pool since such changes require much longer periods of time. Therefore it must be due to environmental influences (15).

Thus the empirical evidence points to the fact that environmentally mediated risk effects are both real and important (18).

MAJOR DEPRESSION (MDD)

Twin studies have demonstrated a role for genetic and environmental factors (19). There is considerable evidence for the familial aggregation of depression in adults (20). A meta-analysis of five recent studies found that first-degree relatives of individuals with MDD have a nearly threefold increase in risk of developing MDD compared with control subjects. The heritability of depressive disorders is around 40% to 50% (21).

Genetically sensitive designs have shown various environmentally mediated effects from specific risk environments for anxiety and depression (7). Kendler, Karkowski, and Prescott (22) referred to negative life events and Pike et al. (23) to family discord and negativity.

Stressful life events such as abuse, poverty or death of a parent are connected with the development of major depression. These events are modulated at least in part via an interaction with genetic predisposition (24-28). This was demonstrated in a study devised by Kendel et al. (29) in which data about stressful life events and the development of major depressive episodes was collected from female-female twin pairs. A monozygotic twin with depressive disorder, as well as her co-twin, constituted those with the highest genetic risks, because they shared all their genes. The fact that both are affected was likely to have been influenced by genetic predisposition.

A monozygotic twin with depressive disorder with a healthy co-twin constituted those with the lowest genetic risks. That is, despite genetic similarity, the co-

twin did not develop depression, therefore the genetic liability was likely to be low.

The results demonstrated that 1. Stressful life events predicted the onset of major depression. 2. The highest probability for a co-twin to develop a depressive disorder after a stressful life event was for those who had high genetic liability (1).

In a prospective longitudinal study by Caspi and colleagues (30), of a birth cohort, the 5HTTLPR polymorphism was found to moderate the impact of stressful life events on depression. The short allele variant was connected with severe depression in relation to stressors. This was replicated in children (26), adolescents (31), and young adults (32). Zalsman et al. (32), in addition to using tri-allelic genotyping of the 5HTTLPR polymorphism, used also a unique rating scale of stressful life events, the St. Paul Ramsey Scale, that takes into account both objective and subjective impact of life events on the individual and not just number of life events in the past.

Two recent meta-analyses one by Risch et al. (33) and one by Munafo et al. (34) with conflicting results on the 5HTTLPR polymorphism interaction with life events raised the question of these studies. Both meta-analyses did not include the tri allelic methodology (32) in their analyses since it was not used by all studies.

ANXIETY DISORDERS AND POST TRAUMATIC STRESS DISORDER (PTSD)

The existence of genetic risk factors has been documented for all major anxiety disorders (35). However, stressful life events also have an etiological effect on the development of anxiety disorders and are likely to have nonspecific effects across disorders (35). For example, sexual abuse in childhood increases the risk for developing generalized anxiety (GAD), panic disorder and other psychopathologies (36, 37). A study by Hettema and others (35-38) found that there are genetic and environmental causes for the comorbidity exhibited in anxiety disorders. Genes predispose to two groups of disorders. One includes GAD, panic disorder, agoraphobia and social phobia while the other includes specific phobias. The remaining associations between the disorders are due to environmental factors (unique and common). Genetic and environmental risk factors for anxiety disorders are similar between men and women (38).

Both quantitative and molecular genetic studies have shown that the relationship between environmental

risks for anxious behaviors is dependent on genetic characteristics (39). Genes increase the likelihood of developing an anxious personality trait by “anxiety sensitivity” (40). When interaction with stressful life events occurs, a threshold for the development of one or more disorders is lower (38).

Relations between stressful life events and later post traumatic stress disorder (PTSD) was well studied by Copeland et al. (41), who conducted a prospective study of 1,420 children. Subjects aged 9, 11 and 13 years at intake were followed up annually through 16 years of age. More than two-thirds of children reported at least one traumatic event by 16 years of age, with 13.4% of those children developing some PTSD symptoms. Few PTSD symptoms or psychiatric disorders were observed for individuals experiencing their first event, and any effects were short-lived. Less than 0.5% of children met the criteria for full-blown DSM-IV PTSD. Violent or sexual trauma was associated with the highest rates of symptoms. The PTSD symptoms were predicted by previous exposure to multiple traumas, anxiety disorders and family adversity. Lifetime co-occurrence of other psychiatric disorders with traumatic events and PTSD symptoms was high, with the highest rates for anxiety and depressive disorders. Researchers concluded that in the general population of children, potentially traumatic events are fairly common and do not often result in PTSD symptoms, except after multiple traumas or a history of anxiety. The prognosis after the first lifetime trauma exposure was generally favorable.

It seems that apart from PTSD, traumatic events are related to many forms of psychopathology, with the strongest links being with anxiety and depressive disorders.

PSYCHOSIS AND SCHIZOPHRENIA

Genetic factors are clearly important in the etiology of schizophrenia, but the environment in which an individual's genes find expression is also crucial to the development of the illness. As the etiology of schizophrenia is unraveled, the picture becomes more complex, but also more obviously relevant to the plight of the individual patient (42). Rates of schizophrenia differ significantly between groups that differ at the social level, e.g., urban/rural comparisons, different neighborhoods, and ethnic minority status (43). More than 10 studies have consistently shown that around one-third of all schizophrenia incidences may be related to environmental factors operating in the urban environment,

and impacting developing children and adolescents to increase the later expression of overt psychotic disorders (44). The effect associated with urban living has grown among more recent birth cohorts, while studies focusing on within-city contrasts have found significant variation in the incidence of schizophrenia associated with neighborhood social characteristics (44).

There is also renewed interest in the relationship between early childhood trauma and risk of psychosis in adulthood. There are a large number of studies of psychiatric inpatients and outpatients in which a majority has psychotic disorders that suggest that the prevalence of childhood trauma in these populations is high. However, these are generally small studies of diagnostically heterogeneous and chronic samples and, as such, can tell us very little about whether childhood trauma is of etiological importance in psychosis (45). Compelling evidence from several countries points to a higher risk of developing schizophrenia and other psychotic disorders among migrant groups (46). Finally, Cougnard et al. (47) suggested that environmental risks for psychosis act cumulatively, and that the level of environmental risk combines synergistically with non-clinical developmental expressions of psychosis to cause pathology and, eventually, need for care.

It is well known that cannabis use is associated with poor outcome in existing schizophrenia and may precipitate psychosis in individuals with preexisting liability. To investigate the overall effect size and consistency of the association between cannabis and psychosis, Henquest et al. (48) performed a meta-analysis from prospective studies and found a pooled odds ratio of 2.1 that could not be explained by confounding or reverse causality. Cannabis is a clear environmental risk factor for psychosis, although evidence suggests that mechanisms of gene-environment interaction are most likely to explain this association (48).

SUICIDE

Suicide is a destructive act of aggression directed towards the self, and is often associated with violent and impulsive traits (49). Adoption studies suggest that there may be a genetic susceptibility to suicide, which is mostly independent of the presence of a psychiatric disorder (50-52). Zalsman et al. published two family based studies of the genetics of suicidality. The first examined the TPH gene polymorphism in 88 adolescents who had recently attempted suicide (53) and

the second examined the association of 5-HTTLPR with suicidal behavior and related traits in 48 Israeli suicidal adolescent inpatients using the HRR method (54). Review of the current literature on the genetics of suicidal behavior shows that no single cause has yet been identified as being significantly associated with suicidality, even when family-based methods are used. However, association to some suicide-related traits (e.g., violence, depression) was reported when multiple measures were applied (55).

The equifinality approach conceptualizes behavior as an outcome of many etiologies, which include, beside genetics, negative life events, non-adaptive cognitions and cognitive style, abnormal affect regulation, low self esteem, neuroendocrine dysregulation and defects in brain structure (56). Environmental factors such as negative life events may act as a significant contributor to suicidal behavior. However, in many cases the exposure to the same environmental stress does not result in increased suicidality (57). A recent cross-sectional sample of Canadian youth between the ages of 12 and 15 revealed statistically significant correlations between suicide ideation and some lesser examined socially based measures. In particular, ability to communicate feelings, negative attachment to parents/guardians, taunting/bullying or abuse, and presence of deviant peers were significant predictors of suicidal ideation illustrating the importance of environmental factors (54). Future studies aim to identify and resolve complex patterns and mechanisms of neurobiological gene-environment interactions, which may contribute to suicide (57).

In summary, environmental risk factors have an important role in psychiatric disorders. Both genetic and environmental risks participate in the development of psychopathology by bi-directional interplay. Large meta-analyses raised the question whether the simple GxE interaction can explain genetic vulnerability to specific psychiatric disorders (58). It seems that there are more factors to add to the equation, for example the time window in which the environmental risk was introduced during development, gender and other factors (59). The field of environmental influences, especially childhood maltreatment and trauma, on psychopathology will be the center of research in the next decade.

References

- Rutter M, Moffitt TE, Caspi A. Gene-environment interplay and psychopathology: multiple varieties but real effects. *J Child Psychol Psychiatry* 2006; 47:226-261.
- Kendler KS, Eaves LJ. Models for the joint effect of genotype and environment on liability to psychiatric illness. *Am J Psychiatry* 1986;143: 279-289.
- Plomin R, DeFries JC, Loehlin JC. Genotype-environment interaction and correlation in the analysis of human behavior. *Psychol Bull* 1977; 84: 309-322.
- Caspi A, Moffitt TE. Gene-environment interactions in psychiatry: Joining forces with neuroscience. *Nat Rev Neurosci* 2006;7:583-590.
- Bell RQ. A reinterpretation of the direction of effects in studies of socialization. *Psychol Rev* 196 ;75:81-95.
- Wachs TD, Plomin RE. Conceptualization and measurement of organism-environment interaction. Washington, DC: American Psychological Association, 1991.
- Rutter M. Environmentally mediated risks for psychopathology: Research strategies and findings. *J Am Acad Child Adolesc Psychiatry* 2005; 44: 3-18.
- Plomin R, Daniels D. Why are children in the same family so different from one another? *Behavioral Brain Sci* 1987; 10:1-15.
- Plomin R. Genetics and experience: The interplay between nature and nurture. Thousand Oaks, Cal.: Sage, 1994.
- Plomin R, Bergeman CS. The nature of nurture: Genetic influence on "environmental" measures. *Behavioral Brain Sci* 1991; 14: 373-427.
- Rowe DC. The limits of family influence: Genes, experience and behavior. New York: Guilford, 1994.
- Scarr S. Developmental theories for the 1990s: Development and individual differences. *Child Dev* 1992;13:19-31.
- Rutter M. Psychosocial influences: Critiques, findings, and research needs. *Dev Psychopathol* 2000;12:375-405.
- Rutter M. Maternal deprivation. In: Bornstein MH, editor. *Handbook of parenting: Vol. 4. Social Conditions and Applied Parenting*, 2nd ed., Mahwah, N.J.: Erlbaum, 2002: pp. 181-202.
- Rutter M, Pickles A, Murray R, Eaves L. Testing hypotheses on specific environmental causal effects on behavior. *Psychol Bull* 2001; 127: 291-324.
- Rutter M, Dunn J, Plomin R, Simnoff E, Pickles A, Maughan B, Ormel J, Meyer J, Eaves LJ. Integrating nature and nurture: Implications of person-environment correlations and interactions for developmental psychopathology. *Dev Psychopathol* 1997; 9: 335-364.
- Rutter M, Smith D, editors. *Psychosocial disorders in young people: Time trends and their causes*. Chichester, England: Wiley, 1995.
- Kendler KS, Baker JH. Genetic influences on measures of the environment: A systematic review. *Psychol Med* 2007; 37:615-626.
- Zalsman G, Huang YY, Oquendo MA, et al. Association of a triallelic serotonin transporter gene promoter region (5-HTTLPR) polymorphism with stressful life events and severity of depression. *Am J Psychiatry* 2006;163: 1588-1593.
- Zalsman G, Oquendo MA, et al. Neurobiology of depression in children and adolescents. *Child Adolesc Psychiatry Clin N Am* 2006;15: 843-868.
- Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. *Am J Psychiatry* 2000; 10: 1552-1562.
- Kendler S, Karkowski LM, Prescott CA. Causal relationship between stressful life events and the onset of major depression. *Am J Psychiatry* 1999; 156: 837-841.
- Pike A, McGuire S, Hetherington EM, Reiss D, Plomin R. Family environment and adolescent depression and antisocial behavior: A multivariate genetic analysis. *Dev Psychol* 1996; 32: 590-604.
- Kendler KS, Karkowski-Shuman L. Stressful life events and genetic liability to major depression: Genetic control of exposure to the environment? *Psychol Med* 1997; 27:539-547.
- Kendler S, Prescott CA. A population-based twin study of life time major depression in men and women. *Arch Gen Psychiatry* 1999; 56:39-44.
- Kaufman J, Yang BZ, Douglas-Palumberi H, Houshyar S, Lipschitz D, Krystal JH, Gelernter J. Social supports and serotonin transporter gene moderate depression in maltreated children. *Proc Natl Acad Sci USA* 2004; 11:17316-17321.
- Moffitt TE, Caspi A, Rutter M. Strategy for investigating interactions between measured genes and measured environment *Arch Gen Psychiatry* 2005; 62:473-481.
- Paykel ES. Life events and affective disorders. *Acta Psychiatr Scand Suppl* 2003; 418: 61-66.
- Kendler S, Kesler RC, Walters EE, MacLean C, Neale MC, Heath AC, Eaves LJ.

- Stressful life events, genetic liability, and onset of an episode of major depression in women. *Am J Psychiatry* 1995;152: 833-842.
30. 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;301:386-389.
 31. Eley TC, Sugden K, Corsico A, et al. Gene-environment interaction analysis of serotonin system markers with adolescent depression. *Mol Psychiatry* 2004;9:908-915.
 32. Zalsman G, Huang Y, Oquendo M, Burke AK, Hu XZ, Brent DA, et al. A triallelic serotonin transporter gene promoter polymorphism (5-HTTLPR), stressful life events and severity of depression. *Am J Psychiatry* 2006;163:1588-1593.
 33. Risch N, Herrell R, Lehner T, Liang KY, Eaves L, et al. Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. *JAMA* 2009;301: 2462-2471.
 34. Munafò MR, Durrant C, Lewis G, Flint J. Gene X environment interactions at the serotonin transporter locus. *Biol Psychiatry* 2009;65:211-219.
 35. Hettema JM, Neale MC, Kendler S. A review and meta-analysis of the genetic epidemiology of anxiety disorders. *Am J Psychiatry* 2001;158: 1568-1578.
 36. Fergusson DM, Horwood LJ, Lynskey MT. Childhood sexual abuse and psychiatric disorder in young adulthood, II: Psychiatric outcomes of childhood sexual abuse. *J Am Acad Child Adolesc Psychiatry* 1996; 35: 1365-1374.
 37. Kendler KS, Bulik C, Silberg J, Hettema JM, Myers J, Prescott CA. Childhood sexual abuse and adult psychiatric and substance use disorders in women: An epidemiological and cotwin control analysis. *Arch Gen Psychiatry* 2000;57:953-959.
 38. Hettema JM, Prescott CA, Myers JM, Neale MC, Kendler KS. The structure of genetic and environmental risk factors for anxiety disorders in men and women. *Arch Gen Psychiatry* 2005;62:182-189.
 39. Lau JYF, Pine DS. Elucidating mechanisms of gene-environment interactions on pediatric anxiety: Integrating findings from neuroscience. *Eur Arch Psychiatry Clin Neurosci* 2008;257:97-106.
 40. Stein MB, Schork NJ, Gelernter J. Gene-by-environment (serotonin transporter and childhood maltreatment) interaction for anxiety sensitivity, an intermediate phenotype for anxiety disorders. *Neuro Psychopharmacol* 2008; 33:312-319.
 41. Copeland WE, Keeler G, Angold A, Costello EJ. Traumatic events and posttraumatic stress in childhood. *Arch Gen Psychiatry* 2007;64:577-584.
 42. Dean K, Murray RM. Environmental risk factors for psychosis. *Dialogues Clin Neurosci* 2005;7:69-80.
 43. Allardyce J, Boydell J. Review: The wider social environment and schizophrenia. *Schizophr Bull* 2006;32: 592-598.
 44. Krabbendam L, Van Os J. Schizophrenia and urbanicity: A major environmental influence - conditional on genetic risk. *Schizophr Bull* 2005;31: 795-799.
 45. Morgan C, Fisher H. Environment and schizophrenia: Environmental factors in schizophrenia: Childhood trauma - a critical review. *Schizophr Bull* 2007; 33: 3-10.
 46. Fearon P, Morgan C. Environmental factors in schizophrenia: The role of migrant studies. *Schizophr Bull* 2006;32: 405-408.
 47. Cougnard A, Marcelis M, Myin-Germeys I, De Graaf R, Vollebergh W, Krabbendam L, et al. Does normal developmental expression of psychosis combine with environmental risk to cause persistence of psychosis? A psychosis proneness-persistence model. *Psychol Med* 2007;37: 513-527.
 48. Henquet C, Murray R, Linszen D, van Os J. The environment and schizophrenia: The role of cannabis use. *Schizophr Bull* 2005;31:608-612.
 49. Apter A, van Praag HM, Plutchik R, Sevy S, Korn M, Brown SL. Interrelationships among anxiety, aggression, impulsivity, and mood: A serotonergically linked cluster? *Psychiatry Res* 1990;32:191-199.
 50. Roy A. Family history of suicide. *Arch Gen Psychiatry* 1983; 40: 971-974.
 51. Roy A, Segal NL, Centerwall BS, Robinette CD. Suicide in twins. *Arch Gen Psychiatry* 1991;48: 29-32.
 52. Statham DJ, Heath AC, Madden PA, Bucholz KK, Bierut L, Dinwiddie SH, et al. Suicidal behaviour: An epidemiological and genetic study. *Psychol Med* 1998;28:839-855.
 53. Zalsman G, Frisch A, King RA, Pauls DL, Grice DE, Gelernter J, et al. Case control and family-based studies of tryptophan hydroxylase gene A218C polymorphism and suicidality in adolescents. *Am J Med Genet* 2001;105: 451-457.
 54. Zalsman G, Frisch A, Bromberg M, Gelernter J, Michaelovsky E, Campino A, et al. Family-based association study of serotonin transporter promoter in suicidal adolescents: No association with suicidality but possible role in violence traits. *Am J Med Genet* 2001;105: 239-245.
 55. Zalsman G, Frisch A, Apter A, Weizman A. Genetics of suicidal behavior: Candidate association genetic approach. *Isr J Psychiatry Relat Sci* 2002; 39: 252-261.
 56. Faraone SV, Kremen WS, Tsuang MT. Genetic transmission of major affective disorders: Quantitative models and linkage analyses. *Psychol Bull* 1990; 108:109-127.
 57. Wasserman D, Geijer T, Sokolowski M, Rozanov V, Wasserman J. Nature and nurture in suicidal behavior, the role of genetics: Some novel findings concerning personality traits and neural conduction. *Physiol Behav* 2007;92:245-249.
 58. Peter T, Roberts LW, Buzdugan R. Suicidal ideation among Canadian youth: A multivariate analysis. *Arch Suicide Res* 2008;12: 263-275.
 59. Zalsman G. Timing is critical: Gene, environment and timing interactions in genetics of suicide in children and adolescents. *Eur Psychiatry* 2010; 25: 284-286.