Gene × Environment Interaction Models in Psychiatric Genetics

Katja Karg and Srijan Sen

Abstract Gene–environment (G × E) interaction research is an emerging area in psychiatry, with the number of G × 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 × 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 × E research for psychiatric genetics. On the practical side, we focus on study characteristics that potentially influence the outcome of G × 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 × 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.

Keywords Genomic · Stress · Behavior · Serotonin

Contents

K. Karg · S. Sen (✉)
University of Michigan, Ann Arbor, MI, USA
e-mail: srijan@umich.edu

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1 Introduction

One of the oldest and most enduring questions in psychiatry is 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 20 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 (Moffitt et al. 2005; Rutter et al. 2006). Therefore, 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 (Caspi 1998; Scarr 1992). In contrast, G × E interactions have been demonstrated consistently in other branches of medicine (van Os et al. 2008). Hence, G × E interaction research is an emerging discipline in psychiatric genetics with growing numbers of novices in need of a comprehensive introduction to the field. In this chapter we aim to give such an introduction, starting with a detailed definition of G × 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 × E interaction research for the field of psychiatric genetics. Finally, we discuss practical aspects of studying G × E interactions, with an emphasis on study designs and assessment methods that may affect the success of G × E interaction studies, and present relevant examples from the field.

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

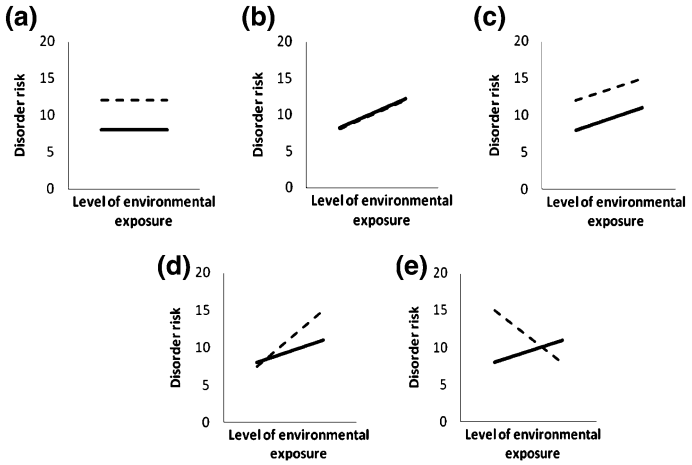

Fig. 1 Illustration of main and interaction effects of genes and environmental exposure on disorder risk. *Solid line* Genotype A, *dashed line* Genotype B. **a** Genetic main effect **b** Environmental main effect **c** Additive effect of genes and environmental exposure **d** Quantitative interaction effect **e** Qualitative interaction effect

main effects. The main effect of either the genetic or the environmental factor can explain the variance for the disorder entirely (Fig. 1a, b) or both factors can coact and explain the variance additively, operating independently alongside each other (Fig. 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. 1d, 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* (Moffitt et al. 2006). In other words, a G × E interaction is defined by differences of genotypes in susceptibility to environmental exposure (Kendler and Eaves 1986). For example, our patient with retinoblastoma has an impaired DNA repair system causing her to be markedly more susceptible to UV light 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. 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. 1e) (Ottman 1990). 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.

1.2 Other Forms of Gene–Environment Co-Action: Gene–Environment Correlations

Genes and environmental factors can co-act in different ways, and not all of them are G × E interactions [see (Moffitt et al. 2006) 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 (Plomin et al. 1977; Rutter and Silberg 2002). Several mechanisms have been proposed to drive rGE (Plomin et al. 1977; Jaffee and Price 2007). 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 (Rutter et al. 2006; Rutter and Silberg 2002). 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 (Jaffee and Price 2007) (further details below).

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.

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. In biological terms, this is equivalent to the deviation from a simple additive main

Table 1 Illustration of the additive and multiplicative model in statistical G × E interaction testing

	E−	E+
(a)		
G−	2	5
G+	3	10 (6)

	Condition for G × E interaction	Example 1	Example 2
(b)			
Additive model	Risk (G+, E+) $\neq^1$ Risk (G+, E−) + Risk (G−, E+) − Risk (G−, E−)	10 $\neq^1$ 3+5−2 (G × E present)	6 $=^1$ 3+5−2 (G × E absent)
Multiplicative model	Risk (G+, E+) $\neq^1$ Risk (G+, E−) × Risk (G−, E+)	10 $\neq^1$ 3 × 5 (G × E present)	6 $\neq^1$ 3 × 5 (G × E present)

In Table a, two numerical examples for disorder risk depending on the absence (−) or presence (+) of exposure to the genetic risk factor (G) and environmental risk factor (E) are given, differing only in the (G+, E+) field. Table b illustrates the statistical problem associated with G × E interaction testing: Whereas example 1 leads to the consistent positive result for G × E interaction across the additive and the multiplicative model, the models yield conflicting results for example 2

[1] Statistical significance of the deviation needs to be tested

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 (Rutter et al. 2009). 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 (Kendler and Gardner 2010) (Table 1a, 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 (Zammit et al. 2010a) and testing for interactions across multiple models is therefore "no different from trawling through many statistical tests looking for those that are significant" (Kendler and Gardner 2010). 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 (Thompson 1991). This situation has caused some leaders to conclude that we might be unable to move back and forth between statistical and biological

interaction models (Kendler and Gardner 2010). The debate remains controversial (Rutter et al. 2006; Zammit et al. 2010a; Caspi and Moffitt 2006; Munafo et al. 2009). One way that investigators have used to circumvent this statistical problem is 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 (Caspi et al. 2003), with mostly positive results (Karg et al. 2010).

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 (Kraft et al. 2007). 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 (Caspi and Moffitt 2006). Third, G × E interaction findings may have clinical relevance and drive the development toward personalized medicine or individual lifestyle recommendations based on the genetic profile (Dempfle et al. 2008; Uher and McGuffin 2007). 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 (Manolio et al. 2008), limiting the potential influence of G × E interaction on advances in psychiatric genetics and clinical practice (Zammit et al. 2010a, b; Hunter et al. 2008). In particular, the power for finding main effects might only marginally increase by including G × E interaction effects in the statistical model (Munafo et al. 2009). 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 (Thompson 1991). Thus, there is an ongoing debate about the benefit of G × E interaction research and the considerable amounts of resources spent in the field (Kendler and Gardner 2010; Uher and McGuffin 2007; Zammit et al. 2010b).

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 (Caspi et al. 2010). 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 (Caspi and Moffitt 2006; Kendler and Gardner 2010 and Rutter 2002). Complementary research guidelines can be found in (Moffitt et al. 2005, 2006).

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 (Hunter 2005). For example, gene–environment correlations can arise in a situation where the presence of a genotype group is correlated with exposure to a particular risk environment. This can result in an overrepresentation of cases with this genotype and therefore steer the study outcome toward 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 (Hunter 2005). 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 (Cardon and Palmer 2003). These genomic control methods should be utilized in modern day G × E studies.

Table 2 Study designs in G × E interaction

	Design	Description	Advantages	Disadvantages
Family-based designs	Twin study	Comparison of disorder frequency between twin pairs in different environments	No genetic data required; reduced selection and stratification bias	High costs and efforts
	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	High costs and efforts
	Sib design	Case-control design with unaffected relative as control	Increased power; reduced selection and stratification bias	High costs and efforts
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	High costs and efforts; time-consuming; Low, possibly biased follow-up rates
	Cross-sectional	Like prospective cohort, but exposure assessed simultaneously with diagnosis	Reduced selection and stratification bias; more cost-efficient compared to prospective cohort design	Increased recall bias
	Retrospective case-control	Comparison of genotype frequencies and exposure between cases and controls	Increased power and more cost-efficient compared to cohort designs	Increased selection and stratification bias; increased recall bias
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	–
	Case-only	Comparison of exposure across groups defined by genotype	Increased power compared to case-control; cost-efficient	High risk of bias due to confounding with rGE
	Exposed-only	Comparison of genotype frequencies across exposed individuals grouped by genotype	Cost-efficient	Risk of bias due to confounding with rGE; increased selection bias

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 (Joormann et al. 2009; Schwarz and Clore 1983). 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 (Monroe 2008). The difficulties in overcoming the problem of recall bias in retrospective studies provide the impetus for specific novel study designs that we will discuss in later sections.

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 (Caspi et al. 2010). Poor measurement quality has been correlated with negative findings (Uher and McGuffin 2007, 2010). 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 (Moffitt et al. 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 Sect. 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 such as life event calendars and memory enhancement (Caspi et al. 2010). Self-report event checklists have been shown to result in more imprecise information (Monroe 2008). 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 (Caspi et al. 2010). 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 excellent possibility to increase the accuracy of assessment (see Caspi et al. (2003), for a good example). A similar set of methodological considerations apply 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 (Eaton et al. 2007). For instance, a wide range of threshold scores (12–23) have been suggested for diagnosing depression with the commonly used Beck Depression Inventory (Nuevo et al. 2009). While commonly used diagnostic instruments for many psychiatric disorders (such as 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 (Eaton et al. 2007).

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 a greater than expected transmission of specific alleles to affected family members (Ewens and Spielman 1995). The specific family-based study designs include twin studies (Ottman 1994), trio designs with an affected individual and both parents (Schaid 1999; Witte et al. 1999), and sib designs with one affected and one unaffected sibling or relative (Gauderman et al. 1999). If the frequency of transmission differs between exposed and non-exposed cases, a G × E interaction is present (Schaid 1999). 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 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 (Hunter 2005). 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, design studies generally draw from a set of unrelated subjects. These studies differ according to how these subjects are selected. Subjects can be can be drawn from a cohort [cohort study design (Collins 2004)], selected and matched as cases and controls [case-control design (Yang and Khoury 1997)], drawn from affected individuals only [case-only design (Khoury and Flanders 1996)], or from individuals exposed to the environmental risk factor only [exposed-only design (Moffitt et al. 2006)].

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 (Yang and Khoury 1997), 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 (Hunter 2005).

Three of the most important findings in psychiatric G × E interaction research were produced by utilizing through a study a prospective cohort study design, the Dunedin Multidisciplinary Health and Development Study (Dunedin Longitudinal Study) (Caspi et al. 2002, 2003, 2005). The Dunedin Longitudinal Study investigated a large birth cohort of 1,037 children born in 1972–73 in Dunedin, New Zealand. The cohort was first assessed at age three and since then followed up every two years for two decades (Silva 1990). Data from this cohort demonstrated significant G × E interaction effects on violent behavior (Caspi et al. 2002), depression (Caspi et al. 2003) and adult psychosis (Caspi et al. 2005). 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 30 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 (Hunter 2005). 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 (McClelland and Judd 1993). 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 (Hunter 2005). 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 longitudinal cohort. As cases and controls stem from the same cohort, confounding from selection bias and population stratification is avoided. In addition, recall bias is eliminated because exposure is assessed

before the diagnose. 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 (Khoury and Flanders 1996; Piegorsch et al. 1994). 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 et al. (2006) 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 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 (Khoury and Flanders 1996). 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 is 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 (Albert et al. 2001).

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 (Koenen et al. 2005). Peritraumatic dissociation is a evolutionary conserved response to life-threatening events and a risk factor for the development of post-traumatic stress disorder (Ozer et al. 2003). 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 (Moffitt et al. 2006). 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 (Moffitt et al. 2006).

3.4 Wide Interaction Studies

With the advent of genome-wide association studies (GWAS) it is now possible to genotype up to one 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) (Khoury and Wacholder 2009). GEWIS allow us to investigate several candidate pathways at once at relatively low costs and hold the promise to 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 (Sebastiani et al. 2005). Without any prior hypothesis it is hard to distinguish false from true positives, especially as interaction effects in complex traits such as mental disorders are supposed to be small. However, systematic approaches to the problem are emerging (Onkamo and Toivonen 2006; Wacholder et al. 2004). Despite the great remaining conceptual challenges, GEWIS paired with thorough phenotyping holds promise in producing advances in the field of G × E interaction research.

4 Empirical Evidence for G × E Interaction in Psychiatric Genetics

G × E interactions in psychiatric genetics have been reported for various disorders such as depression, attention deficit/hyperactivity disorder (ADHD), schizophrenia, obesity and substance use disorders (Table 3). The identified environmental pathogens range from prenatal factors such as maternal smoking (Kahn et al. 2003)

Table 3 Selected G × E interaction findings in psychiatric genetics

Gene	Risk environment	Disorder	Original finding
SLC6A4	Stressful life events	Depression	Caspi et al. (2003)
SLC6A4	Childhood maltreatment	Depression	Caspi et al. (2003)
SLC6A4	Mother's expressed emotion	ADHD	Sonuga-Barke et al. (2009)
SLC6A4	Early life stress	Alcohol abuse	Olsson et al. (2005)
MAOA	Childhood maltreatment	Antisocial personality; Conduct disorder	Caspi et al. (2002)
DRD4	Priming alcohol doses	Alcohol craving	Hutchison et al. (2002a)
DRD4	Smoking cues	Tobacco craving	Hutchison et al. (2002b)
DAT1	Prenatal maternal smoking	ADHD	Kahn et al. (2003)
DAT1	Prenatal maternal use of alcohol	ADHD	Brookes et al. (2006)
DAT1	Season of birth	ADHD	Seeger et al. (2004)
DAT1	Psychosocial adversity in childhood	ADHD	Laucht et al. (2007)
DAT1	Mother's expressed emotion	ADHD	Sonuga-Barke et al. (2009)
DAT1	Institutional deprivation	ADHD	Stevens et al. (2009)
COMT	Cannabis use in adolescence	Adult psychosis	Caspi et al. (2005)
COMT	Low birth weight	ADHD	Thapar et al. (2005)
COMT	Stress	Psychosis	van Winkel et al. (2008)
CRHR1	Stress	Alcohol abuse	Blomeyer et al. (2008)
CRHR1	Childhood trauma	Mood and anxiety disorders	Bradley et al. (2008)
FTO	Physical inactivity	Obesity	Andreasen et al. (2008)
FKBP5	Acute injury	Psychological dissociation	Koenen et al. (2005)
FKBP5	Childhood abuse	Mood and anxiety disorders	Binder et al. (2008)

or maternal alcohol use (Brookes et al. 2006) to factors relevant at birth [e.g. season of birth (Seeger et al. 2004), birth weight (Thapar et al. 2005)] and early development [e.g. childhood maltreatment (Caspi et al. 2003), childhood trauma (Bradley et al. 2008)] to factors affecting adolescence [e.g. cannabis use (Caspi et al. 2005)] and adulthood [e.g. stress (Blomeyer et al. 2008), physical inactivity (Andreasen et al. 2008)]. However, track record of replications has often been poor, casting doubt on the validity of these findings (Thomas 2010). Nonreplication 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 (Caspi et al. 2003). 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 (Karg et al. 2010). 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 such as 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 (Uher and McGuffin 2007; Risch et al. 2009) 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 (Karg et al. 2010) 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 (Caspi et al. 2010). First, several empirical studies link the short 5-HTTLPR variant to stress-sensitive phenotypes such as post-traumatic stress disorder (Xie et al. 2009), post-trauma suicide (Roy et al. 2007), stress-related sleep disturbance (Brummett et al. 2007) and anxiety (Stein et al. 2008). Second, a multitude of neuroimaging studies confirmed increased and faster amygdala

reactivity following threat in carriers of the short allele e.g. (Furman et al. 2010; Heinz et al. 2005) and linked it to specific brain anatomy characteristics e.g. (Pacheco et al. 2009; Pezawas et al. 2005). Third, Rhesus macaques carrying the short variant exhibit greater anxiety-related behaviors in response to adverse rearing conditions compared to their conspecific with the long alternate (Barr et al. 2004; Spinelli et al. 2007). Fourth, in addition to 5-HTT knockout mice, 5-HTT knockout rats showed increased anxiety levels in response to stress (Homberg et al. 2007). 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.

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 (Caspi and Moffitt 2006). 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 (Merikangas and Risch 2003) 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 (Abdolmaleky et al. 2004). 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.

6 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 such as 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.

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