Published in final edited form as:

Curr Top Behav Neurosci. 2012 ; 12: 441–462. doi:10.1007/7854_2011_184.

19 Gene $\times$ Environment Interaction Models in Psychiatric Genetics

Katja Karg and Srijan Sen

Abstract

Gene-environment (G $\times$ E) interaction research is an emerging area in psychiatry, with the number of G $\times$ E studies growing rapidly in the past two decades. This article aims to give a comprehensive introduction to the field, with an emphasis on central theoretical and practical problems that are worth considering before conducting a G $\times$ E interaction study. On the theoretical side, we discuss two fundamental, but controversial questions about (1) the validity of statistical models for biological interaction and (2) the utility of G $\times$ E research for psychiatric genetics. On the practical side, we focus on study characteristics that potentially influence the outcome of G $\times$ E interaction studies and discuss strengths and pitfalls of different study designs, including recent approaches like Genome-Environment Wide Interaction Studies (GEWIS). Finally, we discuss recent developments in G $\times$ E interaction research on the most heavily investigated example in psychiatric genetics, the interaction between a serotonin transporter gene promoter variant (5-HTTLPR) and stress on depression.

19.1 Introduction

One of the oldest and most enduring questions in psychiatry has been whether mental illness is caused by nature (genes) or nurture (environment). Decades of epidemiology studies have tried to answer this question through twin and adoption studies. These studies have demonstrated a moderate genetic component for some disorders (depression and alcohol dependence) and a high genetic component for others (schizophrenia and autism). The relatively high heritability of psychiatric disorders has prompted investigators to look deeply for direct connections between genes and mental illness. Over the past twenty years, thousands of studies have been performed assessing the direct relationship between genes and mental illness in the form of candidate gene association studies, linkage studies and more recently, genome-wide association studies (GWAS). Despite the intense effort, very few direct genetic effects have been identified [1, 2]. Therefore, during the past 20 years, researchers have increasingly directed their attention to the investigation of interactions between genes and environment, a possibility that has traditionally been understudied in behavioral and psychiatric genetics [3, 4]. In contrast G $\times$ E interactions have been demonstrated consistently in other branches of medicine [5]. In this chapter we aim to give such an introduction, starting with a detailed definition of G $\times$ E interaction. We then discuss two fundamental, but controversial theoretical questions about the validity of statistical models for biological interaction and the utility of G $\times$ E interaction research for the field of psychiatric genetics. Finally, we discuss practical aspects of studying G $\times$ E interactions, with an emphasis on study designs and assessment methods, that may affect the success of G $\times$ E interaction studies and present relevant examples from the field.

19.1.1 What is a G×E interaction?

The term “G×E interaction” stems from regression models that seek to divide the population variance for disorder risk into environmental and genetic parts. Effects of these factors that are independent from one another are called main effects. The main effect of either the genetic or the environmental factor can explain the variance for the disorder entirely (Fig. 19.1a and b) or both factors can coact and explain the variance additively, operating independently alongside each other (Fig. 19.1c). Consider a child with a retinoblastoma, a malignant tumor of the retina caused by an inherited mutation in one allele of the tumor suppressor gene *Rb1*. If the patients’ unaffected eye gets injured through an accident and the eyesight of this patient becomes worse, the genetic and the environmental factor operate together on the same outcome (eyesight), but are not involved in the same biological pathway and fully independent factors. In contrast, in an interaction effect, the factors depend from each other (Fig. 19.1d and e). In biological terms, such a G×E interaction effect occurs when *the effect of exposure to an environmental factor on the disorder status depends on the person’s genotype* [7]. In other words, a G×E interaction is defined by differences of genotypes in susceptibility to environmental exposure [8]. For example, our patient with retinoblastoma has an impaired DNA repair system causing her to be markedly more susceptible to UV compared to an individual without the mutation. By exposure to UV light, tumors develop and worsen the patient’s eyesight. Thus, the effect of the exposure to the environmental factor (radiation) on the outcome (eyesight) depends on the person’s genotype, constituting an example for G×E interaction. G×E interactions can be quantitative, i. e. the exposure to the environmental pathogen increases the disorder risk for all genotypes, but to different extends (Fig. 19.1d) or they can be qualitative, i.e. the exposure to the environmental factor increases the risk for one genotype, but decreases it for another (Fig. 19.1e) [9]. With respect to our previous example, a qualitative interaction would occur if UV radiation decreases the risk for retinoblastoma for one genotype, whereas it would increase it for another.

19.1.2 Other forms of Gene-Environment Co-Action: G-E correlations (rGE)

Genes and environmental factors can co-act in different ways, and not all of them are $G \times E$ interactions [see 7, for details]. Gene-environment correlations (rGE) are of particular importance, because they can produce false positive findings in G×E interaction research. rGE can occur when a person’s genotype influences her probability of exposure to environmental risks [10, 11]. Several mechanisms have been proposed to drive rGE [12, 10]. In active rGE an individual actively selects her environment according to her (genetically influenced) traits and behaviors. For instance, an individual characteristically risk seeking and impulsive may be much more prone to risk environments than a cautious individual. The presence of rGE has been demonstrated through twin and adoption studies for a wide range of factors, including the occurrence of life events, such as divorce, job loss and serious accidents [11, 2]. The common nature of rGE underscores the danger in the independence assumption of genotype and environment in G×E interaction research. This assumption can be a major problem for some study designs, in particular case-only studies [12] (further details below).

19.2 Theoretical Considerations for G×E Interaction Studies

There are two fundamental, theoretical questions about G×E interaction studies that are currently the subject of considerable debate in the literature: 1) whether the current state of our knowledge about the neurobiology underlying psychiatric disorders allows us to explore G×E interactions in a meaningful way. 2) Whether the expected benefits derived from this research are important enough to justify the considerable resources that these studies require. We address both questions here and try to accurately represent the two opposing camps in the discussion.

19.2.1 Can we model G×E interaction in statistics?

Although the biological definition of G×E interaction is straightforward, its implementation into statistics is far less clear. Two models are commonly used, the additive and the multiplicative model. The additive model constitutes a G×E interaction when the disorder risk if exposed to both the risk gene (G) and the risk environment (E) differs from the *sum* of the risks if exposed only to G or to E (*Table 1). In biological terms, this is equivalent to the deviation from a simple additive main effects model. This model is used for continuous outcomes, such as depression scores. The multiplicative model constitutes a G×E interaction when the disorder risk if exposed to both G and E differs from the *product* of the risks if exposed only to G or to E. This is used for categorical outcomes, e.g. diagnosis of depression with the two categories “depressed” and “non-depressed”. The biological meaning of a multiplicative model is hard to grasp and most researchers argue that the additive model better reflects biological concepts [13]. The problem is that in some cases, a study result might deviate significantly from a multiplicative model, but not from an additive model, and vice versa [14] (Table 19.1a and b). This is particularly problematic as continuous outcomes can be converted to categorical outcomes by setting an arbitrary threshold. Given sufficient statistical power, this threshold can be chosen so that either of both models indicate a significant interaction effect. Some researchers argue that this model-dependency renders positive G×E interaction findings arbitrary [15] and testing for interactions across multiple models is therefore “no different from trawling through many statistical tests looking for those that are significant” [14]. Therefore, the statistical model to be tested should be carefully selected a priori, based on biological background considerations, and thresholds for categorical data should be set before the analysis. Unfortunately, our current knowledge about neurological pathways is very limited, and, as a result, it is still unclear which statistical model is appropriate [16]. This situation has caused some leaders to conclude that we might be unable to move back and forth between statistical and biological interaction models [14]. The debate remains controversial [17, 18, 2, 15]. One way that investigators have used to circumvent this statistical problem is by utilizing new study designs such as case-only or exposed-only designs. These designs do not rely on testing statistical interactions, but directly test differences in exposure rate (case-only design) or in disorder status (exposed-only design) between genotype groups. To date, these designs have mostly been applied in psychiatric G×E interaction research to investigate the interaction between a serotonin transporter gene promoter variant (5-HTTLPR) and stress on the risk of depression [19], with mostly positive results [20].

19.2.2 Is G×E interaction research worth the effort?

There are three primary arguments for why the identification of G×E interaction effects will substantially advance the field. First, they can help identify new genetic and environmental main effects associated with psychiatric disorders [21]. Some risk genes and environments might be masked from detection in scans for direct genes-to-disorder or environment-to-disorder associations because of genotype-specific environmental effects on the disorder status due to G×E interactions. Second, knowledge about the interaction effect of gene and environment on a psychiatric disorder might enhance the identification of the biological pathway underlying the interaction by revealing the genetic and environmental factors involved and thus channel neuroscience studies in a productive direction [17]. Third, G×E interaction findings may have clinical relevance and drive the development towards personalized medicine or individual lifestyle recommendations based on the genetic profile [22, 23]. They could explain differences in response to pharmacological and psychological treatments by differences in the susceptibility of genotypes to environmental factors. Individuals with high-susceptibility genotypes could be identified and prevented from suffering exposure to the relevant environmental pathogens.

Several researchers have criticized this optimistic view, pointing out that the G×E interaction effects identified to date are small, with odds ratios generally between 0.67 and 1.5 [24], limiting the potential influence of G×E interaction on advances in psychiatric genetics and clinical practice [25, 26, 15]. In particular, the power for finding main effects might only marginally increase by including G×E interaction effects in the statistical model [18] [27]. In addition, G×E findings might help identify the underlying biological pathway only through the detection of qualitative G×E interactions, a case known to be rare in epidemiology [16]. Thus, there is an ongoing debate about the benefit of G×E interaction research and the considerable amounts of resources spent in the field [14, 23, 26].

19.3 Practical Considerations for G×E Interaction Studies

Investigating G×E interactions is challenging. For each participating subject, detailed information from three distinct domains is needed: (1) genotype, (2) environmental exposure, (3) psychiatric disorder status. Fortunately, it has become increasingly inexpensive to reliably determine the genotypes of large numbers of subjects due to improved molecular genetic techniques. Gathering valid information in the domains of environmental exposure and disorder status however, remains expensive and time consuming. This mismatch has led to an increasing number of studies where a huge sample of subjects is genotyped but the quality of phenotype information is comparatively poor. Further, researchers have taken advantage of declined genotyping costs by adding genotype data to studies originally not designed for G×E interaction research [28]. Here we give a brief overview on the consequences of these trends and the other methodological issues associated with G×E interaction research. We will present different study design approaches, each with particular advantages and limitations as well as examples from the psychiatric genetics literature (Table 2*). For further detailed information on G×E interaction testing see [17], [14] and [29]. A complementary research guideline can be found in [1, 7].

19.3.1 Methodological issues in G×E interaction research

Three major methodological confounding issues are important to consider in planning G×E interaction research: Selection bias, population stratification and recall bias. Selection bias can occur when cases and controls are not drawn from the same underlying population, resulting in erroneous conclusions about associations between genotype, environmental exposure and disorder risk [30]. For example, gene-environment correlations can arise in a situation where the presence of a specific genotype group is correlated with exposure to a particular risk environment. This can result in an overrepresentation of cases with this genotype group and therefore steer the study outcome towards false positive findings regarding differences between cases and controls. Population stratification is the presence of a systematic difference in allele frequencies between subpopulations in a population possibly due to different ancestry [30]. Specifically, populations differ with regard to allele frequencies at loci throughout the genome. If these populations also differ in their prevalence of the disorder of interest, spurious associations can be found between this disorder and genetic loci that neither affect the relevant disorder nor are linked to a causative loci. Fortunately, methods have been developed to control for stratification, using unlinked genetic markers to identify and correct for population structure [31]. These genomic control methods should be utilized in modern day G×E studies. The third major problem in G×E interaction research is recall bias. Recall bias occurs when subjects cannot accurately recall past events or when particular events become more or less important in retrospect than when they occurred. In particular, patients often overcount potential environmental causes for their disorder, a phenomenon termed mood-congruent memory revision [32, 33]. Recall bias tends to become greater with the greater length of time between the environmental exposure and its report. However, this retrospective forgetting is often selective and its magnitude and character differs between affected and unaffected individuals [34]. The difficulties in overcoming the problem of recall bias in retrospective studies provides the impetus for specific novel study designs that we will discuss in later sections.

19.3.2 Assessment of Environmental Exposure and Disorder Status

An important, but underappreciated factor affecting the power of G×E studies is the assessment method for environmental exposure [28]. Poor measurement quality has been correlated with negative findings [23, 35]. Simulation studies have demonstrated that in G × E interaction studies, moderate decreases in the measurement accuracy of the environmental variable can result in a 20-fold reduction in statistical power to detect interaction effect (Moffitt et al Arch Gen Psych 2005). In line with this simulation result, in a recent meta-analysis on studies investigating the moderating effect of a serotonin transporter gene polymorphism (5-HTTLPR) on the relationship between stressful life events and depression, we found that studies that utilized more intensive stress assessment methods, such as in-person interviews, were more likely to detect an effect than studies that utilized self-report questionnaires (We will discuss the set of 5-HTTLPR-stress studies in more detail in section 19.4). One reason for these findings is likely that the effect of measurement error, such as, recall bias is more pronounced in self-report questionnaires than in personal interviews because trained interviewers can counteract poor recall by using appropriate techniques like life event calendars and memory enhancement [28]. Self-report event checklists have been shown to result in more imprecise information [34]. Objective measurements may also be

superior to self-report questionnaires because they minimize the effects of recall bias by focusing objective information. Further, the objective stressor design reduces between-subject heterogeneity by the use of clearly operationalized and objectively identifiable environmental factors, resulting in an increase of internal validity [28]. These findings underscore the importance of choosing assessment methods for G×E studies carefully. The use of several independent measurements such as self-report, diagnostic interview or informant reports are an excellent possibility to increase the accuracy of assessment (see Caspi et al [19], for a good example). A similar set of methodological considerations applies to the assessment of disorder status. In comparison to many systemic disorders, psychiatric disorders are difficult to diagnose, relying on arbitrary thresholds on symptom severity scales [38]. For instance, a wide range of threshold scores (12 to 23) have been suggested for diagnosing depression with the commonly used Beck Depression Inventory [39, 40]. While commonly used diagnostic instruments for many psychiatric disorders (like depression, alcohol and drug use disorder) have acceptable measurement characteristics, others perform poorly (e.g. panic disorder, obsessive-compulsive disorder, bipolar disorder and schizophrenia), with particularly poor sensitivity (40%) and specificity (89%) for schizophrenia [38].

19.3.3 Study Designs

G×E interaction study designs can broadly be categorized into family-based designs and population-based designs. Both designs have particular strengths and limitations regarding the methodological issues described above (Table 2). Family-based studies generally assess whether there is an greater than expected transmission of specific alleles to affected family members. The specific family-based study design, include twin studies [41], trio designs with an affected individual and both parents [42, 43], and sib designs with one affected and one unaffected sibling or relative [44] [45]. If the frequency of transmission differs between exposed and non-exposed cases, a G×E interaction is present [42]. The main advantages of family-based designs is a per subject increase in power compared to population-based designs, and robustness against population stratification. However, family-based designs have some major drawbacks and that have limited their use. One is that it is often harder to recruit an adequate number of sibling or twin pairs than unrelated subjects, and the unavailability of living parents can limit the scope of trio studies [30]. Further, newer genomic control methods can robustly control for stratification, rendering the primary advantage of family based methods less useful. Therefore, in most cases of G×E interaction research, population-based designs are used.

In contrast to the Family-based design, Population-based design studies generally draw from a set of unrelated subjects. These studies differ according to how these subjects are selected. Subjects can be drawn from a cohort (cohort study design [46]), selected and matched as cases and controls (case-control design [47]), drawn from affected individuals only (case-only design [48]), or from individuals exposed to the environmental risk factor only (exposed-only design [7]).

Cohort study design—In cohort study designs, the sample studied should accurately represent the target population in terms of genotype, exposure rate, and disorder status.

Information can be assessed either once (cross-sectional design) or repeatedly over time (prospective/longitudinal design). When analyzing the data, subjects can be assigned to groups according to their genotype and their exposure rate (e.g., genotype A with low environmental exposure vs. genotype B with low environmental exposure), and disorder frequencies can be compared between these groups. If high follow-up rates are obtained, the prospective cohort design can provide high-quality data because it efficiently handles the three major methodological issues facing G×E studies: it minimizes selection bias, because the disorder usually occurs after subjects are selected [47], it minimizes population stratification by sampling from a defined cohort and it reduces recall bias to a minimum if the baseline information is assessed early in life of the cohort and when it can be followed several times over years [30].

Three of the most important findings in psychiatric G×E interaction research were produced by utilizing through a study utilizing a prospective cohort study design, the Dunedin Multidisciplinary Health and Development Study (Dunedin Longitudinal Study) [49, 19, 50]. The Dunedin Longitudinal Study investigated a large birth cohort of 1,037 children born in 1972/3 in Dunedin, New Zealand. The cohort was first assessed at age three and since then followed up every two years for two decades [51]. Data from this cohort demonstrated significant G×E interaction effects on violent behavior [49], depression [19] and adult psychosis [50]. These landmark studies provide evidence supporting the strength and accuracy of the prospective cohort design.

The downside of this study design is the long time frame necessary to conduct these studies. For instance, the Dunedin Longitudinal Study was started thirty years before the first G×E interaction finding was published. In addition, large samples are needed because the environmental exposure and/or the disorder might be at low prevalence in the cohort [30]. As a result, many investigators opt for quicker and less expensive designs. The cross-sectional modification of the cohort study assesses cohort information only once. Although this design loses some of the advantages of a prospective study, the cost and time frame necessary to carry out the study is often more feasible.

Retrospective case-control—Another inexpensive and popular alternative to the prospective cohort design is the retrospective case-control design. Here, affected subjects with the disorder are selected and matched with subjects who do not have the disorder ('controls'). This procedure allows for the controlled sampling of subjects with disorder and/or environmental exposure, yielding the advantage of increased power compared to cohort studies [52]. Information about past exposure is gathered and the exposure rates and genotype frequencies are compared between cases and controls. Due to the selection and matching process, this design is particularly prone to selection bias and population stratification, especially when the source population for controls is hard to define [30]. The prospective-nested case-control design is a more sophisticated study design that addresses these methodological problems by selecting cases and controls from a predetermined cohort. Compared to a full cohort approach, this design offers substantial reductions in costs and efforts.

Case-only—Recently, investigators have proposed a study design that eliminates the use of control subjects [48, 53]. In the case-only design, affected subjects are selected from the population and grouped according to their genotype and then compared for their exposure rates. In the presence of G×E interaction, some genotypes are more susceptible to the environmental pathogen than others, resulting in an overrepresentation of subjects with environmental exposure in this genotype group. Therefore, differential distributions of exposure rates across genotype groups can be interpreted as a G×E interaction effect. As an example, Mandelli and colleagues [54] utilized the case-only design to investigate the interaction effect of 5-HTTLPR and stress on depression. They studied a sample of 686 patients diagnosed for major depression or bipolar disorder and classified them into six groups according to their genotype and the presence or absence of environmental exposure to life stress in the year before depression onset. On comparing the proportion of the sample exposed between each genotype group, they found a higher proportions of previously exposed subjects in the genotype groups carrying the short allele. The authors interpreted this finding as evidence for higher stress susceptibility of short allele carriers. However, this conclusion has to be viewed with some caution because the case-only design is prone to confounding. Differential distributions in exposure rates across genotypes can also emerge through G-E correlation, with specific genotypes being more likely to be exposed to the environmental factor than others [48]. In this study, it is possible that short allele carriers are more prone to experience stressful situations and that this causes their overrepresentation in the exposed group. The only safe way to rule out this potential bias would be through the verification of the underlying assumption of gene-environment independency. Therefore, the case-only design should be used only if the independency assumption is verified or for exploratory studies [55].

Exposed-only—A related, but subtly different approach that has become increasingly popular is the exposed-only design. Here, subjects exposed to the same environmental factor are selected, grouped according to their genotype and compared for their disorder status. In the presence of G×E interaction, disorder frequencies should be higher in the genotype group with higher susceptibility to the environmental exposure. However, as we discussed concerning the case-only design, this conclusion is only valid in the absence of G-E correlation. An example might illustrate this problem. A recent study utilized an exposed only design to explore a moderating effect of the FKBP5 (FK506 binding protein 5) gene on the relationship between severe injury and peritraumatic dissociation [56]. Peritraumatic dissociation is a evolutionary conserved response to life-threatening events and a risk factor for the development of post-traumatic stress disorder [57]. The study sample consisted of 46 severely injured hospitalized children who were genotyped and compared for their peritraumatic dissociation scores with logistic regression analysis. The study revealed a significant G×E interaction effect of FKBP5 genotype and severe injury on the development of peritraumatic dissociation. However, this finding could have arisen through rGE, with one genotype group, particularly prone to risk-seeking and therefore more likely to suffer severe injury and corresponding peritraumatic dissociation. This could lead to the erroneous conclusion that this genotype is more susceptible to peritraumatic dissociation than others. In this study however, injury severity was taken into account in the statistical analysis, rendering a false positive result due to rGE less likely. Another elegant way to guard against

bias due to rGE is exact matching for exposure across participants [7]. This allows investigators to bypass the model-dependency problem. Hence, the problem of rGE in exposed-only designs is much easier to handle than in case-only designs where additional empirical evidence is needed. The exposed-only design is thus an attractive cost-efficient design that can be used to test G×E interaction for candidate genes as well as for the discovery of unknown risk genes [7].

19.3.4 Genome-Environment wide Interaction Studies (GEWIS)

With the advent of genome-wide association studies (GWAS) it is now possible to genotype up to 1 million SNPs for each participant, allowing investigators to scan the entire genome for relevant genes without prior hypothesis. While most GWAS to date have explored direct associations, groups have begun to modify GWAS to include assessment of environmental variables in order to conduct gene-environment wide interaction studies (GEWIS) [58]. GEWIS allow us to investigate several candidate pathways at once at relatively low costs and hold the promise identify new possible G×E interactions. The greatest challenge for GEWIS involves finding a balance between dismissing true findings through stringent correction for multiple testing and reporting false positive results. [59]. [58]. Without any prior hypothesis it is hard to distinguish false from true positives, especially as interaction effects in complex traits like mental disorders are supposed to be small. However, systematic approaches to the problem are emerging [60, 61] [reviewed in 62]. Despite the great remaining conceptual challenges, GEWIS paired with thorough phenotyping holds promise in producing advances in the field of G×E interaction research.

19.4 Empirical Evidence for G×E Interaction in Psychiatric Genetics

G×E interactions in psychiatric genetics have been reported for various disorders like depression, attention deficit/hyperactivity disorder (ADHD), schizophrenia, obesity and substance use disorders (Table 3). The identified environmental pathogens range from prenatal factors like maternal smoking [63] or maternal alcohol use [64] to factors relevant at birth (e.g. season of birth [65], birth weight [66]) and early development (e.g. childhood maltreatment [19], childhood trauma [67]) to factors affecting adolescence (e.g. cannabis use [50]) and adulthood (e.g. stress [68], physical inactivity [69]). However, track record of replications has often been poor, casting doubt on the validity of these findings [62]. Non-replication can be due to false negative results, false positive results or true heterogeneity between studies. False negative results in psychiatry studies are most often caused by insufficient power, either due to a small sample size or suboptimal phenotyping or genotyping quality. False positive results can often result from multiple testing and population stratification. True heterogeneity occurs if the interaction exists in some populations studied or with some environmental factors studied but not with others. Here, we present the most heavily investigated example in psychiatric G×E interaction research, a G×E interaction between a polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) and both adult stressful life events and childhood maltreatment on the risk of depression [19]. We will discuss conflicting results between studies exploring this interaction and potential reasons for the conflict.

The original study exploring this interaction utilized a prospective-longitudinal cohort design with almost 1,000 children and found that individuals homozygous or heterozygous for the low-expressing short variant of 5-HTTLPR are more susceptible to depression after stress than individuals homozygous for the alternate long variant. The same pattern was found for childhood maltreatment. This study caused a great deal of excitement in G×E interaction research and encouraged further research on this issue. To date, there have been 55 follow-up studies with some confirming the original finding, some finding evidence of higher stress susceptibility of individuals with the alternate long allele, and others finding no interaction effect at all [20]. This inconsistency might be due to the heterogeneity of studies in many relevant aspects. First, studies exploring the relationship between 5-HTTLPR, stress and depression have utilized very different research designs, including longitudinal, cross-sectional, case-control, case-only, exposure-only and family-based designs. Second, studies have measured many different depression phenotypes using diverse assessment strategies, including clinical interviews and self-report checklists, and diverse depression scales, variously yielding both categorical and continuous outcome measures. Third, studies have investigated an extraordinarily varied set of stressors with various assessment methods. For instance, stressors counted in different studies for stressful life events ranged from becoming homeless, and the death of a parent or spouse to growing up in a household with siblings who quarreled or as the child of a father in an unskilled occupation. Other studies used more specific, but highly diverse stressors like stroke survival, hurricane exposure, bullying victimization or childhood maltreatment. To clarify this confusion, three meta-analyses have been carried out to date. The first two [23, 71] concluded that there was no evidence supporting the presence of an interaction. However, these analyses investigated only small subsamples of all 55 studies due to methodological constraints. The latest meta-analysis [20] included all relevant studies and detected stressor type (stressful life events, childhood maltreatment, and specific medical conditions) and stress assessment method (questionnaire, interview, objective) as two critical sources for variability in study outcomes. In particular, studies with childhood maltreatment or specific medical conditions as environmental stressor were more likely to find a significant G×E effect than studies with broader defined stressful life events, as were studies with objective or interview assessment methods for environmental stressors. This again supports the assumption that measurement quality can affect results in G×E research.

Since this original study, further evidence from various fields has emerged [28]. First, several empirical studies link the short 5-HTTLPR variant to stress-sensitive phenotypes like post-traumatic stress disorder [72], posttrauma suicide attempt [73], stress-related sleep disturbance [74] and anxiety [75]. Second, a multitude of neuroimaging studies confirmed increased and faster amygdala reactivity following threat in carriers of the short allele [e.g. 76, 77] and linked it to specific brain anatomy characteristics [e.g. 78, 79]. Third, rhesus macaques carrying the short variant exhibit greater anxiety-related behaviors in response to adverse rearing conditions compared to their conspecifics with the long alternate [80, 81]. Fourth, in addition to 5-HTT knockout mice, 5-HTT knockout rats showed increased anxiety levels in response to stress [82]. Taken together, these outcomes across a wide variety of techniques, models and species as well as the numerous positive G×E studies robustly

demonstrate the interaction effect between stress and 5-HTTLPR genotype on depression and are to date the most intriguing finding of G×E interaction in psychiatric genetics.

19.5 Future directions

Although much progress has been made in the past two decades, many questions in G×E interaction research in psychiatric genetics remain open. New, more carefully conducted epidemiological studies could shed light on these questions. Another major step for clarification is the identification of the biological mechanisms underlying interaction effects. Not much is known about how environmental factors can interact with a person's genotype and her nervous system to moderate the disorder risk. Therefore, joining forces with neuroscience is an important step in making progress in the field [17]. Many epidemiological studies on G×E interaction in psychiatric genetics were motivated by findings of neuroscience research, and positive epidemiological findings, in turn, can stimulate new studies in neuroscience. The interaction between 5-HTTLPR and life stress on depression provides an example where neuroscience studies can illuminate the black box between genes, environment and disorder [83] and confirm and explain epidemiological findings. Another fruitful approach for advances in the understanding G×E interaction might be the collaboration with epigenetic research. Many environmental risk factors operate early in development, and fine-tuning of neuronal pathways is known to be affected by environmental factors [84]. If these epigenetic modifications depend on the person's genotype, a plausible mechanism is constituted for G×E interaction in psychiatric genetics. Epigenetic studies for psychiatric disorders are still in their infancy, and new exciting insights in the interplay of genes and environment on the development of mental disorders are to be awaited.

Summary

Although the fundamental questions about the validity of statistical models for biological interaction and the utility of G×E interaction findings for advances in psychiatric genetics are still highly debated, novel study designs like case-only and exposed-only designs can overcome at least some of the statistical concerns. Study designs differ broadly in their strengths and limitations regarding selection bias, population stratification and recall bias. Previously undetermined study characteristics that might additionally affect the outcome of G×E interaction studies are the assessment methods for environmental exposure and disorder status, as shown for the G×E interaction effect between the serotonin transporter promoter variant and stress on depression. New insights into the interplay between genes and environment on the development of mental disorders may emerge through more carefully conducted G×E interaction studies as well as through collaboration with neuroscience and epigenetic research.

References

1. Moffitt TE, Caspi A, Rutter M. Strategy for investigating interactions between measured genes and measured environments. *Arch Gen Psychiatry*. 2005; 62(5):473–481. [PubMed: 15867100]
2. Rutter M, Moffitt TE, Caspi A. Gene-environment interplay and psychopathology: Multiple varieties but real effects. *J Child Psychol Psychiatry*. 2006; 47(3–4):226–261. [PubMed: 16492258]

3. Caspi, A. Personality development across the life course. In: Damon, W.; Eisenberg, N., editors. *Handbook of child psychology*. Vol. 3. New York: Wiley; 1998. p. 311-388.
4. Scarr S. Developmental theories for the 1990s: Development and individual differences. *Child Dev.* 1992; 63(1):1–19. [PubMed: 1343618]
5. van Os J, Rutten BP, Poulton R. Gene-environment interactions in schizophrenia: Review of epidemiological findings and future directions. *Schizophr Bull.* 2008; 34(6):1066–1082. [PubMed: 18791076]
6. Khoury MJ, Adams MJ Jr, Flanders WD. An epidemiologic approach to ecogenetics. *Am J Hum Genet.* 1988; 42(1):89–95. [PubMed: 3337114]
7. Moffitt TE, Caspi A, Rutter M. Measured gene-environment interactions in psychopathology: Concepts, research strategies, and implications for research, intervention, and public understanding of genetics. *Perspectives on Psychological Sciences.* 2006; 1(1)
8. Kendler KS, Eaves LJ. Models for the joint effect of genotype and environment on liability to psychiatric illness. *Am J Psychiatry.* 1986; 143(3):279–289. [PubMed: 3953861]
9. Ottman R. An epidemiologic approach to gene-environment interaction. *Genet Epidemiol.* 1990; 7(3):177–185. [PubMed: 2369997]
10. Plomin R, DeFries JC, Loehlin JC. Genotype-environment interaction and correlation in the analysis of human behavior. *Psychol Bull.* 1977; 84(2):309–322. [PubMed: 557211]
11. Rutter M, Silberg J. Gene-environment interplay in relation to emotional and behavioral disturbance. *Annu Rev Psychol.* 2002; 53:463–490. [PubMed: 11752493]
12. Jaffee SR, Price TS. Gene-environment correlations: A review of the evidence and implications for prevention of mental illness. *Mol Psychiatry.* 2007; 12(5):432–442. [PubMed: 17453060]
13. Rutter M, Thapar A, Pickles A. Gene-environment interactions: Biologically valid pathway or artifact? *Arch Gen Psychiatry.* 2009; 66(12):1287–1289. [PubMed: 19996033]
14. Kendler KS, Gardner CO. Interpretation of interactions: Guide for the perplexed. *Br J Psychiatry.* 2010; 197(3):170–171. [PubMed: 20807958]
15. Zammit S, Wiles N, Lewis G. The study of gene-environment interactions in psychiatry: Limited gains at a substantial cost? *Psychological Medicine.* 2010; 40:711–716.
16. Thompson WD. Effect modification and the limits of biological inference from epidemiologic data. *J Clin Epidemiol.* 1991; 44(3):221–232. [PubMed: 1999681]
17. Caspi A, Moffitt TE. Gene-environment interactions in psychiatry: Joining forces with neuroscience. *Nat Rev Neurosci.* 2006; 7(7):583–590. [PubMed: 16791147]
18. Munafo MR, Durrant C, Lewis G, Flint J. Gene $\times$ environment interactions at the serotonin transporter locus. *Biol Psychiatry.* 2009; 65(3):211–219. [PubMed: 18691701]
19. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R. Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science.* 2003; 301(5631):386–389. [PubMed: 12869766]
20. Karg K, Burmeister M, Shedden K, Sen S. The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: Evidence of genetic moderation. *Arch Gen Psychiatry.* 2010
21. Kraft P, Yen YC, Stram DO, Morrison J, Gauderman WJ. Exploiting gene-environment interaction to detect genetic associations. *Hum Hered.* 2007; 63(2):111–119. [PubMed: 17283440]
22. Dempfle A, Scherag A, Hein R, Beckmann L, Chang-Claude J, Schafer H. Gene-environment interactions for complex traits: Definitions, methodological requirements and challenges. *Eur J Hum Genet.* 2008; 16(10):1164–1172. [PubMed: 18523454]
23. Uher R, McGuffin P. The moderation by the serotonin transporter gene of environmental adversity in the aetiology of mental illness: Review and methodological analysis. *Molecular Psychiatry.* 2007; 13(2):131–146. [PubMed: 17700575]
24. Manolio TA, Brooks LD, Collins FS. A hapmap harvest of insights into the genetics of common disease. *J Clin Invest.* 2008; 118(5):1590–1605. [PubMed: 18451988]
25. Hunter DJ, Altshuler D, Rader DJ. From darwin's finches to canaries in the coal mine--mining the genome for new biology. *N Engl J Med.* 2008; 358(26):2760–2763. [PubMed: 18579810]

26. Zammit S, Owen MJ, Lewis G. Misconceptions about gene-environment interactions in psychiatry. *Evid Based Ment Health*. 2010; 13(3):65–68. [PubMed: 20682811]
27. Sullivan PF. Spurious genetic associations. *Biol Psychiatry*. 2007; 61(10):1121–1126. [PubMed: 17346679]
28. Caspi A, Hariri AR, Holmes A, Uher R, Moffitt TE. Genetic sensitivity to the environment: The case of the serotonin transporter gene and its implications for studying complex diseases and traits. *Am J Psychiatry*. 2010; 167(5):509–527. [PubMed: 20231323]
29. Rutter M. The interplay of nature, nurture, and developmental influences: The challenge ahead for mental health. *Arch Gen Psychiatry*. 2002; 59(11):996–1000. [PubMed: 12418932]
30. Hunter DJ. Gene-environment interactions in human diseases. *Nat Rev Genet*. 2005; 6(4):287–298. [PubMed: 15803198]
31. Cardon LR, Palmer LJ. Population stratification and spurious allelic association. *Lancet*. 2003; 361(9357):598–604. [PubMed: 12598158]
32. Joormann J, Hertel PT, LeMoult J, Gotlib IH. Training forgetting of negative material in depression. *J Abnorm Psychol*. 2009; 118(1):34–43. [PubMed: 19222312]
33. Schwarz N, Clore GL. Mood, misattribution, and judgments of well-being: Informative and directive functions of affective states. *Journal of Personality and Social Psychology*. 1983; 45(3):513–523.
34. Monroe SM. Modern approaches to conceptualizing and measuring human life stress. *Annu Rev Clin Psychol*. 2008; 4:33–52. [PubMed: 17716038]
35. Uher R, McGuffin P. The moderation by the serotonin transporter gene of environmental adversity in the etiology of depression, 2009 update. *Mol Psychiatry*. 2010; 15(1):18–22. [PubMed: 20029411]
36. Luan JA, Wong MY, Day NE, Wareham NJ. Sample size determination for studies of gene-environment interaction. *Int J Epidemiol*. 2001; 30(5):1035–1040. [PubMed: 11689518]
37. Wong MY, Day NE, Luan JA, Chan KP, Wareham NJ. The detection of gene-environment interaction for continuous traits: Should we deal with measurement error by bigger studies or better measurement? *Int J Epidemiol*. 2003; 32(1):51–57. [PubMed: 12690008]
38. Eaton WW, Hall ALF, MacDonald R, McKibben J. Case identification in psychiatric epidemiology: A review. *Int Rev Psych*. 2007; 19(5):497–507.
39. Nuevo R, Lehtinen V, Reyna-Liberato PM, Ayuso-Mateos JL. Usefulness of the beck depression inventory as a screening method for depression among the general population of finland. *Scand J Public Health*. 2009; 37(1):28–34. [PubMed: 19141552]
40. Canino G, Alegria M. Psychiatric diagnosis - is it universal or relative to culture? *J Child Psychol Psychiatry*. 2008; 49(3):237–250. [PubMed: 18333929]
41. Ottman R. Epidemiologic analysis of gene-environment interaction in twins. *Genet Epidemiol*. 1994; 11(1):75–86. [PubMed: 8013890]
42. Schaid DJ. Case-parents design for gene-environment interaction. *Genet Epidemiol*. 1999; 16(3):261–273. [PubMed: 10096689]
43. Witte JS, Gauderman WJ, Thomas DC. Asymptotic bias and efficiency in case-control studies of candidate genes and gene-environment interactions: Basic family designs. *Am J Epidemiol*. 1999; 149(8):693–705. [PubMed: 10206618]
44. Gauderman WJ, Witte JS, Thomas DC. Family-based association studies. *J Natl Cancer Inst Monogr*. 1999; (26):31–37. [PubMed: 10854483]
45. Ewens WJ, Spielman RS. The transmission/disequilibrium test: History, subdivision, and admixture. *Am J Hum Genet*. 1995; 57(2):455–464. [PubMed: 7668272]
46. Collins FS. The case for a us prospective cohort study of genes and environment. *Nature*. 2004; 429(6990):475–477. [PubMed: 15164074]
47. Yang Q, Khoury MJ. Evolving methods in genetic epidemiology. Iii. Gene-environment interaction in epidemiologic research. *Epidemiol Rev*. 1997; 19(1):33–43. [PubMed: 9360900]
48. Khoury MJ, Flanders WD. Nontraditional epidemiologic approaches in the analysis of gene-environment interaction: Case-control studies with no controls! *Am J Epidemiol*. 1996; 144(3):207–213. [PubMed: 8686689]

49. Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, Taylor A, Poulton R. Role of genotype in the cycle of violence in maltreated children. *Science*. 2002; 297(5582):851–854. [PubMed: 12161658]
50. Caspi A, Moffitt TE, Cannon M, McClay J, Murray R, Harrington H, Taylor A, Arseneault L, Williams B, Braithwaite A, Poulton R, Craig IW. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-o-methyltransferase gene: Longitudinal evidence of a gene $\times$ environment interaction. *Biol Psychiatry*. 2005; 57(10): 1117–1127. [PubMed: 15866551]
51. Silva PA. The dunedin multidisciplinary health and development study: A 15 year longitudinal study. *Paediatr Perinat Epidemiol*. 1990; 4(1):76–107. [PubMed: 2320503]
52. McClelland GH, Judd CM. Statistical difficulties of detecting interactions and moderator effects. *Psychol Bull*. 1993; 114(2):376–390. [PubMed: 8416037]
53. Piegorsch WW, Weinberg CR, Taylor JA. Non-hierarchical logistic models and case-only designs for assessing susceptibility in population-based case-control studies. *Stat Med*. 1994; 13(2):153–162. [PubMed: 8122051]
54. Mandelli L, Serretti A, Marino E, Pirovano A, Calati R, Colombo C. Interaction between serotonin transporter gene, catechol-o-methyltransferase gene and stressful life events in mood disorders. *The International Journal of Neuropsychopharmacology*. 2006; 10(04):437. [PubMed: 16756688]
55. Albert PS, Ratnasinghe D, Tangrea J, Wacholder S. Limitations of the case-only design for identifying gene-environment interactions. *Am J Epidemiol*. 2001; 154(8):687–693. [PubMed: 11590080]
56. Koenen KC, Saxe G, Purcell S, Smoller JW, Bartholomew D, Miller A, Hall E, Kaplow J, Bosquet M, Moulton S, Baldwin C. Polymorphisms in fkb5 are associated with peritraumatic dissociation in medically injured children. *Mol Psychiatry*. 2005; 10(12):1058–1059. [PubMed: 16088328]
57. Ozer EJ, Best SR, Lipsey TL, Weiss DS. Predictors of posttraumatic stress disorder and symptoms in adults: A meta-analysis. *Psychol Bull*. 2003; 129(1):52–73. [PubMed: 12555794]
58. Khoury MJ, Wacholder S. Invited commentary: From genome-wide association studies to gene-environment-wide interaction studies--challenges and opportunities. *Am J Epidemiol*. 2009; 169(2):227–230. discussion 234–225. [PubMed: 19022826]
59. Sebastiani P, Ramoni MF, Nolan V, Baldwin CT, Steinberg MH. Genetic dissection and prognostic modeling of overt stroke in sickle cell anemia. *Nat Genet*. 2005; 37(4):435–440. [PubMed: 15778708]
60. Onkamo P, Toivonen H. A survey of data mining methods for linkage disequilibrium mapping. *Hum Genomics*. 2006; 2(5):336–340. [PubMed: 16595078]
61. Wacholder S, Chanock S, Garcia-Closas M, El Ghormli L, Rothman N. Assessing the probability that a positive report is false: An approach for molecular epidemiology studies. *J Natl Cancer Inst*. 2004; 96(6):434–442. [PubMed: 15026468]
62. Thomas D. Gene-environment-wide association studies: Emerging approaches. *Nat Rev Genet*. 2010; 11(4):259–272. [PubMed: 20212493]
63. Kahn RS, Khoury J, Nichols WC, Lanphear BP. Role of dopamine transporter genotype and maternal prenatal smoking in childhood hyperactive-impulsive, inattentive, and oppositional behaviors. *J Pediatr*. 2003; 143(1):104–110. [PubMed: 12915833]
64. Brookes KJ, Mill J, Guindalini C, Curran S, Xu X, Knight J, Chen CK, Huang YS, Sethna V, Taylor E, Chen W, Breen G, Asherson P. A common haplotype of the dopamine transporter gene associated with attention-deficit/hyperactivity disorder and interacting with maternal use of alcohol during pregnancy. *Arch Gen Psychiatry*. 2006; 63(1):74–81. [PubMed: 16389200]
65. Seeger G, Schloss P, Schmidt MH, Ruter-Jungfleisch A, Henn FA. Gene-environment interaction in hyperkinetic conduct disorder (hd + cd) as indicated by season of birth variations in dopamine receptor (drd4) gene polymorphism. *Neurosci Lett*. 2004; 366(3):282–286. [PubMed: 15288435]
66. Thapar A, Langley K, Fowler T, Rice F, Turic D, Whittinger N, Aggleton J, Van den Bree M, Owen M, O'Donovan M. Catechol o-methyltransferase gene variant and birth weight predict early-onset antisocial behavior in children with attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry*. 2005; 62(11):1275–1278. [PubMed: 16275815]

67. Bradley RG, Binder EB, Epstein MP, Tang Y, Nair HP, Liu W, Gillespie CF, Berg T, Evces M, Newport DJ, Stowe ZN, Heim CM, Nemeroff CB, Schwartz A, Cubells JF, Ressler KJ. Influence of child abuse on adult depression: Moderation by the corticotropin-releasing hormone receptor gene. *Arch Gen Psychiatry*. 2008; 65(2):190–200. [PubMed: 18250257]
68. Blomeyer D, Treutlein J, Esser G, Schmidt MH, Schumann G, Laucht M. Interaction between *crhr1* gene and stressful life events predicts adolescent heavy alcohol use. *Biol Psychiatry*. 2008; 63(2):146–151. [PubMed: 17597588]
69. Andreasen CH, Stender-Petersen KL, Mogensen MS, Torekov SS, Wegner L, Andersen G, Nielsen AL, Albrechtsen A, Borch-Johnsen K, Rasmussen SS, Clausen JO, Sandbaek A, Lauritzen T, Hansen L, Jorgensen T, Pedersen O, Hansen T. Low physical activity accentuates the effect of the *fto* rs9939609 polymorphism on body fat accumulation. *Diabetes*. 2008; 57(1):95–101. [PubMed: 17942823]
70. Greene CS, Penrod NM, Williams SM, Moore JH. Failure to replicate a genetic association may provide important clues about genetic architecture. *PLoS One*. 2009; 4(6):e5639. [PubMed: 19503614]
71. Risch N, Herrell R, Lehner T, Liang KY, Eaves L, Hoh J, Griem A, Kovacs M, Ott J, Merikangas KR. Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: A meta-analysis. *JAMA: The Journal of the American Medical Association*. 2009; 301(23):2462–2471. [PubMed: 19531786]
72. Xie P, Kranzler HR, Poling J, Stein MB, Anton RF, Brady K, Weiss RD, Farrer L, Gelernter J. Interactive effect of stressful life events and the serotonin transporter 5-HTTLPR genotype on posttraumatic stress disorder diagnosis in 2 independent populations. *Arch Gen Psychiatry*. 2009; 66(11):1201–1209. [PubMed: 19884608]
73. Roy A, Hu XZ, Janal MN, Goldman D. Interaction between childhood trauma and serotonin transporter gene variation in suicide. *Neuropsychopharmacology*. 2007; 32(9):2046–2052. [PubMed: 17356577]
74. Brummett BH, Krystal AD, Ashley-Koch A, Kuhn CM, Zuchner S, Siegler IC, Barefoot JC, Ballard EL, Gwyther LP, Williams RB. Sleep quality varies as a function of 5-HTTLPR genotype and stress. *Psychosom Med*. 2007; 69(7):621–624. [PubMed: 17766685]
75. Stein MB, Schork NJ, Gelernter J. Gene-by-environment (serotonin transporter and childhood maltreatment) interaction for anxiety sensitivity, an intermediate phenotype for anxiety disorders. *Neuropsychopharmacology*. 2008; 33(2):312–319. [PubMed: 17460615]
76. Furman DJ, Hamilton JP, Joormann J, Gotlib IH. Altered timing of amygdala activation during sad mood elaboration as a function of 5-HTTLPR. *Soc Cogn Affect Neurosci*. 2010
77. Heinz A, Braus DF, Smolka MN, Wrase J, Puls I, Hermann D, Klein S, Grusser SM, Flor H, Schumann G, Mann K, Buchel C. Amygdala-prefrontal coupling depends on a genetic variation of the serotonin transporter. *Nat Neurosci*. 2005; 8(1):20–21. [PubMed: 15592465]
78. Pacheco J, Beevers CG, Benavides C, McGeary J, Stice E, Schnyer DM. Frontal-limbic white matter pathway associations with the serotonin transporter gene promoter region (5-HTTLPR) polymorphism. *J Neurosci*. 2009; 29(19):6229–6233. [PubMed: 19439600]
79. Pezawas L, Meyer-Lindenberg A, Drabant EM, Verchinski BA, Munoz KE, Kolachana BS, Egan MF, Mattay VS, Hariri AR, Weinberger DR. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: A genetic susceptibility mechanism for depression. *Nat Neurosci*. 2005; 8(6):828–834. [PubMed: 15880108]
80. Barr CS, Newman TK, Shannon C, Parker C, Dvoskin RL, Becker ML, Schwandt M, Champoux M, Lesch KP, Goldman D, Suomi SJ, Higley JD. Rearing condition and *rh5-HTTLPR* interact to influence limbic-hypothalamic-pituitary-adrenal axis response to stress in infant macaques. *Biol Psychiatry*. 2004; 55(7):733–738. [PubMed: 15039002]
81. Spinelli S, Schwandt ML, Lindell SG, Newman TK, Heilig M, Suomi SJ, Higley JD, Goldman D, Barr CS. Association between the recombinant human serotonin transporter linked promoter region polymorphism and behavior in rhesus macaques during a separation paradigm. *Dev Psychopathol*. 2007; 19(4):977–987. [PubMed: 17931429]
82. Homberg JR, Olivier JD, Smits BM, Mul JD, Mudde J, Verheul M, Nieuwenhuizen OF, Cools AR, Ronken E, Cremers T, Schoffeleers AN, Ellenbroek BA, Cuppen E. Characterization of the

serotonin transporter knockout rat: A selective change in the functioning of the serotonergic system. *Neuroscience*. 2007; 146(4):1662–1676. [PubMed: 17467186]

83. Merikangas KR, Risch N. Will the genomics revolution revolutionize psychiatry? *Am J Psychiatry*. 2003; 160(4):625–635. [PubMed: 12668348]
84. Abdolmaleky HM, Smith CL, Faraone SV, Shafa R, Stone W, Glatt SJ, Tsuang MT. Methylomics in psychiatry: Modulation of gene-environment interactions may be through DNA methylation. *Am J Med Genet B Neuropsychiatr Genet*. 2004; 127B(1):51–59. [PubMed: 15108180]

Figure 19.1.

Illustration of main and interaction effects of genes and environmental exposure on disorder risk. Solid line: Genotype A, dashed line: Genotype B. (a) Genetic main effect; (b) Environmental main effect; (c) Additive effect of genes and environmental exposure; (d) Quantitative interaction effect; (e) Qualitative interaction effect.

Table 1

a Examples for disorder risk depending from the absence (–) or presence (+) of exposure to the genetic risk factor (G) and environmental risk factor (E). For example 2, the (G+, E+) field is substituted by 6.

	E–	E+
G–	2	5
G+	3	10 (6)

b Comparison of statistical models for the constitution of a G×E interaction. Example 1 leads to the consistent positive result for G×E interaction across models, whereas example 2 leads to inconsistent results.

	Condition for G×E interaction	Example 1	Example 2
Additive model	Risk (G+, E+) ¹ Risk (G+, E–) + Risk (G–, E+) – Risk (G–, E–)	10 ¹ 3+5–2 G×E present	6 = ¹ 3+5–2 G×E absent
Multiplicative model	Risk (G+, E+) ¹ Risk (G+, E–) × Risk (G–, E+)	10 ¹ 3×5 G×E present	6 ¹ 3×5 G×E present

¹ Statistical significance of the deviation needs to be tested

Table 2

	Description	Advantages	Disadvantages	Further Reading
Family-based Designs	Twin study	Comparison of disorder frequency between twin pairs in different environments	No genetic data required; reduced selection and stratification bias	Ottman 1994
	Trio design	Comparison of expected genes in cases to possibly transmitted genes from both parents, stratified by case's environment	Increased power; reduced selection and stratification bias	Schaid 1999 Witte et al. 1999
	Sib design	Case-control design with unaffected relative as control	Increased power; reduced selection and stratification bias	Gauderman et al. 1999 Laird and Lange 2006
<hr/>				
Traditional population-based Designs	Prospective cohort	Comparison of disorder frequency across groups defined by genotype and environment; exposure assessed previous to diagnosis	reduced selection and stratification bias; reduced recall bias; high-quality measurement for environmental exposure	Boomsma et al. 2002 Collins 2004
	Cross-sectional	Like prospective cohort, but exposure assessed simultaneously with diagnosis	Increased recall bias	Yang and Khoury 1997
	Retrospective case-control	Comparison of genotype frequencies and exposure between cases and controls	Increased selection and cost-efficient compared to cohort designs	Yang and Khoury 1997
Novel population-based Designs	Prospective nested case-control	Comparison of cases with matched non-affected cohort members	Combined advantages of prospective cohort and retrospective case-control designs	Manolio et al. 2006
	Case-only	Comparison of exposure across groups defined by genotype	Increased power compared to case-control; cost-efficient	Khoury and Flanders 1996 Pegorsen et al. 1994
	Exposed-only	Comparison of genotype frequencies across exposed individuals grouped by genotype	Cost-efficient	Moffitt et al. 2006
Two-stage case-control		Like case-control, but additional subsampling for covariate assessment	Increased power for rare disorders or exposures	Goldstein and Andrieu 1999 Breslow and Chatterjee 1999

Joint case-only and case-control	Description	Advantages	Disadvantages	Further Reading
	Bayesian compromise between case-only and case-control	Like case-only, but with increased robustness	Some bias due to confounding with rGE	Thomas 2010

Table 3

Selected G×E interaction findings in psychiatric genetics.

Gene	Gene Product	Location of Variation	Risk environment	Disorder	Original finding	Reviews
SLC6A4	Serotonin transporter	Promoter region 5-HTTLPR	Stressful life events	Depression	Caspi et al. 2003	Uher and McGuffin 2008 Munafò et al. 2009 Risch et al. 2009 Caspi et al. 2010 Karg et al. 2010
SLC6A4	Serotonin transporter	Promoter region 5-HTTLPR	Childhood maltreatment	Depression	Caspi et al. 2003	Caspi et al. 2010 Karg et al. 2010
SLC6A4	Serotonin transporter	Promoter region 5-HTTLPR	Mother's expressed emotion	ADHD	Sonuga-Barke et al. 2009	Wermter et al. 2010
SLC6A4	Serotonin transporter	Promoter region 5-HTTLPR	Early life stress	Alcohol abuse	Ollson et al. 2005	---
MAOA	Neurotransmitter-metabolizing enzyme monoamine oxidase A	Promoter region	Childhood maltreatment	Antisocial personality; Conduct disorder	Caspi et al. 2001	Kim-Cohen et al. 2006
DRD4	Dopamine D4 receptor gene	Exon 3	Priming alcohol doses	Alcohol craving	Hutchison et al. 2002a	Sher et al. 2010
DRD4	Dopamine D4 receptor gene	Exon 3	Smoking cues	Tobacco craving	Hutchison et al. 2002b	Langley et al. 2005
DAT1	Dopamine transporter	3'-UTR	Prenatal maternal smoking	ADHD	Kahn et al. 2003	---
DAT1	Dopamine active transporter	3' of gene	Prenatal maternal use of alcohol	ADHD	Brookes et al. 2006	---
DAT1	Dopamine active transporter	48bp VNTR	Season of birth	ADHD	Seeger et al. 2004	Wermter et al. 2010 Thapar et al. 2010
DAT1	Dopamine active transporter	3'-UTR	Psychosocial adversity in childhood	ADHD	Laucht et al. 2007	---
DAT1	Dopamine active transporter	3'-UTR	Mother's expressed emotion	ADHD	Sonuga-Barke et al. 2009	---
DAT1	Dopamine active transporter	3'-UTR/Intron 8	Institutional deprivation	ADHD	Stevens et al. 2009	---
COMT	Catechol-o-methyltransferase	Codon 158	Cannabis use in adolescence	Adult psychosis	Caspi et al. 2005	Wermter et al. 2010 Thapar et al. 2010
COMT	Catechol-o-methyltransferase	Codon 158	Low birth weight	ADHD	Thapar et al. 2005	---
COMT	Catechol-o-methyltransferase	Codon 158	Stress	Psychosis	van Winkel et al. 2008	---
CRHR1	Corticotropin-releasing hormone receptor 1	rs1876831	Stress	Alcohol abuse	Blomeyer et al. 2008	---
CRHR1	Corticotropin-releasing hormone receptor 1	Various SNPs from promoter region to 3' end	Childhood trauma	Mood and anxiety disorders	Bradley et al. 2008	---
FTO	Fat mass and obesity associated protein	rs9939609	Physical inactivity	Obesity	Andreassen et al. 2008	Andreassen et al. 2009
FKBP5	FK506 binding protein 5	rs3800373 rs1360780	Acute injury	Psychological dissociation	Koenen et al. 2005	---

Gene	Gene Product	Location of Variation	Risk environment	Disorder	Original finding	Reviews
FKBP5	FK506 binding protein 5	Various SNPs	Childhood abuse	Mood and anxiety disorders	Binder et al. 2008	---