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Review

Gene-environment interaction and psychiatric disorders: Review and future directions

Elham Assary[1], John Paul Vincent[1], Robert Keers, Michael Pluess*

Department of Biological and Experimental Psychology, School of Biological and Chemical Sciences, Queen Mary University of London, London, E14NS, United Kingdom

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ABSTRACT

Empirical studies suggest that psychiatric disorders result from a complex interplay between genetic and environmental factors. Most evidence for such gene-environment interaction (GxE) is based on single candidate gene studies conducted from a Diathesis-Stress perspective. Recognizing the short-comings of candidate gene studies, GxE research has begun to focus on genome-wide and polygenic approaches as well as drawing on different theoretical concepts underlying GxE, such as Differential Susceptibility. After reviewing evidence from candidate GxE studies and presenting alternative theoretical frameworks underpinning GxE research, more recent approaches and findings from whole genome approaches are presented. Finally, we suggest how future GxE studies may unpick the complex interplay between genes and environments in psychiatric disorders.

Contents

* Corresponding author.
E-mail addresses: e.assary@qmul.ac.uk (E. Assary), j.p.vincent@qmul.ac.uk (J.P. Vincent), r.keers@qmul.ac.uk (R. Keers), m.pluess@qmul.ac.uk (M. Pluess).
[1] Authors contributed equally to manuscript.

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1. Introduction

The burden of psychiatric disorders is substantial for both affected individuals and society more generally [1]. Mental health disorders currently account for around a third of all disabilities worldwide, with major depressive disorder, identified as the leading global cause of disability [2]. Research on the predictors of mental health disorders has highlighted the importance of environmental stressors such as childhood maltreatment [3–5]. However, since the application of quantitative behavioural genetics methods (i.e., twin studies) to the field of psychiatry several decades ago, most agree that psychiatric disorders are a product of both genetic and environmental influences [6], with heritability estimates ranging from 37% for major depression [7], to 65%-80% for schizophrenia [8,9] and 60%-85% for bipolar disorder [10–12]. Behavioural genetics research also provided first evidence to suggest that psychiatric disorders reflect the result of the *interaction* between genetic and environmental factors rather than independent main effects [13]. In other words, the effect of genetic factors (i.e., heritability) on a disorder can differ as a function of environmental factors (and vice versa). For example, Kendler et al. [14] found that individuals at lowest genetic risk of major depression (i.e., monozygotic twins with an unaffected co-twin) had a 0.5% probability of developing depression if they were not exposed to stressful life events but a 6.2% probability if they experienced adversity (i.e., environmental effects). These probabilities were 1.1% and 14.6%, respectively, for monozygotic twins with high genetic risk for depression (i.e., monozygotic twins with an affected co-twin) showing that genetic vulnerability for depression is moderated by environmental risk factors. Advances in technology over the last 20 years facilitated examination of gene-environment interplay at the level of an individuals' measured DNA rather than statistical estimation based on twin designs. The first GxE study investigating the interaction between a specific gene and adverse environmental influences on the development of psychopathology was reported by Caspi et al.'s [15] seminal study on the interaction between a genetic polymorphism in the monoamine-oxidase A gene (*MAOA)* and childhood maltreatment in the prediction of antisocial behaviour. Results suggested that carriers of the genotype conferring low levels of *MAOA* gene expression showed higher levels of adulthood antisocial behaviour, but only if they also experienced maltreatment in childhood (in the absence of maltreatment they were no more likely to develop problems than those with less vulnerable genotypes).

In what follows, we will present a concise but comprehensive review of the current state of GxE research in the field of psychiatric genetics. The article is organized into three main parts: first, we will present selected findings from early candidate gene studies of major psychiatric disorders together with an overview of theoretical concepts underlying GxE research; second, we will review more recent studies applying genome-wide methodological approaches; and third, we will conclude by providing several suggestions for future research in the field.

1.1. Candidate gene-X-environment (GxE) studies

The serotonin transporter (*SLC6A4)*, monoamine-oxidase A (*MAOA)*, dopamine receptor D4 (*DRD4)* and D2 *(DRD2)*, catechol-O-methyl transferase (*COMT),* and brain-derived neurotrophic factors (*BDNF)* genes are some of the most commonly examined candidate genes in relation to psychiatric disorders (i.e., depression, antisocial behaviour, schizophrenia, and bipolar disorder). Considering the high comorbidity of psychiatric disorders [16] and their shared genetic aetiology, it is not surprising that many of these candidate genes have been examined and associated with multiple disorders. *BDNF*, for example, has been examined and found to be related to depression and bipolar disorder, as well as schizophrenia [17–19]. In the following section we will present selected GxE studies as illustrative examples involving *5-HTTLPR*, *MAOA*, *COMT* and *DRD4* as four of the most commonly studied candidate genes implicated in depression, antisocial behavior, schizophrenia and attention deficit hyperactivity disorder (ADHD).

1.1.1. 5-HTTLPR *and depression*

The serotonin-transporter-linked polymorphic region (*5-HTTLPR*) is a genetic polymorphism in the promoter region of the serotonin transporter gene (*SLC6A4*) [20]. The protein product of this gene (5-HTT) is expressed in the central and peripheral nervous systems and plays a key role in transporting the neurotransmitter serotonin from synapses to presynaptic neurons. The polymorphism consists of a long (l-allele) and a short (s-allele) variant, based on the insertion or deletion of 44 base pairs close to the beginning of the gene's transcription site. The s-allele has been associated with lower and the l-allele with higher levels of serotonin transporter mRNA transcription [21].

Caspi et al. [22] were the first to examine the moderating effects of *5-HTTLPR* on depression within a GxE framework, hypothesizing that the *5-HTTLPR* s-allele may be implicated in depression by moderating the serotonergic response to stress. In their longitudinal study of 1 037 individuals, Caspi et al. [22] showed that individuals with the *5-HTTLPR* s-allele genotype were at higher risk of depression and suicidality compared to those with the l-allele genotype, but only if they had a history of stressful life events or childhood maltreatment. In the absence of these adversities, there was no difference in depression between those with the s-allele and those with the long-allele. More than fifty studies have aimed to replicate these findings, some with more success than others. For example, Eley at al.'s [23] study on 377 adolescent boys and girls showed that a high-risk family environment was associated with higher depressive symptoms, but only in girls with the short allele. In a longitudinal study of 127 adults, Wilhelm et al. [24] reported higher probability of major depression for s-allele carriers in response to adverse life events (but not in the absence of adversity). In a large Spanish prospective cohort study of 737 adults, Cervilla et al. [25] examined the interaction between *5-HTTLPR* and the number of threatening life events in the past six months in the prediction of interview-ascertained diagnosis of depression. They found that individuals homozygous for the s-allele showed higher a propensity than other genotypes for severe depression, but only in the presence of stressful life events.

Nevertheless, other studies have failed to replicate these results. For example, in a cross-sectional study of 1 206 adults Gillespie et al. [26] found no significant interaction between self-reported stressful life events and *5-HTTLPR* genotype in the prediction of depression. Similarly, Surtees et al. [27] in their study of 4 175 adults found no significant interaction between *5-HTTLPR* and self-reported adverse childhood or adulthood experiences in the prediction of past-year major depression. Subsequent *meta*-analysis studies have found both support for [28–30] and against [31–33] the proposed GxE interaction effect between *5-HTTLPR* and stressful life events on depression. Some concluded that GxE effects involving *5-HTTLPR* are likely false positive findings due to studies being underpowered [31,32]. Karg et al. [28], on the other hand, proposed that previous *meta*-analyses [31,32] were biased by stringent study selection criteria given that their *meta*-analysis which included all available studies at the time ($N = 54$), clearly supported GxE in relation to *5-HTTLPR* and childhood maltreatment in the prediction of depression. Furthermore, Uher and McGuffin [30] provided evidence that the lack of robust replication in previous *meta*-analyses was, at least partly, the result of including studies with low quality measures of stressful life events (i.e., retrospective self-report). In the most recent *meta*-analysis which included 31 studies, Culverhouse et al. [33] did not find support for a sig-

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