CHAPTER 8

The Trilogy of G×E: Conceptualization, Operationalization, and Application

ELENA L. GRIGORENKO, JOHANNA BICK, DANIEL J. CAMPBELL, GABRIELLE LEWINE, JENNIFER ABRAMS, VICTORIA NGUYEN, and JOSEPH T. CHANG

INTRODUCTION

From the beginning of the quest to comprehend the forces of human development (i.e., their typology and etiology), there was a notion that these forces had different sources: there is something that a child gives to this world (i.e., through abilities to be developed into competencies and expertise), and there is something that the world gives to the child (i.e., proximal adults, various experiences, or chance). Justifiably or not, these sources have been viewed as distinct entities and labeled as nature and nurture, respectively. Throughout the history of the developmental sciences, whether embedded in other sciences or forming sciences themselves, nature and nurture and their relationship have been defined across a continuum, from being independent to interdependent, with all possible variations in between.

Fast-forward to today, where the prevailing view in the developmental sciences is that nature and nurture are intertwined. This means that, although separable via extreme main effects, nature and nurture shape developmental trajectories together through co-action, whether at the level of a cohort or an individual. The separation of nature and nurture arises only in relatively rare situations, in fact, in which nature overrides nurture—e.g., severe genomic lesions resulting in high mortality regardless of environmental circumstances, or in which nurture overrides nature (e.g., severe nutrient deficiency resulting in high mortality regardless of the exposed genotype). In other words, it is now commonly recognized that the structural variation in

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[1]Color versions of Figures 8.1 and 8.8 are available at http://onlinelibrary.wiley.com/book/10.1002/9781118963418

the genome alone cannot explain most cases of inherited diseases/disorders. Similarly, it is widely accepted that environments, however defined, cannot explain most cases of acquired diseases/disorders. It is far more probable that environments as well as self-determined behavior (e.g., lifestyle), interacting with the structure of the genome, result in the manifestation and dynamics of these diseases and disorders as well as normative development.

This nature–nurture co-action is exemplified plentifully in numerous phenomena in the developmental sciences, including, but not limited to, the manifestation of differential responses to environments that are demonstrated by humans throughout the life span. Illustrations of such differential responses are abundant and are exemplified, primarily, in the literature on responses to different early rearing conditions in general (e. g., Cicchetti, Rogosch, Gunnar, & Toth, 2010; Lawler, Hostinar, Mliner, & Gunnar, 2014) and variation in caregiving quality in particular (Kochanska, Askan, & Joy, 2007; Suomi, 1997); moreover, these responses are traceable, although manifested in different forms, throughout the life span (Aron & Aron, 1997; Evans & Rothbart, 2007; Posner & Rothbart, 2007). Differential responses are acknowledged when the removal of either nature or nurture susceptibility factors negates the outcome (Caspi & Moffitt, 2006; Rutter, 2006).

These differential responses, whether with regard to typical or atypical development, have been theorized about in a number of models, most notably, the transactional/dual-risk model (Sameroff, 1983) and the diathesis–stress model (Meehl, 1962; Monroe & Simons, 1991; Zubin & Spring, 1977; Zuckerman, 1999). The main theme of these models is that, even upon their initial arrival to this world, children already differ in vulnerability, and those who are deemed vulnerable are likely to be adversely affected, disproportionally or even selectively, by environmental stressors (e.g., child maltreatment, inadequate parenting or schooling, negative life events). Thus, atypical development (or psychopathology) is a systemic outcome of co-effects or synergisms of inherent vulnerabilities (diatheses) and negative environments (stressors). This theme has been further developed in what is known as the differential susceptibility (Belsky, 1997, 2014; Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2007; Belsky & Pluess, 2009; Pluess & Belsky, 2013) and biological sensitivity to context (Boyce & Ellis, 2005; Boyce, Sokolowski, & Robinson, 2012; Ellis, Essex, & Boyce, 2005; Ellis, Jackson, & Boyce, 2006) hypotheses, stipulating that the very same individuals who are deemed vulnerable and suffer the most from adversity, are also the ones who will profit the most from the amelioration of adversity and enrichment of their environment. These hypotheses, although similar in their position on the importance of the co-action of nature and nurture and their inclusion of the notion of developmental plasticity (Belsky & Pluess, 2009), differ in their accents. Thus, in the nature–nurture co-dynamics of the development and emergence of individual differences, the former hypothesis accentuates the part of nature, whereas the latter accentuates the part of nurture. Both hypotheses are grounded in the theory of evolution, emphasizing the rationale for differential responsiveness in a continually volatile environment (Wolf & Krause, 2014; Wolf, van Doorn, & Weissing, 2008) and, correspondingly, for maximizing fitness through diversity (Belsky, 1997) by programming, prenatally and postnatally, hyperreactivity and hypersensitivity to stress to adaptively match those unpredictable environments (Boyce & Ellis, 2005).

Empirically, these hypotheses are rooted in the large literature known as the gene–environment interaction literature (e.g., Bakermans-Kranenburg & van Ijzendoorn, 2006, 2011), which captures an ongoing quest of ever-gaining momentum (Hunter, 2005) for the understanding of the empirical and mechanistic texture of nature–nurture co-action. In this chapter, we intend to introduce this literature and highlight its particularly distinct facets. As an introduction, by definition, is not a comprehensive overview of the field, this chapter is segmented into three parts: the first presents the concept of gene–environment interaction; the second discusses various aspects of the operationalization of the concept; and the third exemplifies issues arising in the actual implementation of the operationalization and application of G×E in empirical research. Thus, the chapter introduces the trilogy of gene–environment interaction (i.e., the presentation and discussion of the phenomenon's conceptualization, operationalization, and implementation).

THE CONCEPT

The most intuitively appealing conceptualization of gene–environment interaction (G×E) is the dependence between two factors—the genetic (G) and environmental (E) in their effects on a trait. The presence of G×E is posited when the effect of the genome depends on the immediate environment in which it exists or when, vice versa, the effect of the environment depends on the genome (Duncan & Keller, 2011). In other words, biologically, G×E interactions signify all of the different ways that

a genetic structural variant may give rise to a particular phenotype within a particular environment, or vice versa (Manolio, Bailey-Wilson, & Collins, 2006). Statistically, G×E indicates differential associations between the genotype and the phenotype in the presence, absence, or dosage of a particular environmental exposure.

From a public health perspective, G×E interactions are highly important (Thomas, 2010a). Broadly speaking, their importance is two-fold, as they have negative and positive facets. The negative facet of G×E is that it can mask a main effect (either G or E), so that the research generates false negatives or inconsistent results (Bos et al., 2005; Ko, Hsu, Hsu, Ko, & Lee, 2004; Ordovas et al., 2002; St-Pierre et al., 2003; Tai et al., 2003). The positive facets of G×E are thought to be numerous (Le Marchand, 2005; Le Marchand & Wilkens, 2008); these aspects reflect both future promises and current shortcomings of this concept. Specifically, first, understanding the mechanics of G×E may produce insights into the biological pathways of typical and atypical development (Thomas, 2010a). Thus, it is possible that many genetic risk factors act synergistically, but do not demonstrate marginal effects (i.e., do not appear to have an impact when examined individually). If so, understanding related interactions would be pursued not for the sake of the discovery of the interaction per se (Kraft, Yen, Stram, Morrison, & Gauderman, 2007), but for the sake of identifying the genetic risk factors. The same logic applies to understanding environmental hazards and their deleterious effects (Hunter, 2005). Second, in situations when both the susceptibility genetic factor and environmental exposure should be present for a disorder to manifest, G×E interactions are viewed as instrumental in altering or diverting the effects of harmful genes by avoiding exposure to harmful environments (Manolio et al., 2006). Third, understanding G×E might aid in both qualifying and quantifying the degree of etiological heterogeneity, whether genetic or environmental (Greene, Penrod, Williams, & Moore, 2009; Ioannidis, 2007). Fourth, ideally, if G×E interactions are of substantial magnitude, they could be incorporated into risk prediction models with consequences for practice in both the domains of public health and personalized medicine (Thomas, 2010b).

Although relatively young, the field of studies of G×E has had an impressive trajectory (Thomas, 2010a). It was formulated prior to the discovery of the structure of DNA, that is, when G was not measurable, and prospered through quantitative genetic (e.g., twin) studies. The field has since learned how to measure G in stages, initially through the utilization of single polymorphisms[2] and now through high-throughput technologies capturing the variation in the whole genome. With the subsequent development of relevant measurement tools (e.g., genotyping and sequencing), the field has flourished. Initially, the G×E field was dominated by candidate–gene (or, more precisely, candidate-polymorphism) studies. The premise for this hypothesis-driven or inferential approach in general, as well as for the selection of gene candidates, was the existence of a known connection between a given environmental factor and the genetic pathway that carried that factor on (e.g., metabolized it, such as the metabolic pathway of alcohol or tobacco).[3] Then, a particular gene within a specific pathway or a particular polymorphism within a specific gene could be singled out and nominated as a candidate gene or a candidate polymorphism, deemed to serve as a proxy or a marker for a specific biological process. As the field's sophistication has grown, the focus of G×E studies has moved from single polymorphisms and single genes to entire pathways, along with the genes, exposures, and various cofactors deemed relevant to these pathways. The same technological and theoretical advancements that increased the complexity of the hypothesis-driven approach to G×E have triggered a hypothesis-free or agnostic approach to studies of G×E. This approach is rooted in the availability of large amounts of genetic data generated, initially, by genome-wide association studies (GWAS, which allow testing for associations between common genetic variants and phenotypic traits) and now by genome-wide sequencing studies (GWSS, which allow the discovery of new rare variants accounting for phenotypic variation). Although the initial investigations of these data intended and attempted to investigate main effects, there is now an increasing interest in investigating interactive effects (Cordell, 2009). Although not all, many GWASes and GWSSes, either by design or by the nature of samples (e.g., in cohort studies), include relevant indicators of environment and, thus, the data they produce might be utilized in G×E studies. These studies might be of two

[2]In whatever type these polymorphisms (i.e., genetic variants at a particular position of the DNA sequences) were available, namely, restriction fragment length polymorphisms—RFLPs, variable number tandem repeat—VNTRs, or single nucleotide polymorphisms—SNPs.

[3]Of note is that there is a certain field specificity in how this approach is manifested in medical (e.g., psychiatry) and behavioral (e.g., developmental psychopathology) candidate–gene G×E studies. The former, in fact, are much more hypothesis oriented than the latter.

kinds: the first aimed at exploring signals that do not reach genome-wide significance in the context of main-effect analyses, but might in the context of interaction-effect analyses (Holmans et al., 2009); and the second aimed at mining patterns of interaction effects to identify novel biological pathways (Sebastiani, Ramoni, Nolan, Baldwin, & Steinberg, 2005).

As the number of G×E studies, conducted either in old (i.e. candidate gene or polymorphism) or new (i.e. whole genome) style, has been increasing exponentially, there has been a push to establish and propagate a set of systematic requirements to guide G×E discovery and replication. Although this chapter is not the forum for setting such requirements, our intention is to highlight and discuss issues that have been flagged as important and problematic in G×E research, and that require understanding and reflection by any individual who aims to be an informed reader and/or a qualified contributor to the G×E literature.

Both historically and currently, the literature contains many different notions of the term *interaction*; the multiple meanings of the term have been and are likely to remain a source of confusion (Clayton & McKeigue, 2001). Due to such ambiguity, it is customary to see disclaimers in the literature that differentiate a *statistical* form of an interaction (i.e., statistical interaction—a quantitative description of the joint effects of multiple factors) from a *biological* form of an interaction (i.e., biological interaction—the causal and biological mechanisms; Cox, 1984; Rutter, Moffitt, & Caspi, 2006; Thompson, 1991). There are historical and conceptual reasons for differentiating these concepts.

Tabery (2007) distinguished so-called biometric and developmental concepts of G×E. He attributed the former to R. A. Fisher and put forth an interpretation of the concept of G×E (GxE_B) within Fisher's general biometric paradigm aimed at partitioning total phenotypic variance into its components, including genetic and environmental ones. As his paradigm was defined by a particular set of assumptions, the concept of G×E was neither native to it nor readily assimilated by it, being viewed as a potential source of bias[4] for other components of the decomposition of phenotypic variance equation. Being aware and concerned about biases, Fisher investigated the concept of G×E quite closely, but in a single empirical investigation, and arrived to the conclusion that, in fact, the magnitude of effects associated with this concept were not impressive and, therefore, not substantial; in fact, it could be eliminated with a transformation of scale.

Tabery (2007) contrasted Fisher's biometric concept of G×E with the *developmental* concept of G×E (GxE_D) conceived by L. Hogben. For Hogben, G×E was a facet of the natural course of events that is as embedded in nature as development itself. In other words, G×E is omnipresent and the question is whether our statistical apparatus can detect it and appraise its magnitude. According to Tabery, the tension between these two interpretations of G×E has shaped the relevant literature in the last century and remains highly present today.

It so happened, as is often the case in science, that these two different interpretations arose from the fact that the two scientists followed rather different scientific and personal pathways to the derivation of G×E interaction, both conceptually and statistically. Fisher, working on the foundations of what is now known as quantitative genetics and behavior genetics, first viewed the environmental variable as randomly distributed (Fisher, 1918). Yet, his later experiences at the Rothamsted Agricultural Research Station, where, reportedly, his charge was to evaluate environmental variation, challenged his view on this randomness and triggered his thinking on the possible "interaction of causes" (Fisher, 1925). To follow up on his thinking experimentally, Fisher examined different combinations of various sorts of potatoes with various types of manure. He stated, as a result of his single experiment, that the deviations from additivity observed in his potato-compost system were not significant; that is, the potato varieties did not exhibit differences in their reaction to different types of manure (Fisher & Mackenzie, 1923), and, therefore, there was no reason to believe that the "interaction of causes" should create important complications to his approach to the decomposition of phenotypic variance. Thus, for Fisher, genetic and environmental forces, especially the former, remained the major causes; any co-action between them, however defined, constituted mere nonstatistically significant deviations from additivity, (i.e., possible qualitatively, but not essential to account for quantitatively)—of "possible, but unproved, importance" (Tabery, 2007, p. 967).

Hogben's (1932) conceptualization of G×E interaction was very different. In part, it was inspired by his own scientific journey while teaching at the London School of Economics (Tabery, 2007). Although unequivocally recognizing the usefulness of differentiating genetic and environmental factors in understanding causality of development, he was highly critical of their separation, even if only for the sake of deriving testable statistical models.

[4]Where bias is defined as "any process at any stage of inference which tends to produce results or conclusions that differ systematically from the truth" (Sackett, 1979, p. 60).

In fact, Hogben underscored the critical nature of a third type of variance, which manifests itself when a particular combination of genetic factors interacts with a particular combination of environmental factors. In doing so, he postulated both the ubiquitous character of G×E in development and the flaw in statistical representations of G and E when their interaction term is omitted.

The ubiquity of G×E comes from the very fact that the genome does not exist without an environment; thus, the developmental version of the G×E concept, or, specifically, GxE_D (Tabery, 2007), is as important a player in human development as G or E individually. The GxE_D interaction could be studied experimentally (Krafka, 1920), although the options for such studies are limited with regard to research on humans. Although not directly referenced by Hogben, similar ideas were developed by Richard Woltereck in Germany in the early twentieth century with regard to his concept of *Reacktionsnorm*, or norm of reaction—a complete set of developmental outcomes that could emerge when the same genotype is immersed in different environments (Sarkar, 1999 & Peirson, 2012).

To summarize, for Fisher, the phenomenon of G×E (GxE_B, today referred to mostly as statistical G×E) did not exist unless it was explicitly detectable (i.e., representable by a statistical term in his variance decomposition equation) and statistically significant. Moreover, even if there were evidence for the significance of the term, the interaction might be removable by transformation of variables and the corresponding portion of the variance manifested on the side of G.

For Hogben (1932), the G×E phenomenon ($G\times E_D$, today referred to mostly as biological G×E) existed a priori, and, if statistical rather than experimental approaches mattered at all, they needed to be perfect to capture it. Thus, Fisher (1925) argued that his biometric machinery could detect the interaction if it was there, while Hogben argued that, in most cases, it was there, even if it was not detectable statistically. After an exchange of letters and a number of cross-referencing debates in the literature, neither conceded. Fisher's position was that the burden of proof was on the opposition; one needed to show that something exists before the discussion of how to assess or measure it could meaningfully take place.

This debate has not been resolved, and, moreover, its essence has framed much of the relevant research today. The relevant discussions have gone through a variety of different stages, engrossing many scientists, and generating many new concepts. Highly engaging, both theoretically and historically, this debate will be represented in this chapter only by a limited number of highlights. Fisher's view of G×E as a mere phantom whose existence needs to be proved has been adopted by many scientists in a number of different contexts (Jensen, 1969, 1973; Lush, 1937). Whatever the phenotypic trait at the focus of discussion, the meagerness of the G×E interaction term, as estimated in a Fisher-style decomposition of variance approach, was compared to the substantial main effects of G and E (and the error term) and, therefore, dismissed. In turn, Hogben's ideas both inspired and framed the thinking of C. H. Waddington, who, pursuing the premise of the developmental preeminence of G×E, introduced the concepts of epigenetics and an epigenetic landscape (i.e., a physical and temporal map of the genetic regulation of development; Waddington, 1957, 1975). The indisputable reality of G×E has also been endorsed by R. Lewontin (1974), who, in his discussion of the biometric approach to phenotypes, asked a very important question about the limitations of this approach for making inferences about the magnitude of genetic effect on a trait (i.e., heritability estimates, or the proportion of phenotypic variance accounted for by genetic variance) in environments that have not yet been encountered (Feldman & Lewontin, 1975).

The debate crystallized in the distinction of two extreme positions, often referred to as *interaction versus interactionism*, where the former represented Fisher's views and the latter—Hogben's. A new interpretation of this debate has surfaced more recently in the work of M. Rutter and colleagues, who discussed the narrow sense (i.e., statistical concept) and broader sense (i.e., biological concept) of the G×E phenomena (Rutter, 2006; Rutter & Pickles, 1991). Regardless of the terms used, the crystallization of this debate recognizes the importance of both conceptualizations of G×E and argues that they often, yet do not always, function sequentially. The ongoing nature of this debate also illuminates the different stages of the field's understanding of how genomes and environments co-act (i.e., in that they are inseparable within an individual, but can be statistically isolated when considered at the population level). In other words, a registration of statistically significant G×E at the population level can be followed up with an investigation of the underlying biological mechanism, either at the individual or group/population level, just as the registration of a biological phenomenon in a particular individual/group can be later investigated at the population level, so that its role as a risk factor in the larger population can be appraised. A recognition that both types of G×E are important may help to reconcile the two extreme views; such an appeasement would be supported by many scientists (e.g., Vreeke, 2000).

THE OPERATIONALIZATION

From Concept to Term

Conceptually, interaction refers to the co-participation of two factors in a causal mechanism (Rothman, 1986). A G×E interaction transpires when subsets of a population (or a specific sample, if not representative of the population), distinguished by a specific genotype (e.g., a polymorphism, a risk-associated haplotype, several causal variants within a gene, or even some complex index of genetic risk, constructed from several causal variants, Thomas, 2010a), differentially respond to varying environmental conditions (Rowe, 2003). This observation is translated into statistical terms, according to which G×E interaction is present when the impact of a specific genotype on one's susceptibility to a disease or disorder depends on exposure to a specific environmental factor; the reverse (from environment to genotype) is also true (Clayton & McKeigue, 2001). Specifically, G and E demonstrate dependence such that genetic influences on the phenotype are conditioned on the environmental context, whereas an organism's phenotypic response to the environment is conditioned on the genotype. Rephrased, G×E interaction can be defined as *differences in the effect* of an environment on disease/disorder risk in carriers of different genotypes or, equivalently, *differences in the effect* of a genotype on disease/disorder risk in persons with different environmental exposures (Ottman, 1996).

In general terms, an interaction is qualitatively indicated when an effect is explained, not merely by independent and relative contribution of one or more variant(s) within a gene (or many variants within many genes) and one or more environmental exposures, but by the joint contribution of these two (G and E) factors. Correspondingly, tests for interaction (G×E) address the fit between a chosen model and the data. A test for the main effect (or the average effect) of exposure assumes the null hypothesis of no difference between risk in exposed and unexposed subgroups, and for genotype assumes the null hypothesis of no differences between risk associated with genetic variability. A test for interaction assumes the null hypothesis of the co-action of these two factors, as described by a specific statistical model. Conventionally, when testing for G×E, a multiplicative model is used, which assumes that the product of functions of the genetic and environmental risk factors explain the relative risk of manifesting a disease/disorder. A joint effect that differs from the predicted value of the specified model is deemed a form of interaction. Or, in other words, the presence of interaction is marked by lack of fit to the statistical model (Clayton & McKeigue, 2001; Thomas, 2010a).

A common measure of effect is the ratio of the incidence of a disease or disorder in exposed to unexposed subgroups, which can be captured (in a case–control study, for example) by an odds ratio. In this context, a multiplicative model for the joint effects of risk factors (e.g., G and E) assumes that the risk ratio between exposed and unexposed subgroups (i.e., subgroups of E) does not vary over subgroups defined by the genetic factor (i.e., subgroups of G). As the presence of interaction entails differences in the risk ratio across different subgroups, statistically, it will mean a lack of fit to the multiplicative model. Of note, the detection of statistical interaction might or might not aid in understanding the underlying biological mechanics associated with G×E. In order to contribute to this understanding, the null hypothesis needs to have a clear biological interpretation. Moreover, the same statistical model for the risk ratio could be associated with many different biological models or mechanisms. In fact, the registration, by statistical means, of the presence of interaction does not imply the strengthening of any corresponding theory of pathogenesis (Eaves, 2006; Rothman & Greenland, 2005; Rothman, Greenland, & Walker, 1980; Thompson, 1991).

The central issue here is that of biological validity, as biologically essential interactions can typically be detected without statistical techniques. An oft-cited example of a biologically valid interaction is that of phenylketonuria (PKU)—a disorder resulting from an interaction of homozygous loss-of-function mutations in the gene encoding the phenylalanine hydroxylase enzyme, and dietary exposure to phenylalanine. As phenylalanine is abundant in the human diet, under typical conditions (i.e., when a baby is exposed to typical early care) the interaction is not statistically detectable because the exposure variable is fixed (i.e., every human baby is exposed to phenylalanine). Yet the knowledge of this interaction is critical as it determines both prevention and intervention.

As evident from the previous historical notes, the field of G×E started with the statistical estimation of the corresponding term, defined within Fisher's model of phenotypic variance decomposition (i.e., the so-called quantitative-genetic model), in which case many components of the equation were unmeasured. Specialized statistical models (Andrieu & Goldstein, 1998; Eaves & Erkanli, 2003; Purcell, 2002) to test for the variance components of G×E have been developed over time. These black box statistical approaches have undoubtedly made a substantial contribution to the fields of quantitative and behavior genetics. However, these advances in statistical modeling have had much less relevance for researchers wanting to utilize the results of the G×E studies to make specific practice-related recommendations. Gradually, different

versions of the general variance-decomposition model have been developed, so that unmeasured terms have been replaced with measured terms (in different combinations).

In this part of the chapter, we will comment on the issues that arise when both of these approaches (i.e., one with unmeasured and the other with measured terms are exercised). The discussion will primarily focus on the concept of statistical interaction, as this is what is utilized in the majority of studies in the developmental sciences in general, and developmental psychopathology in particular.

When Terms Are Unmeasured

In quantitative-genetic (also often referred to as behavior-genetic) studies, G×E interactions are reported primarily in attempts to understand how genetic influences are moderated by different aspects of the environment. In other words, these studies allow researchers to appreciate the magnitude by which the impact of a specific genotype is either augmented or limited by exposure to a specific environmental factor. Yet, depending on what particular model of moderation is assumed, rather distinct types of results and interpretations are expected. Carlson, Mendle, and Harden (2014) exemplified these expectations as follows. The main premise of the diathesis–stress model is that individuals differ in the degree to which they can be negatively affected by adverse environments, and this differential risk can be attributed to individual variations in genetic vulnerability (Monroe & Simons, 1991). In other words, such environments may moderate the role of the genetic factors associated with disease/disorder risk by magnifying the likelihood that genetically vulnerable individuals will develop negative outcomes. This translates into an assumption that genetic variance will be higher in low-quality, adverse environments, and lower in high-quality environments.

Conversely, some models focus on the relationship between specific genetic predispositions and their capacity to benefit from advantageous environments (Bronfenbrenner & Ceci, 1994; Pluess & Belsky, 2013). This translates into the assumption that genetic variance will be higher in high-quality environments and lower in lower quality environments.

Finally, the differential susceptibility model (Belsky et al., 2007; Ellis et al., 2005) assumes the existence of genetic predispositions that are marked by greater plasticity overall, so that both adverse and advantageous environments differentiate these genotypes and magnify the resulting outcomes as more negative or positive than those for carriers of less-sensitive genotypes in negative and positive environments, respectively. This translates into an expectation that genetic variance will be maximized at opposing extremes of the moderating environmental factor (Ellis, Schlomer, Tilley, & Butler, 2012), but will be negligible in average environments (South & Krueger, 2013).

The literature provides a number of illustrations of quantitative-genetic studies of G×E (Jaffee, Price, & Reyes, 2013). For example, it has been demonstrated that in environments that facilitate substance use—that is, those that impose lower taxes on substances (Boardman, 2009), have greater alcohol availability (Boardman, 2009; Kendler, Gardner, & Dick, 2011) or are characterized by greater existence or dominance of social norms encouraging drinking (Boardman, Saint Onge, Haberstick, Timberlake, & Hewitt, 2008; Timberlake et al., 2007), increased affiliation with deviant peer groups in adolescence (Kendler et al., 2011), urban (vs. rural) environment (Dick, Rose, Viken, Kaprio, & Koskenvuo, 2001), avoidance of organized religion (Timberlake et al., 2006), and lower levels of parental monitoring (Dick et al., 2007)—genetic variance in alcohol and tobacco use is higher. A similar pattern of greater amount of genetic variance has been observed for youth externalizing problems when adolescents are exposed to a broad range of adversities in their environment (Hicks, South, DiRago, Iacono, & McGue, 2009). Otherwise, adverse childhood environments appear to suppress genetic influences, compared to more advantaged environments (Carlson et al., 2014), predisposing youth, over and above their genetic differences, to earlier initiation of sexual activity (Belsky, Steinberg, Houts, Halpern-Felsher, & the NICHD Early Child Care Research Network, 2010; Coley & Chase-Lansdale, 1998).

Conversely, a suppression of genetic variance in substance abuse has been demonstrated in environments imposing high social control (Kendler et al., 2012), high parental monitoring (Dick et al., 2007), religious upbringing (Koopmans, Slutske, van Baal, & Boomsma, 1999), and positive marital relationships (Dick et al., 2006). Recently, such a list of positive environments has been extended to include that of competitive, achievement-oriented, high-quality schooling (Benner, Kretsch, Harden, & Crosnoe, 2014), shedding light on the nature of previously reported overlapping genetic influences between, for example, nicotine use and educational attainment (McCaffery et al., 2008), academic mastery and alcohol dependence (Bryant, Schulenberg, Bachman, O'Malley, & Johnston, 2000; Crosnoe, 2006; Kiecolt, Aggen, & Kendler, 2013), and verbal ability and alcohol dependence (Latvala et al., 2009).

Of note, aligned with both the expectation regarding the diversity of possible G×E patterns and the theoretical assumptions outlined above, there are traits and genotypes that benefit from relative social advantage. Thus,

it has been shown that genetic influences on age at the initiation of sexual activity are greater in contexts of relative social advantage and suppressed in more adverse conditions (Carlson et al., 2014; Waldron et al., 2008). Similarly, greater genetic variance has been registered in more advantageous environments for traits of intelligence (i.e., higher levels of SES; Turkheimer, Haley, Waldron, D'Onofrio, & Gottesman, 2003) and early reading (i.e., higher teacher quality; Taylor, Roehrig, Soden Hensler, Connor, & Schatschneider, 2010).

When Terms Are Measured

The term that researchers started to measure first in G×E studies was that of environment. One, although not the only, reason is that by the beginning of the 21st century, the field of epidemiology had accumulated enough data (Hemminki, Lorenzo Bermejo, & Forsti, 2006) to demonstrate that environmental factors, have amplified the background incidence of so-called common complex diseases and disorders in high-income countries to over 10 times the level observed in low-income countries (Buchanan, Weiss, & Fullerton, 2006; Colditz, Sellers, & Trapido, 2006; Willett, 2002). This observation corresponds to the growing recognition that combinations of these environmental factors, characteristic of high-compared to low-income countries, with specific genetic predispositions, are responsible for the most recent epidemics of chronic disease. The challenge of epidemiological research today is to identify these combinations (Weaver, Buckley, & Groopman, 1998) so that the course of the epidemic can be reversed (Chakravarti & Little, 2003). One example of such a combination is the interaction between today's environment of overabundance of calories with presumed famine protective genetic predispositions, which is argued to have contributed to the current obesity epidemic in the United States (F. S. Collins, 2004).

Although quite often in G×E research genetics (G) and environmental (E) have been conceived, rather simplistically, as dichotomous variables, both G and E factors, in reality, are complex and multidimensional (Thomas, 2010a). Consider, for example, air composition, which can be specified as polluted/unpolluted dichotomous E, but whose indicators, in reality, represent a multifarious brew of gases and particles with different properties (Ghio, Carraway, & Madden, 2011; Nieuwenhuijsen, Gómez-Perales, & Colvile, 2007), so that types of polluted air may vary dramatically with regard to the level of danger associated with exposure. In addition, G and E might have other sources of variability, such as time and intensity. With regard to the former, many environmental risk factors can be modified by such time-based factors such as age at or duration of exposure (Thomas, 1988). With regard to the latter, the intensity and number of exposures could be a much more important source of information than whether or not an exposure has occurred (Miller, Schlosser, & Janszen, 2000).

The technological developments in the measurement of both the genome and the environome (i.e., the combination of aspects of the environment that can be systematically extrapolated such as nutritional intake, amount of physical exercise, amount of sleep, level of stress and so forth) coupled with the development of computational capacities, has resulted in a dramatic shift away from G×E studies in which none of the terms are measured toward those in which all of the terms are measured. In addition, the development of robust analytical methods for assessing both main effects and interactions has permitted the interrogation of these complex effects on a population scale (van den Oord, 1999). Yet, this change has also brought up a number of new concerns not previously voiced in the G×E literature. These concerns are many and they will be discussed primarily in the next section of this chapter. Here we mention only those that are relevant to the measurement of genes and environments in the context of G×E studies.

First, as the broader field of genetics (both quantitative and molecular) transitioned from unmeasured to measured G and E, the problem of missing heritability of common traits (Maher, 2008; McCarthy & Hirschhorn, 2008) arose. The field anticipated a translation of the high heritability estimates obtained from quantitative-genetic studies into similarly high heritability estimates obtained from molecular-genetic studies. However, this did not happen. In fact, the latter were estimated to be nowhere near as high as the former. The major effort to qualify and quantify genetic variation triggered, in part, by the Human Genome Project, had produced an ocean of genome-wide association studies (hereafter, GWAS will refer to the method and GWASes will refer to studies carried out using the GWAS method). These studies led to the identification of >1,200 loci whose genetic variants were shown to be associated with >165 common human diseases/disorders and complex traits; collectively, these variants implicated many previously unknown or unconsidered roles for numerous biological pathways (Hirschhorn, 2009; Lander, 2011; Manolio, Brooks, & Collins, 2008). It was expected that these very first GWASes (measuring the genome in this case with single nucleotide polymorphisms, SNPs) would result in the translation of previously obtained heritability estimates into effect sizes for measured G (i.e., specific genetic variants). The GWAS-based estimate of heritability

is the ratio of the heritability due to the variants used in the GWAS (specified as the numerator), estimated directly from their observed effects, to the total heritability (specified as the denominator), obtained either from previous studies or from the same study (if the sample is comprised of related individuals), or inferred indirectly from population data (Zuk, Hechter, Sunyaev, & Lander, 2012). However, these first GWASes and all subsequent ones (until recently, when the data-analytic approach changed and genomewide complex-trait analysis, GCTA, was introduced, e.g., Plomin et al., 2013), reportedly accounted for only a small proportion of the previously published heritability estimates of diseases/disorders and complex traits. This discrepancy between what was expected based on results from quantitative-genetic studies and what was observed based on the results from molecular-genetic studies was labeled as the "missing heritability" problem. As GWASes have become bigger (i.e., larger samples) and better (i.e., denser coverage of the genome), results have improved, with the referenced amount of variance reaching 20–30% or even 50% in isolated cases. However, the puzzle remains, as only a smaller portion of the previously obtained heritability estimates have been mapped onto specific genetic variants measured by GWASes (Lander, 2011).

As the problem of missing heritability became apparent, the dominant explanation was that it arose from incomplete coverage of the genome, i.e., the assumption that there were still some (or many) undiscovered variants not included in the numerator, leading to estimates biased on the lower side. Yet another possibility pertains to the overestimation of the denominator: the phenomenon referred to as *phantom heritability* (Zuk et al., 2012). Such an overestimation can arise, for example, if models do not take into account epistatic genetic interactions within loci (in that effects of each loci may not merely be additive but interact with each other to predict disease/disorder risk) (Zuk et al., 2012). To illustrate their point, Zuk and colleagues (2012) referenced Crohn's disease—an inflammatory bowel disease that impacts various components of the digestive tract. For this disease, in a traditional GWAS paradigm, 71 risk-associated loci have been identified (Franke et al., 2010). If an additive model is assumed, then these loci account for only 21.5% of the heritability, which was previously estimated at 50% (Halme, Paavola-Sakki, Turunen, Färkkilä, & Kontula, 2006), yet, if an epistatic model is assumed, then these loci explain 80% of the adjusted heritability (the phantom heritability was estimated at 62.8%). Unfortunately, it is estimated that very large sample sizes (~500,000) are required to detect genetic interactions even for such a relatively heritable disease as Crohn's. The authors (Zuk et al., 2012) concluded that current estimates (and, therefore, the whole discussion) of missing heritability might not be meaningful, as these estimates were obtained without taking into account genetic interactions. This observation is quite congruent with the worry that most previously reported heritability estimates are, indeed, artificially elevated. In fact, most of these estimates come from twin studies, which tend to provide an upper limit to the genetic component of the variance of a disease/disorder or a trait, and thereby may lead to invalid conclusions (Wallace, 2006).

The second concern relevant to the measurement of G and E, as mentioned above, is that the predominant type of G×E studies involves candidate genes and candidate environments. How are such candidates selected? There is widespread consternation that the assumption that a specific variant in a specific candidate gene (or any other type of genotype) interacts with a specific facet of a general characteristic of a particular environment is marked by a low prior probability (Duncan & Keller, 2011; Ioannidis, 2005). The trouble is that, for most if not all common complex diseases and disorders, even main effects of G and E are still rather mysterious (see the discussion for psychiatric disorders in Flint & Munafò, 2008). This, perhaps, is what explains, at least partially, the fact that almost two decades of candidate gene association studies have produced, arguably, little or no unequivocally accepted findings regarding genetic effects (Burmeister, McInnis, & Zöllner, 2008). This observation is especially worrisome due to the fact that most (if not all) hypotheses about specific candidate genes emerged from strong neuroscience research that uncovered the putative properties and functions of these genes (Hebebrand, Scherag, Schimmelmann, & Hinney, 2010). Thus, these genes—most of which are protein-coding genes—have functional variants that somehow change the properties of the synthesized protein and, thus, are likely to be exonic. It is these variants that have been featured in candidate–gene studies, which were driven primarily by inferential statistics. In this context the argument that the priors[5] in G×E research are low (Duncan & Keller, 2011) sounds reasonable. Realistically, how can it be high, if even the replication landscape for candidate gene studies is so bleak?

The GWAS approach is fundamentally different and hypothesis-free. Correspondingly, it is not surprising that

[5]A prior probability distribution (the prior) of an uncertain quantity *p*, in Bayesian statistics, is a distribution capturing expectations about *p* prior to the accumulation of the relevant evidence.

thus far, results of GWAS do not align with hypotheses generated by candidate–gene research. In fact, out of 531 SNPs labeled as the most robustly associated (SNPs) to various medical and psychiatric phenotypes in GWAS studies, 45% are intronic, 43% are intergenic, and only 11% are exonic (Hindorff et al., 2009). Moreover, when specific polymorphisms in specific candidate genes are investigated (i.e., those that have been featured in numerous candidate gene studies, such as the serotonin transporter gene promoter polymorphism) in GWAS designs, they reportedly do not demonstrate performance above the level of chance (Bosker et al., 2011; Lasky-Su et al., 2008; Need et al., 2009; Sullivan et al., 2008). To summarize, GWASes do not appear to be converging on the expected candidate genes, and the SNPs that GWASes are illuminating are mostly not exonic. This state of affairs has been referred to as a failure of both candidate gene studies (Little et al., 2009) and GWASes (McClellan & King, 2010), as their respective findings do not converge.

Yet several considerations are important to mention here. Many fashionable polymorphisms that are used in G×E candidate gene studies are not present (and cannot be present due to their biological makeup) in GWASes; thus, they need to be imputed. For example, the polymorphism in the promoter region of the serotonin transporter gene may be imputed in Caucasian samples with high (~93–95%) accuracy using multiple SNPs present in some GWAS arrays (Knodt, 2012; Lu et al., 2012). Conducting such imputations for groups other than Caucasians is much more difficult. Importantly, GWASes are designed primarily to investigate main effects of G (or its specific variants). However, the polymorphism in the promoter region of the serotonin transporter gene has not been registered to exert substantial main effects on various aspects of psychopathology and is known primarily through publications on G×E. As GWASes routinely do not test for interactions, perhaps it is not surprising that this polymorphism (or its imputed proxy) is not associated with phenotypic variation in these studies. Finally, often phenotypes used in GWASes and phenotypes used in G×E studies are quite different, even if they might be stated to tap into the same disease/disorder (e.g., depression). GWASes' phenotypes tend to be substantially less detailed and elaborate than the phenotypes showcased in G×E studies. Correspondingly, criticisms that GWASes have not implicated specific candidate genes that have been featured in G×E studies have to be examined carefully with specific caveats (e.g., what polymorphisms and what phenotypes) in mind.

The third concern is self-evident: the nonconvergence of findings from different methodologies is not encouraging and seems to indicate lack of insight into the genetic mechanisms underlying complex human diseases/disorders, at least at the level of formulating specific and verifiable hypotheses pertaining to candidate genetic polymorphisms and candidate genes (Hebebrand et al., 2010). It has been stated (Colhoun, McKeigue, & Davey Smith, 2003) that the overwhelming majority (up to 95%!) of main effect findings obtained in genetic association studies appear to be false positives. This estimate, under the assumption of statistical power between 10% and 90%, in turn, is translated to a prior probability of a true association being 0.3–3.0%. Furthermore, this estimate might well be inflated, as testing main effects demands less statistical power than testing G×E interaction effects, meaning the prior for the latter might be even lower than 0.3–3.0%. In light of these considerations, Duncan and Keller (2011) concluded that under the relatively expectant assumptions of a prior of 5% and power of 55% (which seem rather unrealistic, as small sample sizes are the norm rather than the exception among G×E studies), approximately 63% of positive findings are likely to represent Type I error. These researchers argued that if these assumptions are altered to be more realistic—i.e., a prior of 1% and statistical power of 10%—the false discovery rate is likely to be at 98%. This problem of dealing with false positive findings is quite familiar to epidemiologists, who for a long time and with little satisfaction have been engaged in detecting subtle effects, whether for environments (Taubes, 1995) or genes (Crow, 2011).

Commenting on this situation, Clayton and McKeigue (2001, pp. 1357–1358) noted the following:

> If we could specify in advance that the effect of the environmental factor on disease risk would be restricted to a subgroup of individuals with a particular genotype, there would, of course, be a gain in power from testing only this subgroup for the effect of the environmental factor. In practice, such an extreme situation is unlikely to be frequently encountered in the study of complex diseases, and entails a level of knowledge of underlying biology that would probably render epidemiological studies redundant. In less extreme situations, and where previous knowledge is more limited, a combined test would need to be done for the main effect of environmental exposure and its interaction with genotype. Since such tests have multiple degrees of freedom, the gain in power is much reduced; indeed, power might even be lost.

Fourth, there is both conceptual and statistical uncertainty as to whether the terms, as defined, are really G, E, or G×E, particularly given the findings from earlier quantitative genetic studies (Burton, Tobin, & Hopper,

2005). For example, it has been shown that if the environment, E, is separated into shared (common, C) and nonshared (unique, E) components, then the term GxC will inflate the estimate of G, whereas the term G×E will inflate the estimate of E (Molenaar, Boomsma, & Dolan, 1997). These uncertainties were brought to the forefront in G×E discussions: "Importantly, however, we must acknowledge an almost complete ignorance of the relevant gene–environment interactions—as data accumulate, causes that now seem to be environmental could turn out to be gene–environment interactions" (Hemminki et al., 2006, p. 961). Such interactions could erroneously inflate heritability estimates (Hemminki et al., 2006).

A final concern is that both the genotypic frequency (i.e., the observed frequency of particular genotypes, including those associated with risk) and frequency of exposure (i.e., the observed frequency of encountering the risk environmental factor) are crucial for discovery as well as replication (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010), as the same G×E phenomenon might (1) not manifest when the prevalence of exposure is very low; (2) manifest via statistical interaction when the prevalence is moderate; and (3) manifest via main effect when the prevalence is very high. To maximize statistical power, it is recommended that the distribution of genotypes and exposure within a given sample follow a so-called balanced design, when rates of both derived (i.e., minor) allele frequencies and exposure are at ∼50%. However, such a balance is often unrealistic, especially when utilizing a case–control design or considering more than one polymorphism. Moreover, the number and nature of subgroups resulting from the joint distribution of genotypes and environment is often unknown. Facing such a situation, researchers may be tempted (Flint & Munafò, 2008) to search for the best outcome, exhausting all analytic possibilities in a drive to register nominal statistical significance, in response to publication bias toward positive results (Ioannidis & Trikalinos, 2007). As the number of subgroups and sub-subgroups is large, so is the number of comparisons (Ioannidis, 2006; Patsopoulos, Tatsioni, & Ioannidis, 2007). Such comparisons have been used, for example, in situations when the original effect of G×E failed to be replicated in the whole sample, but was registered to operate in particular subgroups (Eley et al., 2004). Yet, extensive subgrouping is highly susceptible to false positive findings (Brookes et al., 2001).

For the brave who are willing and able to take on G×E studies in spite of the above caveats, specific recommendations have been offered (Moffitt, 2005). These recommendations include seven distinct steps.

The first step assumes a survey of the existing quantitative-genetic literature. It is always helpful if there are studies in which the specific G×E interaction in question has been evaluated already and deemed to be substantive and important, particularly if there is an explicit biological mechanism that has been coupled with this statistically significant interaction. If the relevant publications have not explicitly tested for G×E, particular attention should be given to the estimates of G (in particular, the additive genetic component, A) and E (in particular, the nonshared component of E). As discussed earlier (Molenaar et al., 1997), if G×E is not explicitly modeled, GxC can look like G (A) and G×E can look like E (E). Therefore, moderate-to-large estimates of A and E can signify the presence of potentially large G×E interaction effects (Purcell, 2002).

The second step is to identify a candidate environmental factor, the exposure to which is known to have a (preferably strong) main effect on the phenotype (trait, behavior, disease, or disorder) in question. To illustrate such a factor, Moffitt (2005) referenced early maltreatment for antisocial behavior, arguing that the former is particularly relevant through its association with biological correlates of the latter (DeBellis, 2001), although the behavior itself has been associated with multiple environmental risks (Loeber & Farrington, 1998). As a substep, Moffitt urged researchers to ensure the environmental mediation of the selected risk factor (for an illustation, see Fujisawa, Yamagata, Ozaki, & Ando, 2012). Otherwise, the selection of the environmental risk factor may be misguided, as it might capture the interaction between different genotypes rather than between genotype and environment (which could, in fact, be an issue with the maltreatment—antisocial behavior connection, Schulz-Heik et al., 2007).

The third step provides recommendations for the selection of specific measurements to be used to capture the exposure. Indeed, minimizing measurement error is associated with enhanced power (Luan, Wong, Day, & Wareham, 2001; Wong, Day, Luan, & Wareham, 2004). However, Moffitt's reference to the possibility of related reduction of sample size in situations when near flawless assessments of exposure are used is misguided.

At the fourth step, attention is switched from environments to genes. The main recommendation here is to stay in touch with the literature, as the knowledge of various gene–behavior associations advances rapidly, through the addition of new candidates and the elimination of old candidates (via nonreplication) from the list (Insel & Collins, 2003). Other recommendations are aligned with those that are present in many writings on G×E, and are discussed in

this chapter. Specifically, the genotypes of interest should be relatively prevalent in the general population. Both high and low prevalence of genotypes of interest, although they may be reflective of particular evolutionary dynamics (Hill, 1999; Searle & Blackwell, 1999), can generate various statistical biases (Lachance & Tishkoff, 2013; Vinkhuyzen, Wray, Yang, Goddard, & Visscher, 2013). Similar to the expectations for exposure, it is desirable that the candidate genetic factor be previously implicated as exerting a main effect on the phenotype of interest, although this expectation may not be realistic, given the general landscape of nonreplicability of such main effects. Finally, it is always recommended to look for a candidate that permits the formulation of a biologically plausible hypothesis as a counterpart to the statistical hypotheses. In illustrating these points, Moffitt references the polymorphism in the promoter region of the serotonin transporter (see Illustrations), arguing that the plausibility of the selection of this candidate polymorphism was substantiated by evidence from studies in psychopathology (Caspi et al., 2003), animal models (Bennett et al., 2002; Murphy et al., 2001), and human brain imaging research (Hariri et al., 2002). She also references both experimental research (e.g., Sayette, Griffin, & Sayers, 2010) and large-scale efforts documenting the range of responses of different genotypes to various environmental risks (Kaiser, 2003) as particularly important sources of nomination of candidates for G×E studies.

The fifth step is the statistical test itself. Although a reference is made, in passing, to a variety of designs used in the field (Moffitt, Caspi, & Rutter, 2005; Ottman, 1990; van Os & Sham, 2003; Yang & Khoury, 1997), the representative population-based cohort is endorsed as the most informative. It is argued that this type of design allows not only an appraisal of the presence or absence of the interaction (by the statistical test of G×E), but also an evaluation of the magnitude of this interaction. Of note is that such population-based cohorts require large sample sizes in order to capture a full distribution of E and provide enough power for various statistical tests.

The sixth step is to ensure the specificity and robustness of the registered effect by exploring the model via substitution of different candidates, both genetic and environmental. It is argued that, although it is vital to be hypothesis-driven in setting up the evaluation of G×E, having registered it, it is important to evaluate the original hypothesis among other plausible hypotheses (Licinio, 2003).

The seventh and final step calls for replication, although it is not specified whether this request pertains to replication within the same research effort (i.e., with a different sample by the same investigator), by different investigators on the same data, or some other form of replication. This recommendation acknowledges the tentative nature of an isolated G×E discovery but argues that its presentation (whether the interaction is ultimately true or not) should trigger both attempts at replication and collateral research.

So far, we have presented the literature on G×E focusing on the emergence and history of the concept and its operationalization. In the next part of this chapter, we will summarize the literature through the lens of the current state of affairs in the field of G×E.

THE ANALYSES

Almost 15 years of intensive research into G×E have generated many published reports, which, in turn, have provided the foundation for meta-analyses, systematic reviews, targeted literature reviews, and opinion pieces (e.g., Calati, Gressier, Balestri, & Serretti, 2013; Decoster, van Os, Myin-Germeys, De Hert, & van Winkel, 2012; Duncan & Keller, 2011; Eaves, 2006; Flint & Munafò, 2008; Gressier et al., 2013; Karg, Burmeister, Shedden, & Sen, 2011; Keller, 2014; Modinos et al., 2013; Munafò, Durrant, Lewis, & Flint, 2009; Munafò & Flint, 2009; Risch et al., 2009; Uher & McGuffin, 2008). In general, the field is in a curious state. On one hand, the number of empirical reports on G×E, whether positive or negative, has been growing both overall and annually, as exemplified by studies of the specific polymorphism in the promoter region of the serotonin transporter gene. Figure 8.1 captures the studies discussed in the following illustrations and listed in the Appendix; the × axis shows the number of publications, and the y axis shows the year of publication. In other words, this research is still widely funded, which motivates researchers to engage with it and

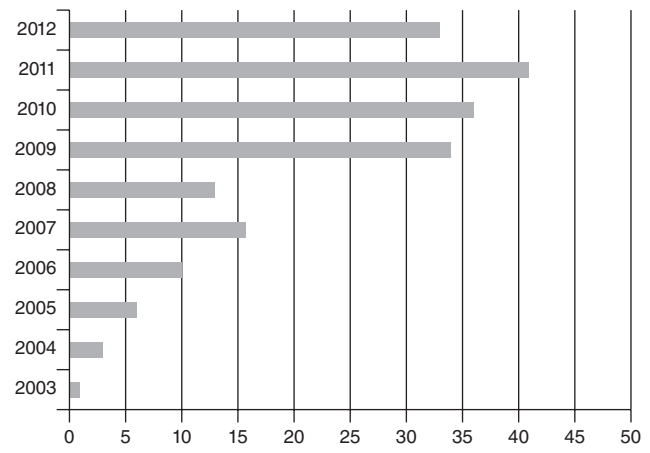

Figure 8.1 Number of publications on G×E, by publication year. See footnote 1.

publish extensively on it. On the other hand, meta-analyses and literature reviews on G×E have generated results and comments that are unabashedly skeptical. It seems that the larger the literature grows, the more incredulity it generates; yet, it still keeps growing! This incredulity stems from concerns pertaining both to the content (definitional) and the formal (analytical) aspects of this literature. As the former has been discussed already, this section of the chapter will focus on the latter.

As for analytical concerns, observations have been made with regard to the following. First, en masse, the literature on G×E is characterized by a low replication rate (Kaufman, Gelernter, Kaffman, Caspi, & Moffitt, 2010; Munafò, Durrant, Lewis, & Flint, 2010). Second, although low even in the published literature, the replication rate is, probably, even lower among all attempts to replicate due to publication bias toward positive findings but not null findings. That is, it is impossible to know how many attempts at replication have failed and therefore have not been published (i.e., the file drawer problem), and the specific magnitude of this capitalization is difficult to appraise (Munafò & Flint, 2009). In fact, it has been argued that the false discovery rate in the G×E literature is substantially higher than the Type I error rate of .05 (Duncan & Keller, 2011; Flint & Munafò, 2008) commonly utilized in inferential statistics. Third, as a whole, studies conducted on small samples are common in this literature, thereby adding additional complications associated with insufficient statistical power to detect effects, especially statistical interactions. This can, somewhat counterintuitively, serve to inflate the rate of false-positive results reported in the literature, as null findings are less likely to be published in small-sample underpowered studies relative to the likelihood that positive findings are reported in such samples, whereas the likelihood of reporting both null and positive findings is more equal in sufficiently powered, large sample studies (Burmeister et al., 2008).

In essence, there is an expectation that the fate of G×E findings will be similar to that of GWAS findings (Murcray, Lewinger, & Gauderman, 2009) when the GWAS field leapt from small- to large-sample studies and was not able to replicate the majority of its previously celebrated findings (Bosker et al., 2011; Collins, Kim, Sklar, O'Donovan, & Sullivan, 2012; Need et al., 2009; Sanders et al., 2008; Sullivan et al., 2008). Although such a situation is anticipated, we certainly hope that it will not transpire. Yet if it does, it is important to understand why it has transpired and, moreover, be as accurate and comprehensive as possible in appraising the findings that are in the literature on G×E. In the next part of the chapter, we consider a number of characteristics of G×E studies that may explain why successful replications have proven difficult to realize.

Measurement Error

As discussed already, G×E studies are highly susceptible to measurement error in the assessment of genetic (Wong et al., 2004) and environmental exposure (Caspi et al., 2010; Luan et al., 2001) indicators. The former is viewed as less threatening, as quality control for genetic data is typically set at a threshold of 1% or less, and error per se can be quantified exactly by genotyping the same individuals on the same markers twice. The latter is thought to be much more concerning, as the magnitude of measurement error in exposure can be large, especially if captured by retrospective self-reports. Moreover, if measurement error around the exposure variable is high, even relatively small genotyping errors can result in a discernible impact on interaction estimates. In turn, poor measurement leads to a substantial loss of information. For example, it has been demonstrated that the mode of measurement of exposure (e.g., stressful life events) can have an overpowering effect on indicators of both frequency of occurrence and predictive power of this exposure (Monroe & Reid, 2008), which can bias the results of the interaction regression. Thus, care must be exercised in determining how indicators of exposure are ascertained. There is a direct connection between reducing measurement error and improving the statistical power of a study, which suggests that minimizing measurement error may be a more cost effective alternative in conducting G×E analyses than increasing the sample size. In quantifying environment or exposure, it is suggested that precise objective measures be used, such as environmental sampling or observational measures and experimental techniques capturing biological indicators of stress, rather than subjective reports.

It has been argued that smaller G×E studies tend to use these higher precision prospective measures, whereas larger ones tend to use lower precision retrospective reports (Caspi et al., 2010; Lotrich & Lenze, 2009). While this may be true, sufficient sample size for a study depends on a number of indicators, measurement error being only one of them. Even with the use of these more precise measurement tools, small studies can still be underpowered, and therefore more susceptible to either inflated false positive rates or publication biases, than larger ones, and it is generally difficult to justify a certain sample size without the use of comprehensive statistical power calculations. It is important to note that the presence of measurement error does not signify only one type of bias. The problem

is that if either factor (G or E) has been measured with error, the relation between them will be altered and biased toward a multiplicative model (Clayton & McKeigue, 2001). Specifically, Clayton and McKeigue illustrated that if the presence of interaction is established through lack of fit to a multiplicative model, the test for interaction will be conservative if there is measurement error, such that if the null hypothesis is correct, the test will not yield significant results more often than expected by chance. If any other definition of interaction is used, the bias of the test (conservative or liberal) in the presence of measurement error is difficult to predict.

There are ways to correct for measurement error in environmental variables (Thomas, Stram, & Dwyer, 1993), but these corrections typically require clear ideas of what the errors are, how they arise, and what their time-based properties are. Of note, in large-scale studies, exposures might not even be measured at the individual level, but rather, may be assigned based on some other information indicating ecologic-level exposures (e.g., exposure to natural disaster as a mere fact of having a registered address in the area where the disaster occurred, even though a given person might or might have not been in the area at the moment of the disaster), or obtained from another prediction model. Such uncertainties can lead to the manifestation of unpredictable biases, which may be especially detrimental to the model's accuracy if these biases are differential with respect to the phenotype. As a result, spurious interactions can be introduced (Holmans et al., 2009).

It is worth noting that even though there are methods of correction for measurement errors in indicators of G and E that are well established in studies testing for main effects, they have rarely been used in studying G×E (Lobach, Carroll, Spinka, Gail, & Chatterjee, 2008; Wong, Day, Luan, & Wareham, 2004). Nevertheless, interactions are less likely to be biased than main effects, except when the measurement errors are differentially associated with both exposure and genotype and, as a result, the measurement error is not equal for G and E factors (Thomas, 2010a).

Confounders

Yet another relevant issue that has been comprehensively addressed in the recent literature (Keller, 2014) pertains to controlling for potential confounders. The general point that an interaction term of interest should be adjusted for the effects of confounding variables has been put to force in other behavioral sciences (Hull, Tedlie, & Lehn, 1992; Yzerbyt, Muller, & Judd, 2004), but has not penetrated the field of G×E research. In its typical form, the analytical facet of G×E studies includes three variables—the genetic polymorphism (typically dummy-coded), the environmental factor (typically either continuous or somehow categorized), and the interaction effect (typically captured by the product of the two main effect variables). These variables are then placed in a linear or logistic regression with a predicted variable of conceptual interest (e.g., delinquent behavior, academic achievement, mental health indicator). Keller (2014) and others (Hebebrand et al., 2010) rightfully noticed, however, that there are additional variables—race/ethnicity, gender, age, socioeconomic status, education, IQ, among many—known to be predictive of outcomes of interest, as main effects or members of other interaction terms, that are often treated by G×E researchers as noise to be controlled for. To that end, these potentially important variables are either residualized out prior to fitting the regression, or else they are included as covariates. Keller, however, argued that the proper account for the confounding effects of these additional variables can be achieved only if the full factorial model is tested, specifically, if all of the covariate × environment and covariate × gene interaction terms are tested for in the same model where the G×E interaction is featured. For example, to adjust the G×E term for gender and general cognitive ability, the regression should include the following terms in addition to the two main effects (of G and E), and their interaction (G×E): the main effects of the covariates—gender, general cognitive ability, and the interaction of the covariates with both G and E—gender × G, gender × E, general cognitive ability × G, and general cognitive ability × E.

Keller (2014) attributed his view on how best to adjust for confounding variables to Yzerbyt and colleagues (2004) but provided an application of this general solution to G×E models specifically. He also elaborated on the nature of related biases, and illustrated the profound gap between his expectations for adjustments to avoid confounding and the selected G×E literature he reviewed—in fact, not a single study that was featured as novel by Duncan and Keller (2011) met Keller's expectation. Although such a lack of proper statistical treatment, on its own, might not mean that the previously published G×E findings were not real, it does generate uncertainty about them (Keller, 2014). In all fairness, Keller (2014) acknowledged that the recommended treatment could be objected to, specifically, via references to model overfitting and multicollinearity. The pros and cons related to either approach are discussed in the broader epidemiological and other related literature (e.g., Chen et al., 2008; Kalil, Mattei, Florescu, Sun, & Kalil, 2010; Kim, Watkinson, & Anastassiou, 2011; Mizushima,

Tsuchida, & Yamori, 1999; Singh, Repsilber, Liebscher, Taher, & Fuellen, 2013), with no unequivocal outcome.

Scaling

There is a debate in the literature on how G×E interaction effects should be scaled. In psychology, the presence of interaction is typically detected via adding an interaction (product) term to a regression model and establishing the statistical significance of this term. In linear regression analyses, the product term's coefficient captures the degree of deviation from the additivity of main effects on the outcome (Kendler & Gardner, 2010). In logistic regression analyses, the product term's coefficient captures the degree of departure from multiplicativity in the risk of the outcome (Knol, van der Tweel, Grobbee, Numans, & Geerlings, 2007). Although it has been argued (Darroch, 1997) that the additive model of interaction is preferable, in fact, the literature is replete with examples of both types of regression analyses.

Because the field of G×E interaction, particularly as delineated in this chapter, is defined first and foremost by the statistical conceptualization of the interaction, making inferences regarding the mechanistic or biological relationships between the predictors and outcomes requires adherence to a set of conditions and assumptions (VanderWeele, Hernández-Díaz, & Hernán, 2010). One of the issues relates to the scaling of the interaction effects (Kendler & Gardner, 2010). Thus, simple scale transformations, e.g., logarithmic transformations that are commonly used for normalization purposes, can yield a statistically significant although spurious interaction, whereas *bona fide* interactions can disappear (Eaves, 2006; Kendler & Gardner, 2010; Thompson, 1991). The issue of scaling in the G×E field has been (Rothman et al., 1980) and remains (Eaves, 2006; Rothman & Greenland, 2005) disputed without an adequate resolution.

To gain a more concrete appreciation for how the concept of scaling removes interactions in a G×E study, we performed two simple simulation studies.

Simulation 1

We started by generating genotypes and environmental exposures for 500 participants. Genotypes, using the variable name geno, were sampled randomly from the set {0,1}, with 75% probability of a 1 and 25% probability of a 0. This represented a very simple case of a single gene under a dominant heritability model, in which the gene is captured by two alleles, B and b, with B being dominant over b. The genotypes BB and Bb were assigned the value 1, and the genotype bb was assigned the value 0.

TABLE 8.1 Contingency table of genotype (geno) and environmental exposure (env) in simulated dataset.

	env	
geno	0	1
0	69	60
1	172	199

We then generated an environment, with the variable name env, as a simple yes-no exposure to an environmental factor, with a 0 (no exposure) 50% of the time, and a 1 (exposure) 50% of the time.

We assumed environmental exposure to be independent of genotype as both variables were generated independently. Table 8.1 is the contingency table showing the randomly generated data.

This indicates that of the sample of 500 participants, there were 371 participants with either BB or Bb genotypes and 129 participants with the bb genotype; there were 241 unexposed and 259 exposed individuals. Of the BB and Bb participants, 172 were unexposed and 199 were exposed to the environmental factor; of the bb carriers, 69 were unexposed and 172 were exposed to the factor.

Next, we created a continuous (noncategorical) phenotype from the genotype and environmental exposure of each participant. We defined the genotype effect, g, and the environment effect, e, as the contribution of each feature to the phenotype, and assigned them values of 2 and 1, respectively. We then defined phenotype as an additive function of genotype and environment with the expected value of phenotype for each subject, given the genotype and environment, is g*geno + e*env. Table 8.2, the contingency table of means was thus.

Here we created an additive model. To do so, we added the same fixed value (in this case 2) to every column, going from the first row to the second row; and, we added the same fixed value (1) to each row, going from the first column to the second column.

The actual phenotype of each participant was the expected mean for that participant, plus some randomly generated (Gaussian) noise. As we started with a standard deviation for a noise level of 0.05, the following

TABLE 8.2 Table of expected means of the phenotype for each genotype/environment combination.

	env	
geno	0	1
0	0	1
1	2	3

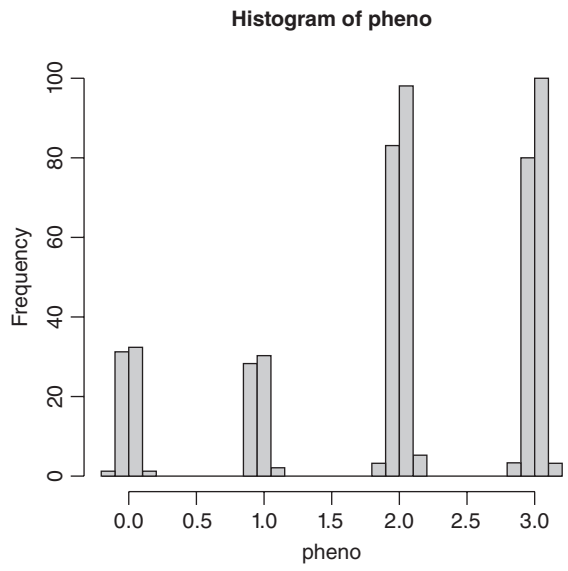

Figure 8.2 Histogram of simulated phenotypes using a standard deviation of 0.05.

distribution of phenotype values was produced, as indicated in Figure 8.2.

In this case, with a small level of noise in relation to the magnitudes of the G and E effects (indicated here by g and e, respectively), the values of genotype and phenotype were quite obvious for each participant. In the second step of our simulation, we increased the standard deviation of the noise to 1 so that the statistical problem was not so trivial. This increase in noise changed the distribution of phenotypes, as indicated in Figure 8.3.

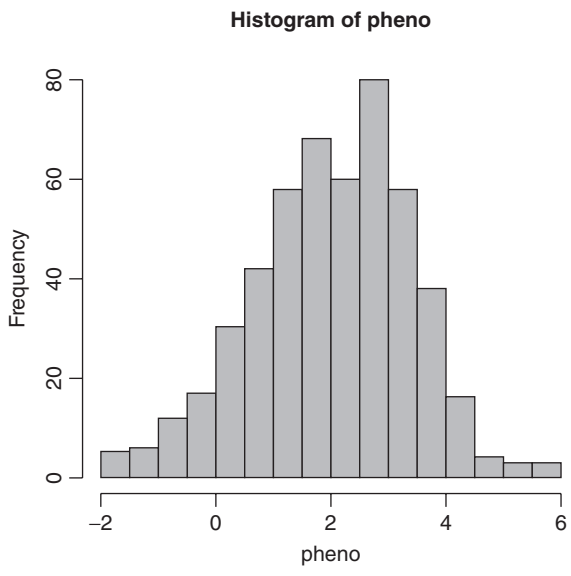

Figure 8.3 Histogram of simulated phenotypes using a standard deviation of 1.

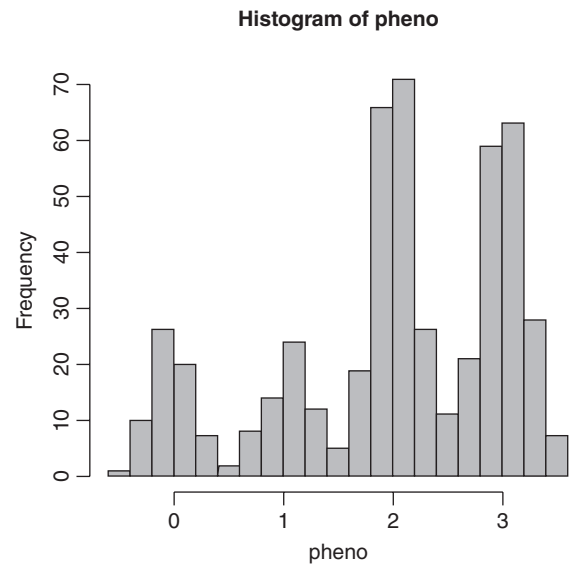

Figure 8.4 Histogram of phenotypes using a standard deviation of 0.2.

This increase in noise relative to the effect sizes (G and E) caused the distribution of phenotype values to resemble a continuous spectrum. In contrast to the previous example, the genotype and phenotype values were no longer clear.

As a third simulation (Figure 8.4), we established a noise level somewhere in the middle, e.g., 0.2. In this scenario, the distribution of phenotypes was different enough to estimate the specific genotype and environment effects, as shown below. However, the issues related to noise were not trivial, even in this circumstance.

Consider the average value of the phenotype for each genotype–environment value (Table 8.3).

These data are consistent with the parameters used to construct the model. This model is an additive model with no interactions between gene and environment, because it was constructed that way.

However, in practice, one never knows what the true underlying model is: one might have a good idea of what it should be, based on prior evidence, but all a researcher really has is the phenotype, genotype, and environment values and a guess for the model. We then guessed that we had an additive model with a G×E interaction, and used

TABLE 8.3 Table of observed means of the phenotype for each genotype/environment combination in simulated data.

	env	
geno	0	1
0	−0.0197	1.0338
1	2.0133	3.0059

TABLE 8.4 Table of observed means of the phenotype for each genotype/environment combination in simulated data, after scaling the phenotypes by an exponential transformation.

	env	
geno	0	1
0	1.04	11.82
1	113.97	1140.07

regression to estimate the effects (Table 8.4); that is, we regressed pheno on geno, env, and geno X env. R, gives the following output:

```
Call : lm(pheno ~ geno + env + geno:env)
Coefficients:
           Estimate Std. Error t value Pr(>|t|)
(Intercept) -0.01970   0.02487  -0.792    0.429
geno         2.03303   0.02883  70.519   <2e-16 ***
env          1.05346   0.03589  29.349   <2e-16 ***
geno:env    -0.06086   0.04144  -1.469    0.143
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05
                                        '.' 0.1 ' ' 1
Call : lm(pheno ~ geno + env + geno:env)
Coefficients:
           Estimate Std. Error t value Pr(>|t|)
(Intercept) -0.01970   0.02487  -0.792    0.429
geno         2.03303   0.02883  70.519   <2e-16 ***
env          1.05346   0.03589  29.349   <2e-16 ***
geno:env    -0.06086   0.04144  -1.469    0.143
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05
                                        '.' 0.1 ' ' 1
Call : lm(pheno ~ geno + env + geno:env)
Coefficients:
           Estimate Std. Error t value Pr(>|t|)
```

There are two things to notice here. First, our estimates for geno and env (in other words, g and e) were highly significant, and very close to the true values of 2 and 1, respectively. Second, the G×E variable was not significant—there was no statistical evidence for a G×E interaction. This was no surprise to us, but it might have been if this were real data instead of simulated data.

Next, to show what would happen if we scaled the data in a different way, we took the pheno values calculated above and replaced them with 10^{pheno} (that is, the inverse of taking the logarithm, base 10) (Table 8.4). We called this new phenotype variable pheno2.

In Figure 8.5 are the histogram of pheno2 and a table of means for each G×E combination.

We transformed our additive model into a multiplicative model: the second column became 10 times the first column, and the second row 100 times the first row. (These

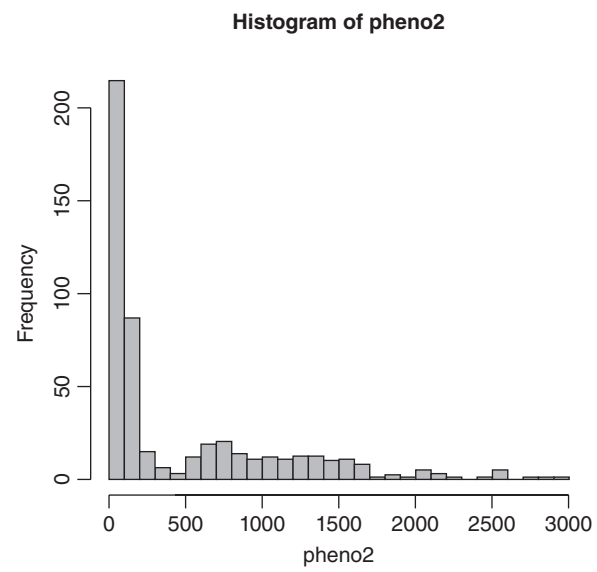

Figure 8.5 Histogram of phenotypes using a standard deviation of 0.2, after scaling the phenotypes by an exponential transformation.

multiplicative factors are not an accident—they are equal to 10^1 and 10^2, where 1 and 2 were our values of e and g.)

We then ran the same regression model—an additive equation with interaction—on these rescaled data:

```
Call: lm(pheno2 ~ geno + env + geno:env)
Coefficients:
           Estimate Std. Error t value Pr(>|t|)
(Intercept)    1.043     42.229   0.025   0.9803
geno         112.925     48.955   2.307   0.0215 *
env           10.779     60.952   0.177   0.8597
geno:env    1015.325     70.368  14.429   <2e-16 ***
Call: lm(pheno2 ~ geno + env + geno:env)
Coefficients:
           Estimate Std. Error t value Pr(>|t|)
(Intercept)    1.043     42.229   0.025   0.9803
geno         112.925     48.955   2.307   0.0215 *
env           10.779     60.952   0.177   0.8597
geno:env    1015.325     70.368  14.429   <2e-16 ***
Call: lm(pheno2 ~ geno + env + geno:env)
Coefficients:
           Estimate Std. Error t value Pr(>|t|)
(Intercept)    1.043     42.229   0.025   0.9803
geno         112.925     48.955   2.307   0.0215 *
env           10.779     60.952   0.177   0.8597
geno:env    1015.325     70.368  14.429   <2e-16 ***
```

This analysis showed an extremely highly significant interaction effect. Also, among the main effects, only genotype was significant, and to a much lesser extent than in the previous model.

What can we learn from this? Suppose the data came from a biological process that was truly multiplicative; that is, that the multiplicative model was a true reflection

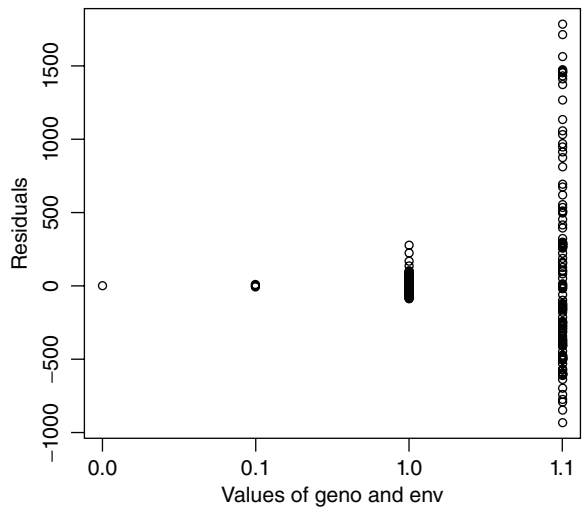

Figure 8.6 Model residuals using exponentially-transformed phenotypes, as a function of genotype and environmental exposure. Note the large difference in variance of the residuals among different combinations of genotype and environmental exposure.

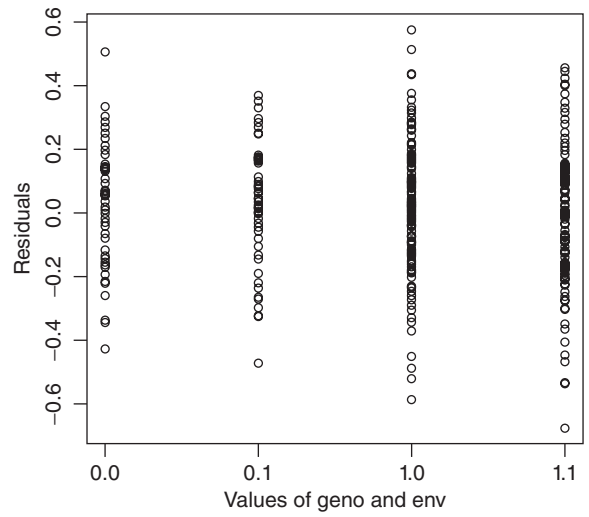

Figure 8.7 Model residuals using unscaled phenotypes, as a function of genotype and environmental exposure. Variance of residuals is approximately the same across all genotype/environment pairs.

of reality and the interaction term above always appeared using this type of additive model. We could then propose taking the logarithm of the phenotype variable—and if we do that, then we would get the first regression model with no significant interaction term (note that if we took the log with respect to a base other than 10, the estimated coefficients would change but the nonsignificance of the interaction term would not). In other words, if we have a significant interaction term in one model, it can be wiped out in another model by transforming one of the variables.

Another lesson to be learned is that the two regression models here were not equally valid. One of the assumptions of a regression model is that the variance of the error term should not depend on the explanatory variables. For our second model, when the additive model applied to pheno2, this was not the case: Figure 8.6 of the residuals against the combinations of genes and environments shows that that the residuals exhibited a huge variance for the 1–1 case, but a variance near zero for the 0–0 case.

This type of structural dependence of residuals on variables used in the model is a hint that the model is inappropriate for the data, and that transformations of the data *should* have been applied. For comparison, we looked at this plot of residuals for our first model (Figure 8.7), when pheno was on its original scale (or equivalently, after taking logs of pheno2).

This is preferred—the residuals now appear to be independent of both genotype and environment.

Simulation 2

In Figure 8.8 we give an account of an interesting example from L. Eaves (2006) of a scenario in which a standard analysis of affectedness by logistic regression is likely to show a significant G×E interaction, whereas a good case can be made that there is no such interaction in the disease etiology. The disease model assumes additive effects of a candidate gene and measured environment on a latent liability to the disease, and a person is affected if that person's liability is greater than a threshold that is constant over the population.

Before describing our second simulation, we consider the example illustrated by Figure 8.8. For simplicity we consider two possible genotypes G = 1 and G = 2; this could be a SNP locus with a dominant allele, for example. There are four possible values for the environmental variable E = 1, 2, 3, or 4. For each genotype G = 1 and G = 2, there is a baseline distribution of liability when E = 1, and each additional unit of E adds a constant increment to the liability—it is important to emphasize that these increments take a constant value (0.35 in this example) not depending on the value of G. In this sense, there is no interaction between G and E in the etiology of the disease. The two baseline liability distributions (one for G = 1 and one for G = 2) are shown as the two probability density functions in the first row (corresponding to E = 1) of the figure above. Both of these baseline liability distributions happen to be bimodal mixtures of two Normal distributions. This may look a bit exotic but helps make

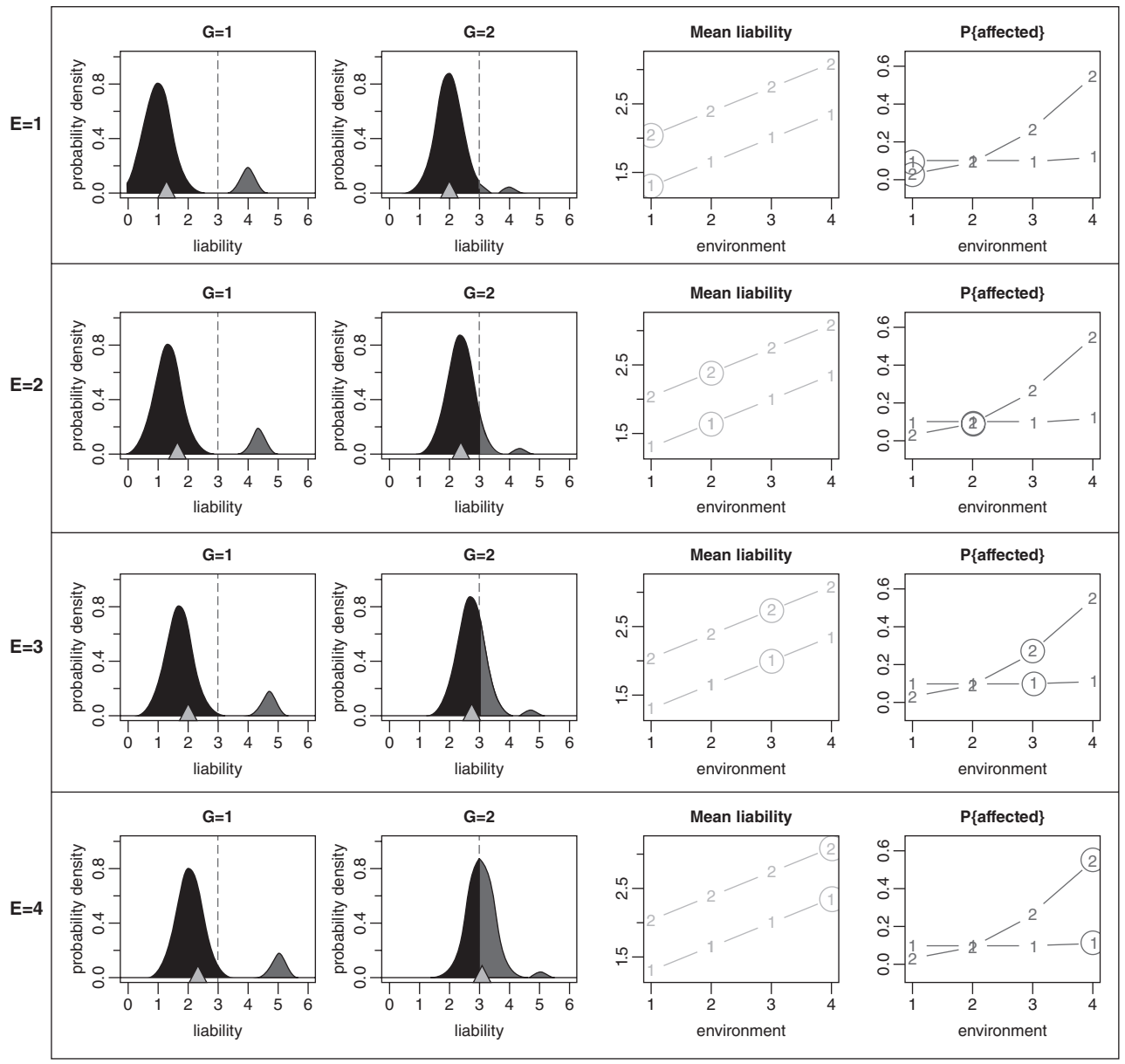

Figure 8.8 Illustrating an example of Eaves (2006) having G×E interaction in a model of affectedness but no G×E interaction in the corresponding model of liability. See footnote 1.

the phenomenon easy to generate and visualize, and, as we intend to show elsewhere, similar phenomena can also be manifested with simpler Normal distributions.

Scanning down the first column of Figure 8.8 we see that when G = 1, the effect of each unit of E is to shift the liability distribution to the right by a constant amount, here 0.35. Similarly, scanning down the second column, when G = 2, the effect of each unit of E is precisely the same, adding 0.35 to the liability. The green triangles in the first two columns show the mean liabilities in the various (G,E) combinations. Notice how moving from one plot to the next in a column simply shifts the liability distributions and their means to the right by 0.35. These mean liabilities are illustrated in the green plots in the third column of Figure 8.8. In both the third and fourth columns of the figure above, the 1's and 2's in the plot indicate which genotype is being plotted, and the points corresponding to the value of E in a row are circled. So in the third column, the circled green values mark the two mean liabilities for G = 1 and G = 2 for the value of E shown in that row. Since the effect of environment on liability is the same for all genotypes, there is clearly no interaction between

genotype and environment in determining liability. This is reflected in the third column of figure above, which shows the classic configuration of parallel lines, signifying no interaction.

However the situation is very different if we look at the probability of being affected. We assume each person is affected if his or her liability is greater than 3.0. In the liability densities shown in the first two columns of Figure 8.8, the threshold at 3 is shown as a red dotted line, and the red areas under the liability density curves to the right of the threshold represent the probability of being affected in each (G, E) combination. These probabilities are plotted in the fourth column of Figure 8.8. For example, when E = 1, looking at the two liability density plots in the first row, we see the red area is larger when G = 1 than when G = 2; in the P{affected} plot in the E = 1 row, this corresponds to the circled red 1 being above the circled red 2. In contrast, when E = 4 in the bottom row, we see that the red area for G = 2 is much larger than that for G = 1; this corresponds to the circled 2 in the P{affected} plot in the fourth row being well above the circled 1. The nonparallel (indeed, crossing) nature of the curves showing the dependence of P{affected}on E for the two values of G suggests an interaction.

To investigate the kind of behavior we can expect when standard data analysis methods are applied to a scenario like this, we simulated 1000 data sets, each of which consisted of 1000 people having genotypes, environments, liabilities, and affectedness generated according to specifications following Eaves (1996). Analyzing the liabilities by ordinary least squares regression showed no evidence of G×E interaction: the P values for the interaction term were uniformly distributed between 0 and 1, with 46 of the 1000 P values (4.6%) falling below 5%, as expected when there is no interaction. On the other hand, using logistic regression to analyze the affectedness typically showed a very highly significant G×E interaction; in fact, the median P value for the interaction was only 0.0000032, and fully 99.6% of the P values for G×E fell below 0.05. Taking a look at how these two analyses came out for a very typical data set came out as follows, with the ordinary regression for liability gave output

```
Call: lm(formula = liab ~ g + e + g:e)

Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)  0.27959    0.13410   2.085   0.0373 *
g            0.59320    0.07854   7.553 9.62e-14 ***
e            0.41732    0.07696   5.423 7.37e-08 ***
g:e         -0.01054    0.04402  -0.239   0.8108
```

whereas the logistic regression for affectedness gave output that included an impressively significant interaction

```
Call: glm(formula = dx ~ g + e + g:e, family
                  = binomial)
Coefficients:
            Estimate Std. Error z value Pr(>|z|)
(Intercept)  -1.1273     0.6101  -1.848 0.064651 .
g            -1.4386     0.3931  -3.659 0.000253 ***
e            -0.5886     0.2946  -1.997 0.045772 *
g:e           0.7752     0.1704   4.549 5.38e-06 ***
```

So was there an interaction in these examples, or not? As we have seen, a case could conceivably be made for both answers in both examples. However, if an explanation involving interaction relies on a particular scaling of the variables, and another reasonable scaling exists in which the interaction disappears and a simple additive model fits well, one might well prefer the simple additive model. In the first simulation, a very simple, ubiquitous transformation—taking logarithms—was sufficient to transform a multiplicative process that appeared to have a strong interaction to an additive process with no interaction. In the second example, a simple binary transformation generated an appearance of G×E, even though the main effects of G and E on an underlying quantitative trait (the liability) were purely additive. So the liability provided a simple additive description of the disease process with no G×E interaction, but as the liability is a latent variable it may require more ingenuity or sophisticated methods to uncover this simple description.

These simulations raise a more general concern pertaining to the definition of G×E interaction (Flint & Munafò, 2008). Indeed, given that statistical interactions are susceptible to scaling effects, the issue is how useful this term actually is, especially if the null hypothesis, however formulated, has no discernible biological meaning.

Types of Interactions

It is assumed that only 1–2% of cancer syndromes can be explained by inherited cancer syndromes of high penetrance (Ponder, 2001). In fact, the population-attributable fractions of known environmental factors are considered to be up to 90% for cancer syndromes (Doll & Peto, 1981; Higginson, 1968). Similarly, the population-attributable fractions of known environmental factors are considered to be up to 70% for coronary heart disease, stroke, and type 2 diabetes (Willett, 2002). However, recent understanding of the related causation reflects a number of complexities. Specifically, it appears that some environmental factors

(e.g., tobacco smoking and asbestos exposure for lung cancer) interact and increase risk multiplicatively, not additively (IARC, 1990, 2004). Moreover, there appears to be a tremendous amount of individual variation in how environmental exposures are converted into cellular mechanisms and the role of genetic factors (e.g., carcinogen metabolism, DNA repair, cell-cycle control and apoptosis) in this conversion (Vogelstein & Kinzler, 2002). Thus, what were previously considered straight environmental factors might, in fact, reflect the co-action of G and E, which leads to the etiological conclusion that most diseases/disorders are interactions of G and E or multiple Gs and multiple Es (Guttmacher, Collins, & Carmona, 2004). Multiple dimensions have been discussed in the literature that allows the classification of G×E interactions. Here we exemplify some of these dimensions.

First, Ottman (1990, 1996) discussed a number of biologically plausible types of relationships between G and E with regard to their differential effects on disease risk. In the first model, exemplified by PKU, the effect of G is to generate or magnify the role of a risk factor, which can also be generated by E. In the second model, G exacerbates the effect of the risk factor but has no effect if the person is not exposed to this factor (E). This model is exemplified by the relationship between an autosomal recessive disorder, Xeroderma Pigmentosum, and ultraviolet (UV) radiation with regard to skin cancer. Although, in the general population, excessive exposure to UV radiation increases risk for skin cancer, this exposure is substantially riskier (and, thus, results in an elevated odds ratio) for individuals with this disorder, as they are deficient in an enzyme required for the repair of DNA damage induced by UV radiation. Per the third model, E exacerbates the effect of G, but not in individuals with the low-risk genotype. For example, individuals with the autosomal dominant disorder, Porphyria Variegata, develop skin problems of different severity (i.e., excessive blistering, scarring, changes in pigmentation under exposure to sunlight). Although an exposure to barbiturates is inoffensive in the general population, such individuals respond to the same exposure with acute attacks that might result in paralysis or even death. In the fourth model, both G and E risk factors are required to increase risk. To illustrate, most individuals with an X-linked recessive disorder glucose-6-phosphate dehydrogenase (G6PD) deficiency are asymptomatic; yet the consumption of fava beans (an ingredient widely used by the general population) by these individuals might result in the development of severe hemolytic anemia. Finally, in the fifth model, both G and E risk factors have some unique impact on the disease/disorder risk so that their co-occurrence either elevates or decreases the risk compared to their occurrence in isolation. An illustration of this model comes from the development of chronic obstructive pulmonary disease (COPD) in the context of a-1-antitrypsin deficiency (i.e., an inherited disorder causing dysfunction of the lungs and liver) and smoking; in fact, risk of COPD is elevated both in nonsmokers with a-1-antitrypsin deficiency and in smokers without a-1-antitrypsin deficiency, but is particularly increased in smokers with a-1-antitrypsin deficiency.

Second, as in epidemiology (Gail & Simon, 1985), two types of interactions are differentiated in G×E research. Crossover (qualitative) interactions are stated to transpire when a particular level of a factor (either G or E) is superior for some subset (or subsets) of the sample, whereas a different level of a factor is superior for other subsets. Noncrossover (quantitative) interactions are said to manifest when there is variation in the magnitude, but not the direction of the effect. The theoretical and practical values of these interactions are different, with the former being associated with higher significance and the latter with lower significance. The interactions also differ with regard to associated methodological vulnerabilities, such as sample size and power as well as high rate of false-positive effects (Bogdan, Agrawal, Gaffrey, Tillman, & Luby, 2014).

Third, another important typology pertains to the differentiation of essential and removable interactions (Wu et al., 2009). This differentiation occurred in the accrual of data from GWAS. While working with SNP × SNP interactions of different orders, these two types of interactions were defined such that an interaction is essential when the direction (and, possibly, but not critically, the magnitude) of the effect for at least one of the SNPs is changed in the presence of the other SNP (or SNPs). The interaction is removable when only the magnitude (but not the direction) of the effect of at least one SNP is changed in the presence of the other SNP (SNPs). This differentiation and systematic screening of all possible interactions is a chance to detect more interesting and stronger effects (Chen, Liu, Zhang, & Zhang, 2007; Marchini, Donnelly, & Cardon, 2005). The corresponding number of interactions, however, even limiting the scope of consideration to two-way interactions, is staggering, with a count of a million and more.

The importance of such constellations of interactions is obvious as most candidate gene studies are embedded in conceptual models featuring a specific biochemical pathway (or often multiple pathways), including more than one

gene and more than one polymorphism. To illustrate, the Southern California Children's Health Study, investigating the impact of air pollution on children's health in general and the manifestation of asthma in particular, is based on a theory engaging such etiological factors as inflammation, oxidative stress, and anti-oxidant intake (Gilliland, McConnell, Peters, & Gong, 1999). Similar reasoning is applicable to environmental or to a mixture of environmental and genetic factors; although the original study of G×E in cannabis usage (Caspi et al., 2005) tested for a direct interaction, subsequent studies tested for three-way (Henquet et al., 2009; Henquet et al., 2006) and four-way (Peerbooms et al., 2012) interactions.

The translation of this theoretical model into specific hypotheses assumed the simultaneous investigation of multiple genes representing such pathways. Indeed, polymorphisms in these genes, genes themselves, and pathways can interact; these interactions should be properly modelled and analyzed. Furthermore, these genetic interactions can be layered with interactions with specific environmental factors. There are various methods that are suitable for multivariate analysis of high-dimensional data. These methods include standard multiple regression techniques, various machine learning, and pattern recognition methods (Cordell, 2009; Hoh, Wille, & Ott, 2001; McKinney, Reif, Ritchie, & Moore, 2006; Moore & Williams, 2009; Ritchie & Motsinger, 2005).

G×E Study Designs

To explore main and interaction effects of genes and environments, studies of G×E utilize conventional epidemiological designs such as cohort, case–control, or a hybrid of the two (e.g., case–cohort; Andrieu & Goldstein, 1998; Manolio et al., 2006; Yang & Khoury, 1997). Just as in epidemiological research, the selection among designs is driven by weighing their strengths and weaknesses vis-à-vis factors such as biases and confounding variables, temporal sequences of exposure and disease, data accessibility and quality, and capacity to investigate common and rare diseases, disorders, and risk factors (Thomas, 2010a).

In addition, the literature contains a specific line of discourse pertaining to the utilization of traditional epidemiological designs specifically for the purposes of G×E studies (e.g., Collins, 2004; Manolio et al., 2006). As of today, the most present design in the G×E literature is that of case–control. In this design, a sample of carefully chosen people with (cases) and without (controls) the disease/disorder should be ascertained for a specific primary outcome so that similarities and differences between the two groups can be investigated with regard to the distributions of genetic (e.g., frequencies of specific polymorphisms) and environmental (e.g., frequencies of specific exposures) factors (Gordis, 2000). In other words, these studies aim at investigating all individuals who are cases of disease/disorder, or are a representative sample of cases compared with a representative sample of all individuals who are free of disease/disorder. The literature acknowledges many advantages of case–control studies, specifically their relative ease of administration and low costs, their suitability for studies of rare diseases/disorders, and their capacity to sample multiple exposures retrospectively, maximizing the success of identifying true risk factors.

The majority of case–control studies are retrospective; thus, although they ascertain cases after the onset of the disease/disorder, they collect information about genetic and environmental risk factors that predates the onset of the disorder and, in so doing, make a priori assumptions about causality (Doll, 2002). It follows that they are exposed to multiple sources of bias. Indeed, as the corresponding literature has accumulated, the shortcomings of case–control studies have become a limiting factor in the utilization of this design. Among many such shortcomings, the most relevant to this discussion are the following:

1. The tendency for individuals with positive family history to participate at higher odds (Bhatti et al., 2005; Wang, Fridinger, Sheedy, & Khoury, 2001), which biases sample structure in a particular way
2. The tendency for clinically diagnosed cases to represent the most severe tail of the distribution (Guo, 1998), which biases the prevalence-incidence estimates (Neyman, 1955) and overlooks specific cases such as short-episode or fatal cases (Taube, 1968)
3. The difficulty for undiagnosed controls to constitute a bias-free group (Schlesselman, 1982; Wacholder, Silverman, McLaughlin, & Mandel, 1992) and the degree of comparability (by geographic and ethnical ancestry and by predominant environmental exposures) of cases and controls (Helgason, Yngvadottir, Hrafnkelsson, Gulcher, & Stefansson, 2005; Rosenberg, Li, Ward, & Pritchard, 2003)
4. The difficulty of accurately documenting exposure, as most of these studies rely on recalled rather than evidenced exposures to environmental (Feinstein, 1985) or genetic (Silberberg, Wlodarczyk, Fryer, Ray, & Hensley) risk factors.

In realizing the magnitude of these biases and the difficulties associated with the qualification and quantification of risk at the population level (Austin, Hill, Flanders, &

Greenberg, 1994; Hill, 1965) even when specific adjustments for these biases can be applied (e.g., Ben-Shlomo, Smith, Shipley, & Marmot, 1993), it has been argued that the estimates of risk at the population level is best obtained through prospective, population-based cohort studies (Gordis, 2000).

A number of arguments are put forth when the advantages of cohort studies are discussed (e.g., Manolio et al., 2006). First, in contrast to case–control studies, prospective cohort studies utilize representative samples of the population before disease/disorder onset. The underlying idea here is to follow a representative sample from before, throughout, and after specified time points (Manolio, 2003). These time points can be defined in a number of ways, e.g., as bracketing the age at onset of a particular disease/disorder (e.g., type 1 diabetes) or as developmental stages (e.g., infancy, childhood, adolescence, adulthood). The main aim of this design is to ascertain, in the population as a whole rather than among already affected individuals, risk factors for the manifestation of the disease/disorder or biomarkers for the disease/disorder's development. Thus, reduction of many related types of bias is the chief consideration for choosing prospective cohort design over case–control design. Second, cohort studies are particularly important for understanding the etiology and course of diseases/disorders with regard to investigating risk factors that are subject to recall biases (Langholz, Rothman, Wacholder, & Thomas, 1999). Third, prospective cohort design allows a comprehensive and standardized collection of various indicators of premorbid exposure in accord with the main objectives of the study. The problem of recall bias is not relevant, as exposure information is collected prior to the onset of the disease/disorder (Colman & Jones, 2004). Fourth, all members of the cohort are recruited and followed in a systematic way, so that the resulting sample is truly representative and all types of cases of disease/disorder are marked by equal probability of detection. Thereby, the case identification bias that is so problematic in case–control studies is minimized (Manolio et al., 2006). Fifth, unlike the case with case–control studies, multiple diseases/disorders can be studied simultaneously and the time window for disease/disorder onset can be established more precisely (Manolio et al., 2006).

Prospective cohort studies impose a number of requirements (Manolio et al., 2006). First, it is assumed that individuals ascertained into the cohort are characterized by similar genetic (e.g., ancestry) and environmental (e.g., dietary preferences) factors that are distinct from those who are not included in the cohort. Second, it is assumed that participants who are excluded due to attrition are similar to the remaining participants with regard to disease/disorder risks, both genetic as well as environmental. Third, inclusion/exclusion criteria, recruitment, and definition of outcomes should be unified for all members of the cohort. In other words, to avoid biases and ensure the similarity of data collection between cohort members who are and are not exposed to risk factors, whether genetic or environmental, it is assumed that the probability of disease/disorder diagnosis is independent of the exposure to the environmental risk factors, as well as of potentially confounding factors such as age, access to care, and other critical exposures. It is particularly important to document and track changes in exposure history; thus, exposure information should be collected repeatedly (Zeger, Liang, & Albert, 1998). Fourth, it is assumed that all members of the cohort are systematically evaluated for the occurrence of diseases/disorders. The critical feature of prospective cohort studies is that all cohort members have equal probability for the detection and diagnoses of diseases/disorders, regardless of their access to medical care. Therefore, cohort studies cannot rely on the identification of outcomes in the course of everyday clinical care and must embed regular evaluations of the cohort participants into the study procedures. Such evaluations, given their time-consuming and resource-heavy implementation, are the target of criticism of cohort studies. Fifth, and most importantly, it is assumed that prospective cohort studies adequately capture both incidence and accumulation of diseases/disorders and, thus, are characterized by large sample sizes. Sixth, it is assumed that these studies provide an opportunity to comprehensively sample risk factors of interest prior to the onset of cases.

To summarize, it has been argued that prospective cohort studies (Manolio et al., 2006) are particularly suited to (1) studying the full range of disease/disorder manifestations (e.g., diseases/disorders with high mortality at onset like pancreatic cancer or with a long preclinical phase such as type 2 diabetes; Collins, 2004); (2) the identification of predictive biomarkers manifesting prior to the clinical presentation of the disease/disorder (Langholz & Goldstein, 1996); (3) the identification of risk factors that transform after the onset of disease/disorder due to treatment, change in lifestyle, or imperfect or biased recall (Colman & Jones, 2004); (4) the investigation of common complex diseases/disorders of a polygenetic nature (Foster & Sharp, 2005); (5) the simultaneous investigation of multiple outcomes (ARIC Investigators, 1989; Colditz, Manson, & Hankinson, 1997; Kolonel et al., 2000; Leibowitz et al., 1980; Lloyd-Jones, Larson, Beiser, & Levy, 1999; Newman

et al., 2006; Troyer, Mubiru, Leach, & Naylor, 2004; Tsai et al., 2002; Women's Health Initiative Study Group, 1998); (6) confirmation and extension of findings obtained by other means—i.e., via other designs, such as case–control studies (Aleksic et al., 2002; Ellenberg & Nelson, 1980; Kannel, 1995) and dispelling misconceptions (Kannel, 1995; Stamler, 1991); and (7) providing, with adequate protection, wide access to data and samples for analysis and reanalysis (Marshall, 1997).

There are multiple examples of large-scale cohort studies that contribute to the world's general understanding of the epidemiology of health and disease/disorders, including studies in the United Kingdom (Foster & Sharp, 2005; Harvey, Matthews, Collins, Cooper, & U.K. Biobank Musculoskeletal Advisory Group, 2013; Pramanik et al., 2012; Swanson, 2012; Ul-Haq et al., 2014), Iceland (Winickoff, 2001), Germany (Aleksic, Jahn, Heckenkamp, Wielckens, & Brunkwall, 2005; Wichmann, 2005; Wichmann & Gieger, 2007), Sweden (Abbott, 1999), Canada (Gibson et al., 2008; Godard, Ozdemir, Fortin, & Egalite, 2010; Kosseim et al., 2013; Webster, 2008), France (Goldberg & Zins, 2014; Spira, 2014), and Japan (Yuasa & Kishi, 2009). These samples are of considerable size. For example, the UK BioBank, with a case population of 10,000, is considered to be adequately powered to detect risks of <1.15 for G and 1.50-2.00 for G×E (G. D. Smith et al., 2005). However, the public-health significance of genetic risk below 1.50 is not apparent, although it is of etiological and general scientific interest (Terwilliger & Weiss, 2003). Moreover, there are ethical, legal, and social issues related to establishing, maintaining, and using biobanks (Gottweis, Chen, & Starkbaum, 2011; Haga & Beskow, 2008; Kaiser, 2002; Weisbrot, 2012).

Notwithstanding such concerns, it has been argued that there is no comparable study in the United States and there is a need for (at least) one (F. S. Collins, 2004). The justification for this need is that, although there are many prospective cohort studies (Kannel, 2000; Riboli & Kaaks, 1997; The Women's Health Initiative Study Group, 1998), not a single one is substantially large or comprehensive enough to address the modern dominant causes of morbidity and mortality that may occur during the life span or to cover the diverse characteristics of the general U.S. population (Manolio et al., 2006). To illustrate the magnitude of effort that is envisioned in this context, consider the following excerpt from a power calculation, conducted to set up a framework for research using prospective cohorts (Manolio et al., 2006).

> According to our estimates, a prospective cohort study of 1,000,000 subjects would have sufficient power to detect an environmental exposure odds ratio of ≥1.5 for diseases of ≥0.05% incidence per year, such as colorectal cancer, whereas a study of 200,000 people could only detect an environmental odds ratio of ≥2.3 for diseases with this incidence. The minimum detectable odds ratios for genetic factors were slightly lower (indicating the power of the study was higher), mainly because a single individual has two "chances" of carrying a dominant risk allele. For interactions, however, the minimum detectable odds ratios were much higher (that is, the power was lower), as would be expected from the much smaller number of participants exposed to both genetic and environmental risk factors. Whereas a prospective cohort study of 1,000,000 had sufficient power to detect a G×E interaction odds ratio of ≥1.4 for diseases of ≥0.5% incidence a year, a study of 200,000 could only detect this G×E interaction odds ratio for diseases of ≥3% incidence. For a disease of 0.05% incidence, the minimum detectable odds ratio was about 2.4 in the 1,000,000-person study, and as much as 7.0 in the 200,000-person study. Minimum detectable gene–gene odds ratios were slightly lower than G×E odds ratios. Genetic and environmental marginal odds ratios and interaction odds ratios of at least 1.5 are likely to be important to detect, as this is the magnitude of risk associated with genetic variants that is known to be important in complex diseases such as diabetes (Altshuler et al., 2000; Grant et al., 2006). A cohort of 200,000 will provide adequate power within 5 years for only the most common diseases, such as cataracts and hypertension, and will miss these effects for important diseases such as myocardial infarction, diabetes and all cancers. By contrast, a cohort size of 500,000—the number recommended by the NHGRI Expert Panel for a US cohort—will capture many more of these effects. For rarer diseases such as Parkinson disease or schizophrenia, G×E interactions would probably not be detectable within 5 years, even with 1,000,000 participants, but might be approached by continued follow-up and accrual of additional cases (or pooling with other cohort studies) over time. Conversely, G×E interactions for more common diseases, such as hypertension, could be examined early in follow-up and could be assessed for consistency in key subgroups. Of course, consideration of higher order interactions (gene-by-gene-by-gene, or multiple interacting genetic and environmental factors) will require larger sample sizes and might not be approachable within a single study, even for the most common outcomes. (Manolio et al., 2006, PP. 817–818)

Although the envisioned efforts are breathtaking and impressive, the value of cohort studies is not universally accepted (Barbour, 2003; Khoury, 2004). The main points of criticism are the necessity for large sample sizes and long durations, both of which are associated with high costs (Clayton & McKeigue, 2001). Other criticisms of prospective cohort studies point to their lack of flexibility and innovation, as they are locked into particular constraints by design and original hypotheses (Jamrozik, Weller, &

Heller, 2005; Kannel, 2000; Taubes, 1995). Moreover, there are concerns about a multiple testing issue (Terwilliger & Weiss, 2003), as there are a large, and perhaps infinite number of models that could fit the generated data. Arguing against forming new prospective cohorts (the anticipated cost of which is estimated at $3 billion), some (Willett et al., 2007) have suggested assembling cohorts using a combination of samples from existing studies. Although appealing from a cost-reducing standpoint, such a strategy has a number of drawbacks, specifically, lack of standardization of measures across samples, inability to take advantage of new developments in measurement (e.g., dietary intake) and exposure assessments, lack of representation of all strata of the society, uneven age bands (most if not all of existing cohorts include individuals younger than 50, yet it is important to cover a whole spectrum of life span, from birth to death), and constraints pertaining to free and open access to the data by qualified investigators (Collins & Manolio, 2007). These concerns are part of an ongoing discourse, where both sides are trying to negotiate the best possible solution that utilizes both approaches, to whatever degree possible.

In sum, given that both of the major designs used for studying G×E (i.e., case–control and cohort designs) are less than ideal and come with their own array of pros and cons, the field has been challenged with the development of methodological innovations that might overcome the limitations of both or either approaches.

One such innovation is the nested case–control design (i.e., subsamples of both controls and incidence cases from the cohort), which represents an attempt to capitalize on the strengths of both designs while compensating for their weaknesses. The case–control within a cohort or nested case–control design (Mantel, 1973; Prentice, 1986) assumes the utilization of an informative subgroup of cohort members. Although a subtype of the classic case–control design, this design is more resistant to various biases because it permits selection of incident cases and a sample of disease-free controls from an already-established prospective cohort. In other words, as various environmental indicators are collected for the cohort in an outgoing fashion, critical exposures are assumed to be measured before the onset of diseases/disorders of interest. Moreover, biological samples in cohort studies are typically collected if, at the study entry, they can provide unique preexposure information. This design allows the construction of subsamples of cohort members as grouping meets specific objectives of an investigation (e.g., examining the impact of exposure to a particular environmental toxin at a particular geographic location). The use of biobanks, then, overcomes the concern of reverse causation by relying on stored specimens and the information on exposure, both of which were obtained at enrollment.

Yet another innovative design is referred to as Mendelian randomization—a technique that permits an investigation of the causal effect of modifiable exposure to a disease/disorder while capitalizing on the availability of the measured variation in genes of known function (Gray & Wheatley, 1991; Greenland, 2000; McGrath, Mortensen, Visscher, & Wray, 2013; Relton & Smith, 2012). The logic behind this design is as follows: in an ideal genetic association study, Mendelian laws are assumed to guarantee the comparative evaluations of groups of individuals, so that groups established based on specific genotypes (e.g., AA, aa, and Aa) will be comparable to a randomized comparison. This is reasonable given that these genotype-based groups should not differ systematically, except for the effect of linkage disequilibrium (i.e., the dependency between genetic sites that extend over the locus under study due to the phenomenon of linkage disequilibrium). This design is thought to be less susceptible to reverse causation and confounding (Clayton & McKeigue, 2001; Didelez & Sheehan, 2007; Julier et al., 1991; Smith & Ebrahim, 2003) and has been used in G×E studies (Lewis et al., 2011).

In addition, there are numerous nonconventional epidemiological designs applicable to the analyses of G×E interactions. One such design is a cluster of family-based association tests (FBATs), which can be exemplified through case–parent trios (Schaid, 1999), case–sibling pairs (Gauderman, Witter, & Thomas, 1999), extended pedigrees (Laird & Lange, 2006), and other combinations of relatives (Cui et al., 2003; Guttmacher et al., 2004). The FBATs are designed to avoid bias from population stratification. In general, population stratification is of concern for studies of G×E only if there are differential relationships between gene and environmental factors in the population of the substructures (e.g., dissimilar genetic ancestries in exposed and unexposed individuals). One of the most frequently utilized designs is that of the case-parent trio design (Shin, Infante-Rivard, Graham, & McNeney, 2012). In this design, the exposure information is collected only on the cases, and the comparison carried out is that of the relative genetic risks between exposed and unexposed cases. Notably, this design assumes that the parents are also genotyped; this information is especially important for studies of early-onset diseases. Yet another oft-used design is that of discordant sibships (Dabelea et al., 2000; Hoffmann et al., 2011). In this design, the exposure information is collected on all cases and controls and the interaction is tested by means of standard

conditional logistic regression. In addition, the literature contains examples of the utilization of twin studies (Boomsma, Busjahn, & Peltonen, 2002), family segregation (Andrieu & Demenais, 1997), and linkage analyses (Gauderman & Faucett, 1997; Gauderman & Siegmund, 2001; Schaid, Olson, Gauderman, & Elston, 2003) for testing the existence of G×E with unknown genes or specific genetic regions (Yang & Khoury, 1997). Yet, although FBATs are quite powerful for testing G×E interactions, assuming that relatives' exposures are not highly correlated (Gauderman et al., 1999), these designs lack power for testing main effects. In fact, their power for testing main effects is substantially less than that of conventional case–control studies that utilize unrelated controls.

Another design that could be used only to test interactions, not main effects, is the case-case or case-only design (Piegorsch, Weinberg, & Taylor, 1994). This design was developed to overcome the poor power for the detection of multiplicative interactions attributed to small numbers of cases or controls in cells at the cross-overs of risk factors for G and E (i.e., where the risk is present for both G and E) in the standard case–control design (i.e., the counts in the cells where both G and E risk factors are manifested can be low). The key feature of this design is the assumption of G×E independence in the general (source) population; specifically, this assumption allows one to avoid estimating this association among control individuals, which, in turn, increases power for the test of interaction. If this assumption is not violated (e.g., as it is in the case of air pollution), then the case-only design will generate reasonable estimates of odds ratios for G×E. However, if this assumption is violated, the design will generate a biased estimate of the interaction and an elevated Type I error rate (Albert, Ratnasinghe, Tangrea, & Wacholder, 2001). In reasoning through the bias vs. efficiency predicament, a two-part process might be helpful, wherein first, a formal test for the adequacy of the G×E independence assumption is carried out, and, second, the results of this test are used to determine whether the more robust case–control or the more powerful case-only design should be utilized. Yet this process has its own caveats (Mukherjee et al., 2008). First, the majority of G×E studies are still carried out on samples of modest size and would therefore be underpowered to test for the independence of G and E, likely resulting in a biased process. Second, the corresponding calculations for the variance components in the underlying model can be challenging given the model's uncertainty. The field has offered ways to overcome some of these caveats. For example, a method called empirical-Bayes (EB)-type shrinkage estimator has been developed (Mukherjee & Chatterjee, 2007) to achieve a balance between bias and efficiency. In other words, this estimator can maintain optimal or close to optimal mean squared errors among all of the different estimators of interactions irrespective of the true state of the G×E relationship. Empirical interrogations of this estimator suggest that it is unbiased asymptotically. Furthermore, most violations of the assumption of G and E independence are not egregious (Liu, Fallin, & Kao, 2004). The usage of the estimator, then, in conjunction with the increase in the sample size, is thought to result in an eventual decrease in Type I errors (Mukherjee et al., 2008). This estimator appears to present an approach to detecting and estimating G×E interactions from case–control studies by maintaining a desired level of Type I error. Moreover, it does this in the context of realistic assumptions of G and E dependence while improving power compared with the traditional case–control studies that assume G and E independence.

Yet another type of nonconventional design is that of a two-phase case–control design (White, 1982). This design leverages readily available surrogate indicators of exposure (e.g., self-reported retrospective accounts of exposure, phase one) to choose individuals for more detailed assessment of exposure or genotyping (e.g., indicators of exposure based on particular biomarkers, phase two). Phase one typically capitalizes on the existence of both disease/disorder status and the surrogate indicator of exposure present in an ongoing case–control or cohort study, so that a sample for phase two can be built using independent sampling. Thus, although phase one might be relatively inexpensive, phase two can be quite expensive because information on exact doses, confounders, or modifiers requires additional data collection (Breslow & Chatterjee, 1999). Optimally, in phase two, more rare cells (typically, the exposed cases) are overrepresented. In the analyses, the information from both phases is combined so that corrections for biased sampling in phase two can be introduced. An illustration of the utilization of the two-phase case–control design comes from the Atherosclerosis Risk in Communities (ARIC) study, where the interaction between polymorphisms in *GSTM1*/*GSTT1* genes and cigarette smoking on the risk of coronary heart disease was investigated (Breslow, Lumley, Ballantyne, Chambless, & Kulich, 2009; Li et al., 2000). The literature has examples of direct (Caporaso et al., 2009; Thorgeirsson et al., 2008) and indirect associations (Thomas, 2000). A two-phase design was used in a randomized trial of estrogen plus progestin to evaluate interactions of treatment with thrombosis biomarkers (Dai, LeBlanc, & Kooperberg, 2009).

According to the results of this study, estimates of the interaction effect were much more accurate than the estimates obtained from either the case–control study or the two-phase study (and corresponding estimators) in which G and E independence was not assumed.

The two-phase design has a number of derivatives, one of which is countermatching. In this design, each case is matched to one or more controls on the basis of exposure; each matched set should contain the same number of exposed individuals. An illustration of countermatching comes from studies of breast cancer (Langholz & Goldstein, 1996). Notably, the usage of this design has been stated to increase power both for main effects and for interactions (Andrieu, Goldstein, Thomas, & Langholz, 2001).

Finally, it is important to note alterations in established designs such as those of GWAS using either microarray (Engelman et al., 2009) or sequencing (Bickeböller, Houwing-Duistermaat, Wang, & Yan, 2011) data. Now GWAS is used to carry out whole-genome analyses for environmentally responsive variants, known as Genome–Environment-Wide Interaction Study (GEWIS; Khoury & Wacholder, 2009). The expected advantages include both improvement in the targeting of interventions and treatment and the provision of more data for understanding mechanisms of complex human diseases and disorders (Caspi & Moffitt, 2006). However, as GEWIS is new, it has a number of challenges, chiefly those dealing with multiple testing (Caspi & Moffitt, 2006), handling effects of nested environments (Rodgers, Ezzati, Vander Hoorn, Lopez, & Lin, 2004), utilizing existing specimens and medical and other records (Modinos et al., 2013), and interpreting G×E findings (Zammit, Lewis, Dalman, & Allebeck, 2010). To date, there are only limited examples of GEWIS. For example, GEWIS has been utilized to examine the role of genetic moderators in the effect of coffee drinking on Parkinson's disease (Hamza et al., 2011).

As Clayton and McKeigue (2001) pointed out, "The prospects for epidemiology in the post-genome era depend on understanding how to use genetic associations to test hypotheses about causal pathways, rather than on modelling the joint effects of genotype and environment" (p. 1359).

Power

As it gains experience and wisdom, the field is able to look back and reflect on its own accomplishments and failures. Thus, it is a well-recognized problem that the majority of early candidate–gene studies recruited samples that were substantially too small (Wacholder, Chanock, Garcia-Closas, El Ghormli, & Rothman, 2004). As sample size is directly related to effect size, there is always a question of what magnitude is considered to be of enough importance and interest to justify a research effort. The current trend in the literature is to view odds ratios of 1.4 as important, interesting, and potentially significant for public health (Hemminki et al., 2006). Detecting effect sizes of this magnitude calls for large sample sizes. Furthermore, the requirements for sample size increase exponentially when whole-genome rather than candidate gene studies are considered (Wang, Barratt, Clayton, & Todd, 2005). Perhaps unsurprisingly, the cost–benefit ratio of an association study that requires a sample of 10,000 cases and 10,000 controls to identify a gene whose variant is associated with an odds ratio of 1.4 has been questioned (Wang et al., 2005).

It is a well-established observation—empirically and theoretically, in both data-based and simulation-based studies—that statistical power is lower for interactions compared to main effects. It is also widely understood that the consequences of lower power are twofold: when underpowered, true effects are more likely to be missed; while conversely, the proportion of false discoveries among all discoveries is more likely to be high. In general, the power needed to establish and evaluate the impact of any predictor is positively related to the variance of that predictor; lower power to detect interactions is chiefly due to the fact that the dispersion of the product term in nonexperimental settings tends to be low (McClelland & Judd, 1993). On the other hand, power is maximized when the sample is drawn from the extremes of the distributions of main effects. While capitalizing on extremes is possible and suitable in experimental studies, it may be impossible and even inappropriate for human research, especially in the realm of public health.

Many researchers (e.g., Boks et al., 2007; Garcia-Closas & Lubin, 1999; Hwang, Beaty, Liang, Coresh, & Khoury, 1994; Smith & Day, 1984) have specifically investigated the statistical power of G×E studies and have similarly concluded that the power to detect G×E interactions is substantially lower than the power to detect either G or E main effects. Sampling alterations (e.g., the utilization of the extremes design) are possible with environmental/exposure extremes (i.e., sampling from high and low environments at equal numbers), but are near impossible with genotypic extremes (i.e., ascertaining the two types of homozygous carriers at the same frequency). Correspondingly, the way to maximize the variance in the product term is to maximize the variance in first-order (i.e., main effects or G and E) terms (Boks et al., 2007). For example, for a single-polymorphism/single-exposure study, it would mean

looking for a polymorphism in which the frequency of the derived (i.e., minor) allele in the population of interest is as close to 50% as possible; an exposure factor observed at its extremes at approximately the same numbers (e.g., 50% are highly or severely exposed to the factor of interest and 50%—never or only slightly exposed) would also be needed. Moreover, as described already, other considerations, such as sampling strategy (Cologne et al., 2004), study design (Kraft & Hunter, 2005), measurement error in the terms (Burton et al., 2009), correlations between variables capturing G and E (McClelland & Judd, 1993), and types and distributions of outcome and exposure variables (Luan et al., 2001) also impact statistical power to qualify and quantify the G×E interaction.

When these general considerations are applied to the literature on G×E, the overwhelming conclusion is that, so far, G×E studies have been underpowered (Burton et al., 2009; Duncan & Keller, 2011; Luan et al., 2001). This consistent conclusion has been reached in a number of studies (Mukherjee, Ahn, Gruber, Ghosh, & Chatterjee, 2010) for a variety of designs and circumstances: case–control studies (Foppa & Spiegelman, 1997; Garcia-Closas & Lubin, 1999; Hwang et al., 1994; Luan et al., 2001), case-only designs (Yang, Khoury, & Flanders, 1997), and association studies for detecting genetic main effects, where the use of G×E interaction is indirect (Hein, Beckmann, & Chang-Claude, 2008; Kraft et al., 2007). It is noteworthy that the largest studies of putative G×E effects to date have largely produced null results (Surtees et al., 2006), again, raising the suspicion that findings in smaller studies may, in fact, embody false positives.

Notwithstanding the study design, there are other factors that are important to consider in the determination of sample size. These factors are allele frequency, mode of inheritance, the prevalence of exposure (or its distribution if continuous), odds ratio for the main effects of G and E and the interaction effect of G×E, significance level, and desired power (Thomas, 2010a). Moreover, power appears to be sensitive to the nature of the estimators used to qualify and quantify G×E (Mukherjee et al., 2008). There are multiple pieces of software for the relevant power calculations, most notably, QUANTO (http://hydra.usc.edu/gxe, Gauderman, 2002) and POWER (Garcia-Closas & Lubin, 1999).

It appears that the current state of affairs in the field of G×E studies is characterized by the winner's curse phenomenon (Capen, Clapp, & Campbell, 1971): when the power is low, discovery studies presenting positive findings are more likely to report substantial effect sizes (Flint & Munafò, 2008). Such an ascertainment bias leading to an overestimation of genetic effects has been discussed (Goring, Terwilliger, & Blangero, 2001), as well as illustrated in the field of genetic association studies (Lohmueller, Pearce, Pike, Lander, & Hirschhorn, 2003). Thus, in a meta-analysis of 301 association studies, out of 25 loci detected as significantly associated, for 24, the odds ratios reported in replication studies were substantially lower compared with the initial report (Lohmueller et al., 2003). It is assumed that the pattern of results for G×E studies is similar (Flint & Munafò, 2008). The genetic association studies whose results have been replicated, as well as the replication studies, have utilized samples that included thousands (Zeggini et al., 2007) and tens of thousands (Cox et al., 2007) of individuals. G×E studies, compared with these genetic association studies, use sample sizes that are smaller, despite the fact that power calculation procedures prescribe the opposite. Although there are some large samples (>4,000, Surtees et al., 2006), they represent exceptions to the rule, and the average size of G×E samples is much smaller. For example, for the 18 studies of the serotonin transporter, the average sample size was 600 (Uher & McGuffin, 2008). The general rule is that if the interaction is of the same magnitude as the main effect and the power is maintained at the same level, the sample size for a study of G×E must be increased fourfold (Brookes et al., 2001; Smith & Day, 1984). This ratio, however, changes dramatically (to 100 or greater) if subtler (<20% of the main effect) effect sizes for interactions are considered (Brookes et al., 2001). Improved (i.e., with denser marker coverage) and enhanced (i.e., with larger sample size) GWASes should also include detailed indicators of environment, so that not only G, but also E is measured (Vineis, 2004; Willett, 2002). As discussed already, in many situations, interaction terms (either G×E or GxG) can bias and overestimate heritability estimates if they are not measured and modeled properly.

Replication

In general, it has been observed that the degree of replicability in the field of G×E is low. There are many different sources of heterogeneity in G×E studies, both for G (e.g., the ancestral population allele frequency) and for E (e.g., different sizes or chemical constituents of particulate air pollution across regions), as well as for confounders (e.g., co-pollutants, ethnic distributions with differing genetic background risk) that are inevitable and par for the course (Thomas, 2010a). If explained, understood, and accounted for, these sources of heterogeneity can provide insights into the etiology of the disease/disorder (Greene et al., 2009). Yet if sources of heterogeneity are attributable to spurious

inconsistency resulting from methodological limitations, data differences, and random differences between various studies, they turn into sources of noise (Thomas, 2010a).

Moreover, even if the field has conscientiously invested in attempting to replicate a finding, there is still ambiguity with regard to understanding and interpreting the results generated by such attempts. For example, the influential study by Caspi and colleagues on the connections among variation in the promoter of the serotonin transporter gene, stress, and depression (Caspi et al., 2003) has generated numerous replication attempts that have yielded contradictory results. Meta-analytic approaches have also generated conflicting conclusions: for one meta-study that exercised an inclusive approach, the phenomenon is replicable (Karg et al., 2011), whereas for another exercising a less inclusive approach, the phenomenon is, in fact, an epiphenomenon propagated by publication bias (Duncan & Keller, 2011). It is important to mention that results of meta-analyses themselves might be biased, depending on how the specific studies to be included are selected (Egger, Smith, & Phillips, 1997).

It has been suggested that the poor track record of replicating previously reported findings of G×E interactions is partially attributable to lack of power in both the discovery and replication samples (Burton et al., 2009; Ioannidis, Trikalinos, & Khoury, 2006; Matullo, Berwick, & Vineis, 2005). It is clear that better powered studies are needed for both discovery and replication attempts. Yet, this realization triggers another concern: as discussed above, it is not clear whether the results of large-scale studies aimed at dissecting a small effect of G×E are worth the effort, as their public health significance is questionable. It has been argued that specific genes involved in interactions are more likely to be affected through marginal rather than interactive effects (Clayton & McKeigue, 2001). The counterargument is that even when marginal effects are not detectable, there could be statistically significant interaction effects, which will be missed if the focus is exclusively on marginal effects. Indeed, it has been stated that the presence of interactions in the absence of main effects is a ubiquitous phenomenon in nature (Moore, 2003; Moore & Williams, 2009). Yet most examples of such universality come from studies at the molecular and cellular rather than the epidemiological level, although there are some examples of specific G factors that appear to group only with specific E factors, and that very combination generates excessive risk (Guttmacher et al., 2004).

In summary, there is much concern about the low rates of replication in the field of G×E. Yet these concerns are not limited to this field; in fact, the field of G×E is only one of many in which concerns about replicability and effectiveness of research are profound (Macleod et al., 2014).

Publication Biases

Both scientists and scientific journals are leery of publishing so-called null results (i.e., results that do not generate new findings). Among the many reasons for this phenomenon, the main one is that null results (or nonreplications, if a study was an attempt to replicate a previous finding) cannot be viewed as definitive: the inability to reject the null hypothesis does not mean that the null hypothesis is proven. Simply put, both attention and rewards in science are given mostly for the discovery of something new rather than the negation of something old. This publication bias, although logically understood, is assumed to be quite harmful to scientific literature in general and to the G×E literature in particular (Duncan & Keller, 2011), due both to its ubiquity (Thornton & Lee, 2000) and its distortion of the true significance of discovery findings (Ioannidis, 2005). The impact of this harm is difficult to quantify precisely, although some relevant estimates suggest that it is qualitatively large (Duncan & Keller, 2011), as per the hypothesis that many negative results go unpublished, amounting to an increased field-wide Type I error rate.

Another type of bias is nested within the bias against the publication of null results. This bias is captured by the disproportional publication of attempts at replication depending on (1) the nature of the finding (positive or negative), (2) the sample size used, and (3) whether an attempt at replication was coupled with a novel finding or presented by itself. It appears that the threshold for a publication of a nonreplication is substantially higher (i.e., a much larger sample size, sixfold compared with positive studies) if required, and a broader scope of work (i.e., a positive result on an additional G×E) is anticipated (Duncan & Keller, 2011).

It is important to note that the G×E literature is not unique in terms of producing a publication pattern characterized by a small number of high-profile findings, followed by a mixture of replications and nonreplications (Flint & Munafò, 2008). Such a pattern has been seen before in the literatures on GWAS (Munafò et al., 2003; Munafò, Matheson, & Flint, 2007) and endophenotypes (Flint & Munafò, 2007; Munafò, Brown, & Hariri, 2008).

Illustrations

So far, we have reviewed the general set of considerations for conducting G×E studies and have exemplified issues

and observations that have been accumulated by the field. In this section of the chapter, we will illustrate these generalities with two scenarios: one statistical (using a variety of diverse phenotypes and exposures and a single variant of G) and the other biological (using a cluster of related phenotypes, a single type of E, and a type of G).

Understanding the Variation in the Promoter of the Serotonin Transporter Gene

In mammals, serotonin (5-HT) is a major neurotransmitter, involved in numerous highly important biological processes like food intake, sleep, reproduction, circadian rhythm, thermo-regulation, pain, learning and memory, perception, social behavior, and mood regulation (Kriegebaum, Gutknecht, Schmitt, Lesch, & Reif, 2010). Its function in the brain is to substantiate a major type of brain signaling. Multiple proteins regulate the synthesis, degradation, transport, and reception of serotonin, and the production of these proteins involves multiple genes (Duman & Canli, 2010). Specifically, the synthesis of serotonin starts from the amino acid tryptophan and is two staged: the first rate-limiting step is catalyzed by tryptophan hydroxylase (TPH, the production of whose isoforms is controlled by two genes: TPH1, expressed primarily in the periphery; and TPH2, expressed primarily in the CNS). The degradation of serotonin engages enzymes monoamine oxidase A and B, encoded by the X-linked MAOA (central to the degradation of serotonin following its reuptake from the synaptic cleft by the serotonin transporter) and MAOB (central to the degradation of dopamine) genes, respectively. Serotonin is transported into the vesicles near the presynaptic membrane of neurons by the vesicular monoamine transporter (Vmat). The reuptake of extracellular serotonin is necessary for regulating serotonergic transmission and tone. This process is accomplished by the serotonin transporter, a protein encoded by the serotonin transporter gene (referred to as 5-HTT, SERT, or SLC6A4 and located at 17q11.1-q12) that enables the reuptake of excess serotonin from the synaptic cleft. Postsynaptically, serotonin binds to multiple serotonin receptor subtypes, which are encoded by 16 different genes.

In humans (but not exclusively), the SLC6A4 gene is highly polymorphic. One of the most studied polymorphisms in this gene is a common VNTR polymorphism in the promoter region (known as 5-HTTLPR polymorphism). This polymorphism exists in the form of two alleles: a short (*s*, composed of 14 copies of 20–23 base-pair repeated units); and a long (*l*, composed of 16 copies of the repeat unit) variants. The allele *l* has an embedded SNP (rs25531), which involves an A to G substitution. The presence of the G allele is associated with an expression rate similar to the *s*-allele (Hu et al., 2006). Although the allele frequencies for both polymorphisms (VNTR and SNP) vary in different populations, neither is rare, generating a robust source of individual differences in the functional properties of the synthesized protein. Individuals homozygous for the short variant (*s*-carriers) are thought to be characterized as demonstrating lower mRNA transcription (Lesch et al., 1996), increased extracellular 5-HT levels (Mathews et al., 2004; Montañez, Owens, Gould, Murphy, & Daws, 2003), and altered 5-HT receptor densities/function (D.-K. Kim et al., 2005), although recent work has suggested a more complex mechanism, such as regional up- and down-regulation of specific 5-HT receptors (Hariri & Holmes, 2006). The VNTR polymorphism is one of the most studied for associations between structural variability in the genome (i.e., variation at this site) and a plethora of behavioral traits (emotional regulation, Hariri & Holmes, 2006; coping with stress, Homberg, 2012; social conformity, Homberg & Lesch, 2011; social behavior, Kiser, Steemers, Branchi, & Homberg, 2012; emotionality, Murrough & Charney, 2011). As investigations of this polymorphism account for a substantial portion of the behavioral G×E literature, we have undertaken a descriptive characterization of this work.

To accomplish this task, we identified, using the PubMed, PMC, and Medline databases, a set of empirical articles published between January 2000 and December 2012 (including those published electronically, even if the journal publication date was in 2013); no unpublished work (i.e., dissertations) was included. Two literature searches were performed, using selection algorithms (1) ((“alleles” OR “genotypes” OR “genes” OR “polymorphisms”) AND (“G×E” OR “G by E” OR “gene × environment” OR “gene by environment”)) AND (Humans) and (2) ((“alleles” OR “genotypes” OR “genes” OR “polymorphisms” OR “G×E” OR “G by E” OR “gene × environment” OR “gene by environment”)) AND (“serotonin transporter” OR “HTTLPR”) AND (“humans”). The resulting pool of articles ($n > 1{,}000$) was examined with the following inclusion-exclusion criteria. The publications were included if the study examined an interaction between the serotonin transporter gene promoter polymorphism and an environmental exposure indicator deemed relevant to developmental psychopathology as a predictor of a psychological/psychiatric outcome (some of these studies also examined additional variants in other genes). The articles were excluded if (1) exposure indicators were obstetric complications, environmental toxins, diet, physical exercise, medical conditions, or

hormonal intervention; (2) no exposure indicator was identified and the interaction term included G and such factors as indicators of temperament, personality factors, or other psychiatric disorders (e.g., depression, anxiety, addiction); (3) outcome variables were other (nonpsychiatric) medical diseases or disorders (e.g., Crohn's disease, obesity); (4) the sample included related individuals of any kind (twins, other sibling pairs, or any other family members); and (5) more than one variant in the *SLC6A4* gene was investigated (e.g., haplotypes were analyzed). The application of inclusion–exclusion criteria resulted in the selection of 192 articles (see Appendix).

These articles were reviewed to extrapolate answers to a number of specific questions systematically. In general, the intent of the analyses presented here was to see whether this literature contains indications of the utilization of the best practices in the field (i.e., regarding observations and recommendations discussed in this chapter) in the selected publications. Thus, both the extrapolations and interpretations are based on the descriptive analyses of these studies as a group.

The first set of questions dealt with the sample size and the design of the analyzed studies. The sample size ranged from $n = 24$ to $n = 4{,}334$. Importantly, indicators of central tendency were quite variable: mean = 594.5, median = 301, mode = 118 (sd = 769.8). Taken together, this set of studies was still quite far from what is recommended as the standard in the field in terms of sample size. The majority of the samples were characterized cross sectionally ($n = 123$, 64.1%), but a substantial number of samples ($n = 69$, 35.9%) contained longitudinal data. All studies utilized a version of the traditional case–control design, even if there were previously collected longitudinal data.

Second, the studies were diverse in terms of utilizing samples including only women ($n = 27$, 14.1%), only men ($n = 9$, 4.7%), or both genders ($n = 156$, 81.3%). The studies were also diverse in terms of including different races and ethnicities.

The third block of questions pertained to issues of measurement error, both in G and E variables, however defined. In general, details of measurement were not well explicated in this set of studies, although many contained conventional psychometric indicators of the assessments that were utilized either to measure the outcomes or the exposure (E). The presentation of the measurement approach toward G was predominantly characterized by missing information with regard to the error rate for genotyping: only 34 studies (17.7%) reported error rates. Furthermore, only a handful of studies reflected on whether these rates met the expectations established in the field and discussed possible related biases. Notably, very few publications contained information pertaining to the presence of missing data and the process by which this missing data was accounted for (n = 28, 14.6%).

Fourth, only a very small proportion of outcome variables (6.8%) were transformed.

The fifth set of questions had to do with the range of outcomes, exposures, and polymorphisms (see exclusion and inclusion criteria above) utilized in the articles. All three were observed to present considerable ranges: 1–59 for outcomes (mean = 2.7, median = 2, mode = 1, sd = 4.7), 1–35 for exposures (mean = 2.2, median = 1, mode = 1, sd = 2.9), and 1–14 for polymorphisms (mean = 1.8, median = 1, mode = 1, sd = 2.0). Importantly, only 23 studies (12%) exercised any type of correction for multiple comparisons. The most frequently used was the Bonferroni, with other methods such as false discovery rate (FDR) applied only rarely.

Sixth, among the statistical techniques utilized for testing interaction effects, preferences were given to ANOVA/ANCOVA or MANOVA/MANCOVA (~20%) or different types of regression approaches (linear or logistic, ~60%). Typically, the statistical software used was not specified. When specified, the software was not tailored for G×E analyses in the majority of cases, and, therefore, was not necessarily the best vehicle to analyze the data.

Seventh, relatively few studies ($n = 45$, 23.4%) reported the obtained effect sizes and discussed their practical meaning.

Curiously, there were journals that were particularly receptive to the G×E studies involving the serotonin transporter gene during the period of time between 2000 and 2012. Thus, *Biological Psychiatry* published 15 and *Journal of Affective Disorders* published 12 of the 192 articles commented on here.

In this section, we summarized studies utilizing the statistical concept of G×E. Clearly, this interpretation of G×E attracts a lot of attention in the field and appears to generate studies, with the rate of published studies increasing over time. Interestingly, there appears to be a delayed reaction of the field to the criticisms that have been explicated in multiple reviews and meta-analyses. As this summary of the 192 articles demonstrates, the majority of the studies are still underpowered, have not paid enough attention to the issue of multiple comparisons, may not be sensitive enough to issues of measurement error, variable transformations and tracking confounders, and, most importantly, do not discuss the robustness, meaningfulness, or practical significance of the established interactions.

Understanding the Reaction Range in the Acquisition of Academic Skills

It is impossible, in modern society, to overestimate the impact of key academic skills such as reading, mathematics, and science reasoning on subsequent life success and life outcomes. This impact is omnipresent worldwide, and the effectiveness of country-specific primary and secondary educational systems is judged, in part, by how well students score on international competitions, such as the OECD Programme for International Student Assessment (PISA). In the twenty-first century, PISA has become "the world's premier yardstick for evaluating the quality, equity and efficiency of school systems in providing young people with these skills" (http://www.oecd.org/pisa/keyfindings/pisa-2012-results-overview.pdf, p. 2). While the importance of these skills is not disputed, there are two additional considerations that are also rather axiomatic at this stage. First, it is accepted, with the exception of a few rare developmental trajectories (i.e., extreme giftedness or circumscribed skills manifested in certain types of atypical development like autism), that all academic skills are constructed by a child as he or she experiences schooling. In other words, a child acquiring these skills builds a number of new cognitive (i.e., brain-based) representations that will guide the processing of relevant information. The formation of these representations requires a functional reorganization of the brain. Second, it is also known that, within any educational system (whether it is high-scoring such as Chinese, Taiwanese, or Finnish; mid-range-scoring such as German, Spanish, Russian, or American; or low-scoring such as Mexican or Indian, as per a number of PISA cycles), a tremendous amount of individual difference scatters student performance across the continuum. The presence of individual differences has been of interest to researchers around the world. As schooling was put in place only in the first half of the last century, the research into the student-based variation in learning that occurs even when teaching is homogenized has a history of only about 50 years. Yet these 50 years of research have unequivocally established that the efficiency of mastering the key academic skills of reading, mathematics, and scientific reasoning is tightly connected to variation in both the brain (in terms of its processing of the relevant information) and the genome (both structurally and functionally). Thus, the understanding of both the acquisition of, and individual variation in, core academic skills requires the investigation of how structurally diverse genomes assume the task of reorganizing the neural connections of the brain through schooling to acquire the academic skills of reading, mathematics, and scientific reasoning under the pressure of particular educational systems. In other words, this understanding requires a differentiation of the mechanism (or mechanisms) that delivers the environment (teaching or schooling) under the skin, so that a biological machinery (i.e., within a child) that ensures both the initial acquisition of skills and their further automatization and that explains individual differences in both the acquisition and utilization of these skills may unfold. It is argued here that one such mechanism is that of epigenetic regulation in general and DNA methylation in particular.

Five bodies of literature substantiate this argument.

First, the literature substantiates a high degree of genetic control in both the acquisition and maintenance of these three academic skills (reading, mathematics, and scientific reasoning), with some variation across skills. The literature also offers evidence that, while the degree of genetic control seems to be stronger in individuals who exhibit low performance on the academic tasks that utilize these skills, there is no reason to believe that the mechanisms of genetic control for poorer performers are different from the mechanisms of genetic control for stronger performers. In fact, it appears that whatever these mechanisms are, they operate across the range of academic performance (Elliott & Grigorenko, 2014).

Second, similar to other complex phenotypes, academic skills such as reading and reading-related components are highly heritable. However the currently considered candidate genes and corresponding polymorphisms do not account for meaningful portions of the previously estimated heritability. This phenomenon, which applies to these specific phenotypes among many others, has been referred to as the missing heritability problem. Concordantly, although limited, there is growing literature on the importance of G×E for the acquisition of academic skills (Pennington et al., 2009; Rosenberg, Pennington, Willcutt, & Olson, 2012; Taylor et al., 2010).

Third, there are large literatures (Fields, 2011), although uneven for the three skills, substantiating the presence of distinct distributed brain signatures that differentiate individuals who (1) are engaged in particular tasks requiring skills of reading, mathematics, and scientific reasoning as compared to individuals who are engaged in other types of tasks (or when the same individual is engaged in different types of tasks); (2) have acquired the skills versus those who have not (i.e., either when comparing young children who have not yet begun their formal education to older children who have completed

of primary education, or adults who have corresponding functional skills against those who do not have them, for example, literate and illiterate adults, or adults who can and cannot perform operations involving quantitative or scientific reasoning); and (3) perform within the normal range (i.e., within a particular quantification, whether 1, 1.5, or 2—whatever the criterion dictates—standard deviations around the population mean) compared with those who perform outside the normal range (i.e., outside of the established criterion, as defined already).

Fourth, there is a growing body of research indicating the role of epigenetic mechanisms in general and DNA methylation mechanisms in particular in all types of learning (Levenson & Sweatt, 2005). This research, however, has been conducted predominantly on animal models. The human epigenetic literature, however, has assessed the role of this mechanism only in social learning, and there is not a single study that investigates the role of this mechanism in cognitive/academic-related learning to date.

Fifth, there is now a strengthening line of reasoning which connects the literatures on the missing heritability problem, G×E studies, and epigenetics (Slatkin, 2009).

Thus, we argue that the acquisition of academic skills, all of which are both heritable and sensitive to environmental exposure (i.e., pedagogy), exemplifies the biological concept of G×E. As was the case 100 years ago, there is substantially less research on this biological interpretation of G×E compared to its statistical interpretation, but the reasoning presented in this chapter can and certainly should be translated into testable hypotheses.

FUTURE DIRECTIONS

Three observations appear to be instrumental in summarizing the material presented in this chapter in light of future developments. First, there is a critical mass of literature, spread across multiple fields of inquiry (epidemiology, genetics, psychology, and other fields) that indicates that designing, implementing, and interpreting G×E studies require conscientious consideration of a number of methodological caveats. Future studies of G×E should be judged being both aware and proactive about these caveats. The field is too advanced now to forgive any naïveté in those who wish to practice in it. Second, methodological rigor should be expected not only of publications, but also of proposals for G×E studies. In other words, funders should be educated along with researchers on the pros and cons of G×E studies. Finally, the whole field should carefully consider the practical implementations of G×E research. Even when carried out as rigorously as possible, what can the field learn from this research and at what cost? Answers to these questions should surely frame the future of G×E research.

CONCLUSIONS

There is no question that G×E studies have made an impact on the fields of developmental psychopathology, neuropsychiatric genetics, and genetic epidemiology, among others. As is obvious from the discourse above, this impact is complex and has instigated numerous kinds of actions and reactions.

First, there are hopes. The appeal of studying G×E is in the possible applications of the most reliable findings (yet to be secured!). Given the state of the field, it is difficult to predict what findings will be deemed reliable and what applications might be derived from these findings. Specifically, such findings can form a foundation—or at least lead to a set of guidelines—for targeting interventions for individuals at high risk (Khoury & Wagener, 1995). Three types of such guidelines have been discussed. The first type of recommendation (following the established the presence of the statistical G×E interaction) involves avoiding specific exposure. For example, researchers (Vandenbroucke et al., 1994) investigated whether the occurrence of venous thrombosis in young women who use oral contraceptives might be explained by the factor V Leiden mutation (this mutation results in resistance to activated protein C and, therefore, increases susceptibility to thrombosis). The reported differential increases in risk (Vandenbroucke et al., 1994) were four-fold among users of oral contraceptives, eight-fold among carriers of the mutation,, and 30-fold among carriers who used contraceptives. Clearly, carriers should consider alternative methods of contraception. The second type of recommendation involves forming relevant public-health policies. For example, in a study in Rwanda (Kolassa et al., 2010), individuals with extremely high levels of trauma exposure were stratified based on their genotypes at the serotonin transporter gene promoter site. It was reported that the individuals with the ss genotype were marked by a higher chance of manifesting lifetime PTSD regardless of the number of traumatic experiences, whereas the individuals with the l allele (i.e., ll or sl) had an elevated chance of developing lifetime PTSD only when the number of traumatic experiences was elevated. In the Florida Hurricane Study, individuals with the *s* allele were characterized by (1) the elevated

risk of PTSD only when their exposure to hurricane was higher and their social support was lower, compared to the rest of the sample (Kilpatrick et al., 2007); and (2) the decreased risk of PTSD in low-risk environments, but with an increased risk in high-risk environments (Koenen et al., 2009). Assuming that the multiple inconsistencies of G×E studies may be resolved and the robust findings replicated, relevant policies can be established to diversify services for individuals in disaster zones. The third type of recommendation involves seeking and receiving particular interventions in accordance with a particular genotype. In general, it has been stated (Baird, 2001; Rose, 1992) that in the realm of public health, the predicted health gains are superior in situations when the whole population, not just the high-risk group is targeted. This superiority is justified (Wallace, 2006), in particular, by the relative unimportance of genetic mechanisms in the risk of common complex disorders/diseases (e.g., lung cancer); the complexity of various types of interactions, GxG and G×E (e.g., schizophrenia); and the simplicity of the representation of environmental exposure, as typically captured by a single environmental factor. At the present time, there is no convincing support for the idea that delivering interventions based on individual genotypes improves the desired outcome. Yet, there are hopes that such examples will appear (Benner et al., 2014; Tucker-Drob & Harden, 2012), as, at least in developmental psychopathology, it has been suggested that "differential susceptibility may ideally lead to differential intervention and thus more effective treatment" (van Ijzendoorn et al., 2011, p. 50). There is also hope that the biological interpretation of G×E will help the field connect currently unconnected dots (e.g., to understand in detail the acquisition of highly heritable skills, for example, academic skills, which require a specific type of environmental exposure for each individual).

Second, there are precautions. In particular, two scientific journals, *Behavior Genetics* (Hewitt, 2012) and the *Journal of Abnormal Child Psychology* (Johnston, Lahey, & Matthys, 2013), have established requirements to be met before manuscripts presenting candidate–gene main or interaction effects can be considered for review. These requirements reflect many of the caveats of the field that we have discussed in this chapter. Thus, 15 years of G×E studies have taught the field to be particularly sensitive to the methodological aspects of research in general and the reproducibility of the results in particular.

Third, there are commentaries. This chapter was conceived as a constellation of observations from the literature on G×E, which is large and continues to grow, regardless of precautions. Although hopes for G×E remain high, so far, their realization has, in general, not risen to the level of our expectations. If anything, this discrepancy, as well as the numerous issues discussed in this chapter, "provides significant reason to pause for reflection" (Eaves, 2006, p. 1).

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APPENDIX

G×E publications reviewed to create Figure 8.1

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Queries in Chapter 8

Q1. As per design we treat Tables and Figures are float so we set top/bottom and changed sentences end with colon to period, please check and confirm.