# Gene-Environment Interaction

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## Abstract

With the advent of increasingly accessible technologies for typing genetic variation, studies of gene-environment (G × E) interactions have proliferated in psychological research. Among the aims of such studies are testing developmental hypotheses and models of the etiology of behavioral disorders, defining boundaries of genetic and environmental influences, and identifying individuals most susceptible to risk exposures or most amenable to preventive and therapeutic interventions. This research also coincides with the emergence of unanticipated difficulties in detecting genetic variants of direct association with behavioral traits and disorders, which may be obscured if genetic effects are expressed only in predisposing environments. In this essay we consider these and other rationales for positing G × E interactions, review conceptual models meant to inform G × E interpretations from a psychological perspective, discuss points of common critique to which G × E research is vulnerable, and address the role of the environment in G × E interactions.

## Contents





## INTRODUCTION

Universally acknowledged in principle, gene-environment (G × E) interaction presently appears to divide scientists as much as it binds a duality of nature and nurture. On the one hand, putative G × E interactions affecting behavior are now published by the handful monthly, extending to virtually all topics of psychological science and appearing regularly in journals of cognition; development; personality and psychopathology; health psychology; and social, cognitive, and affective neuroscience. The recent emergence of these literatures is abetted by increasingly accessible technologies for typing genetic variation, and undoubtedly also by the opportunities they afford to engage fundamental questions of heredity and environment that have variously intrigued, provoked, and inflamed psychology for a century. Yet, as enthusiastically as many psychologists embrace the prospect that genes moderate an environment's stamp or that some genetic effects on behavior may be conditioned by predisposing circumstance, others find the whole enterprise plagued with weaknesses, including inflated claims, genetic naïveté and woolly-headed biologizing, statistical inadequacies, rampant replication failures, publication bias, and a curious preoccupation with a small collection of dubious gene polymorphisms. It is not surprising then to see much G × E literature dismissed wholesale, as in a recent analysis of G × E studies of psychiatric disorders that attributed "most or even all" G × E findings to likely type I errors (Duncan & Keller 2011), or to read another refer to the sometimes uneasy alliance of psychology and molecular genetics by admonishing investigators to "play nice in the sandbox" of G × E research (Dick 2011, p. 401). Such controversy aside, the proliferation of G × E literature in recent years coincides with dampening expectations of rapid progress in identifying genes of direct association with psychological traits and disorders (phenotypes). In this context, we introduce G × E interaction here as one of several hypotheses offered to explain why discovered genetic variants have so far accounted for only a small portion of heritable variation in behavioral phenotypes. We then consider other

rationales for positing G × E interactions, discuss prevailing conceptual models of G × E interaction in psychology, and highlight key areas of critique of G × E literature. In closing, we consider the role of the environment in G × E interaction, and in particular, how environmental influences are expressed and what implications pervasive gene-environment correlations have for interpreting G × E research.

## PROGRESS IN GENE DISCOVERY

As the Human Genome Project neared completion of a first draft of the genome in 2000, a doyen of behavioral genetics, Robert Plomin, predicted psychology might soon be "awash" in genes (Plomin & Crabbe 2000). Thirteen years on, Plomin amended his forecast in light of unanticipated delays in gene discovery (Plomin 2013). These were not delays due to want of effort, as the intervening years saw a succession of methods deployed to locate genetic variation underlying heritable behaviors. The first approach was linkage analysis, which had already been applied for a number of years. Linkage analysis seeks variants of DNA sequence (markers) that co-occur with the presence of a disease or disordered condition in pedigreed families containing affected and unaffected members. Such co-occurrence, or co-inheritance, places the marker in proximity to a causal genetic variant, but because only a few hundred markers are commonly used, positive linkage signals may still be many, perhaps millions, of base-pairs (units of DNA sequence) distant from the responsible gene. Linkage analysis identified chromosomal regions associated with hundreds of Mendelian disorders that, like Huntington disease, are caused by single mutations. When extended to complex disorders, such as schizophrenia, bipolar disorder, or major depression, however, few replicated linkage signals emerged (Freitag 2007, Kendler 2011, Riley & Kendler 2006). This result directed attention to a major drawback of linkage analysis, namely its ability to detect only variants with large effects, and these were often limited to a select number of family pedigrees. The lack of success suggested, too, that many disorders may conform better to a polygenic model of inheritance, entailing many genes, each of small effect (Risch & Merikangas 1996).

A second approach, capable of detecting even modest associations, targets specific genes based on their suspected relevance to the phenotype of interest. Not surprisingly, in behavioral studies such "candidate genes" often encode components of neurotransmission, neuroendocrine function, or related cellular processes lying in plausible biological pathways. The aim of this approach is to determine whether the level of a quantitative trait or the presence of a disorder associates above chance with one or another variant (allele) of a known gene polymorphism or with a particular combination of alleles of multiple polymorphisms within the same gene (haplotypes). Unlike linkage analyses, candidate gene studies typically test for association in samples of unrelated individuals and often emphasize functional variation, such as promoter variants that affect the transcriptional efficiency of genes or base-pair substitutions in gene coding regions (exons) that alter the amino acid sequence of a protein.

Among notable successes are the discovery of a major risk allele for late-onset Alzheimer's disease in the gene encoding the lipid transport molecule, apolipoprotein E (*APOE*) (Poirier et al. 1993), and genetic variation in the ethanol-metabolizing enzyme, alcohol dehydrogenase 1B (*ADH1B*), which modulates risk for alcohol dependence and related medical sequelae (e.g., Bierut et al. 2012, Li et al. 2011). These and similar findings encouraged many psychologists to include molecular variation in their own research, with much of this work focusing on a limited number of candidate gene polymorphisms that could be genotyped at feasible cost and added to existing protocols. With the accumulation of studies, it became apparent that, unlike the two examples cited above, many candidate associations fare poorly in replication. The first polymorphism

prominently related to a human personality trait, novelty seeking, was a widely studied variant of the dopamine D4 receptor (*DRD4*) (Ebstein et al. 1996). Although this finding attracted much attention, the association proved equivocal in later research (e.g., Kluger et al. 2002, Munafo et al. 2008b), and weak or similarly inconclusive findings have emerged in meta-analyses of other highly cited candidate gene associations for personality and psychopathology, health-related behaviors, and cognition (e.g., Barnett et al. 2008; Chabris et al. 2012; Gyekis et al. 2013; Mandelman & Grigorenko 2012; Munafo et al. 2005, 2009b; Vassos et al. 2013). Nor is the replication problem limited to studies of behavioral phenotypes; a review of over 160 early candidate gene associations in diverse medical conditions found the vast majority of attempted replications unsuccessful (Hirschhorn et al. 2002). Although several explanations have been posited, including underpowered studies, heterogeneous or poorly measured phenotypes, and dilution of effects by unknown or untested moderators, the poor reproducibility of many candidate gene associations has lessened enthusiasm for this approach, at least among geneticists (Munafo 2006).

Another limitation of the candidate gene study is its reliance on a prior hypothesis, which narrows the search space for genetic variation to components of prevailing biological models and, hence, rarely nominates more than a handful of the estimated 20,000 to 25,000 human genes. And by prioritizing coding sequences and adjacent regions, candidate gene studies neglect large expanses of the genome that do not code for protein. Until recently, these regions were largely dismissed as uninformative, but such DNA may harbor abundant functional elements, such as sequences encoding untranslated RNA transcripts that can exert regulatory influences on far distant genes (Ecker 2012, Mendes et al. 2006).

Ultimately, sequencing entire genomes should reveal all sources of genetic variation among individuals, yet even with steeply declining costs, whole-genome sequencing may not gain wide feasibility for some time (Durbin et al. 2010). Until then, and for several years now, the most powerful method of gene discovery is the genome-wide association (GWA) study. GWA studies use DNA microarrays (chips) containing probes for hundreds of thousands or, typically now, a million or more single-nucleotide polymorphisms (SNPs) that tag common variation across the genome. Unlike the candidate gene approach, but similar to linkage analysis, GWA studies require no mechanistic hypotheses and therefore have the potential to identify genes implicating previously unrecognized biological pathways. Also, even small genetic effects can be detected in GWA studies, although the enormous number of SNPs tested for association demands very large samples and stringent statistical thresholds to adjust for multiple testing. Despite these hurdles, GWA studies have found novel loci (locations of DNA sequence) related to many complex physical traits and disorders, often well replicated and sustained on meta-analytic review (Visscher et al. 2012a).

One early success was the discovery in 2007 of the fat mass and obesity-associated *FTO* gene, which contains a SNP whose minor (less-frequent) allele is associated with a >20% increased risk of obesity and ~2- to 3-pound-higher body weight (e.g., Frayling et al. 2007, Willer et al. 2009). When treated as a candidate gene in studies of eating habits, the *FTO* risk allele also predicted a variety of behaviors relevant to obesity, including greater caloric intake and fat consumption (e.g., Cecil et al. 2008), more frequent eating episodes (McCaffery et al. 2012), and insensitivity to satiety-related cues (Wardle et al. 2009). An additional 31 SNPs, plus *FTO*, were also found to be associated with body mass index (BMI) in a recent study of 250,000 individuals, although *FTO* alone accounted for one-third of the variance in BMI attributable to all SNPs, and all loci together accounted for only about 1.5% of variance in BMI (Speliotes et al. 2010). In another example, GWA studies identified nearly a dozen blood pressure–associated SNPs (Levy et al. 2009, Newton-Cheh et al. 2009), and yet again, little of the total variance (~1%) can be explained by the aggregate of discovered variants. In other instances, GWA-identified loci account for a

somewhat larger proportion of phenotypic variation. About 10% of the variance in height was predicted by 180 loci of genomewide significance (i.e., surviving correction for multiple testing) in a sample of over 180,000 individuals (Lango Allen et al. 2010), and about 50 loci similarly account for around 10% of risk for type 2 diabetes (Visscher et al. 2012a). It is also noteworthy that, except in a few instances such as the *APOE* risk allele for Alzheimer's disease, most reported candidate gene associations have not replicated in GWA studies (e.g., Bosker et al. 2011, Siontis et al. 2010).

GWA studies of behavioral phenotypes are not as plentiful as those of physical attributes and diseases, nor are their study samples typically as large or the number of significant loci detected as numerous (Visscher et al. 2012b). In the largest psychiatric GWA study to date, which included approximately 60,000 cases and controls, Smoller and colleagues (2013) sought variants of shared association across five disorders: autism spectrum disorder, attention deficit-hyperactivity disorder, bipolar disorder, major depressive disorder, and schizophrenia. Their analysis showed evidence of common genetic contribution across several adult-onset psychiatric phenotypes and implicated calcium channel pathways as a potential mechanism. Nonetheless, identified SNPs from this and prior studies typically account for a maximum of 3% to 6% of the variance in diverse behavioral disorders (e.g., Anney et al. 2012, Major Depress. Disord. Work. Group Psychiatr. GWAS Consort. et al. 2013, Psychiatr. GWAS Consort. Bipolar Disord. Work. Group 2011, Saccone et al. 2010, Schizophr. Psychiatr. GWAS Consort. 2011, Smoller et al. 2013, Sullivan et al. 2012). Similarly, few GWA signals have emerged for general cognitive abilities in either children or adults (e.g., Benyamin et al. 2013, Davies et al. 2011, Docherty et al. 2010) or, aside from *APOE*, for cognitive decline with aging (e.g., De Jager et al. 2012). Finally, a few GWA studies have examined major personality traits (e.g., de Moor et al. 2012, Service et al. 2012, Terracciano et al. 2010, van den Oord et al. 2008, Verweij et al. 2010), but again show only sporadic associations. Also, most of these reflect nominal (not genomewide) significance, rarely replicate in independent samples, and in no instance account for more than about 1% of variance in the associated trait.

## The Missing Heritability

Do the limitations of linkage analysis, equivocal candidate gene associations, and so-far limited yield on GWA studies signal fundamental problems in gene detection or merely obstacles in the path of discovery? With respect to GWA studies at least, proponents might argue that GWA not only is suited to identifying most common variants for complex traits and disorders, but in fact has achieved much already. By one recent estimate, GWA studies have found over 2,000 phenotype-associated loci since 2007, nearly all previously unknown and providing as many new targets for biological investigation (Visscher et al. 2012a). To the point that GWA studies tend only to find variants of small effect, aggregating top GWA "hits" into multilocus composites, or genetic risk scores, can amplify phenotype prediction and has shown some utility in clinical research. For instance, a genetic risk score composed of 13 SNPs derived from GWA studies of myocardial infarction and coronary heart disease modestly predicted incident coronary disease and atherosclerosis in the Framingham Heart Study (Thanassoulis et al. 2012), and a composite of the BMI-associated variants identified by Speliotes et al. (2010) predicted rapid juvenile growth and later obesity in a longitudinally studied birth cohort (Belsky et al. 2012).

Still, the phenotypic variance accounted for by all SNPs of genomewide significance is minimal for nearly all outcomes and rarely exceeds 10% (Manolio et al. 2009). This proportion is even lower for behavioral traits and disorders, where 5% or less of the variance is commonly explained and only a handful of SNPs have been identified with robust significance (Plomin 2013). In contrast, biometric family studies (e.g., twin studies) typically show genetic influences accounting

for 30% to 50% of individual differences in most behavioral traits (Turkheimer 2000). Specific cognitive abilities have somewhat greater genetic variance, and in some psychopathologies, such as schizophrenia and autism, genetic liability may reach 80% or 90% (Plomin et al. 2008). How is it that these genetic effects can be so appreciable and yet the sum of SNPs detected in GWA studies explains only a fraction of heritable differences among individuals? Where is the remaining genetic variation? This question is widely known as the problem of the "missing heritability" (Maher 2008).

## Where Is the Missing Heritability?

Several possibilities have been prominently discussed. First, many phenotype-associated loci may be of small effect size and difficult to isolate individually. A recently developed quantitative method, labeled genomewide complex trait analysis, permits estimation of the collective actions of all loci genotyped on GWA arrays (Lee et al. 2011, Yang et al. 2011) and has shown much heritable variation captured in their cumulative effects. Basically, this approach quantifies the genetic relatedness of paired combinations of subjects in a GWA sample using all genotyped SNPs, then asks how strongly this index of genetic similarity covaries with pairwise similarity in the study phenotype. Genetic variation estimated by this technique explained 30% to 40% of the variance in schizophrenia and bipolar disorder (Visscher et al. 2012b), around 30% of the variance in major depression (Lubke et al. 2012), 40% to 50% of individual differences in intelligence (Chabris et al. 2012, Davies et al. 2011, Plomin et al. 2012); 20% of variation in smoking-related phenotypes (Lubke et al. 2012), and ~4% to 12% of the variance in various personality traits (Verweij et al. 2012, Vinkhuyzen et al. 2012). These estimates, even the smallest, far exceed the sum of individual GWA-identified SNPs for corresponding traits and disorders and suggest that many, probably thousands, of variants of extremely small effect underlie much of the heritable variation in these phenotypes. The fact that they elude detection in traditional GWA analyses follows from their tiny effect sizes, which only the statistical power afforded by enormous study samples could accommodate. Hence, it is not surprising that most GWA studies of behavior yield few "hits" of genomewide significance, and virtually all conclude with a plea for ever larger samples.

Still, estimates of heritability are generally larger in traditional twin and family studies than those cited above from genomewide trait analysis. This suggests there is genetic variation not tagged by the million and more SNPs now genotyped on DNA microarrays. Because their intent is to encompass common variation, commercial chips usually emphasize SNPs for which the frequency of the less prevalent allele (the minor allele frequency) is >5%, although more recent arrays may include SNPs with a minor allele frequency as low as 1% to 2%. But SNPs of very low minor allele frequency (e.g., <0.05%) are not well captured, leading to the hypothesis that some heritable variation might be carried by rare causal variants, many of which could exert moderate or large effects but require extensive DNA sequencing to identify (Cirulli & Goldstein 2010, Manolio et al. 2009).

Other genetic influences could reside in structural variants of DNA that are also poorly tagged on existing microarrays. In one class of structural variation, called copy number variants, large genomic segments are duplicated a varying number of times, and some copy number variants have been associated with schizophrenia, autism, and mental retardation (Conrad et al. 2010, Sullivan et al. 2012). These often have large effects (in schizophrenia, for instance, odds ratios range from 3 to >20), but because they are also extremely rare, account for little variance overall (Sullivan et al. 2012, Visscher et al. 2012b). Another reason heritability estimates may be larger in twin modeling, compared to genomewide analysis from SNP arrays, is that twin studies reflect both additive and nonadditive genetic variance, which includes genetic dominance and gene-gene

interactions (epistasis). Although estimated nonadditive genetic effects in twin studies tend to be small for most behavioral phenotypes, it is possible that some of the genetic variance eluding GWA detection lies in interactions among genes (Plomin 2013). Hence, the so-called missing heritability may be attributed to a combination of causes, including a very large number of common variants of very small effect size, rare variants to which GWA studies are insensitive, additionally rare structural variations, and perhaps some gene-gene interaction.

## Is There a Role for G × E Interaction?

Yet a further possibility is that some or much genetic variation is expressed conditionally, as a function of environmental factors to which some, but not all, individuals are exposed (Manolio et al. 2009, Plomin 2013, Sullivan et al. 2012, Uher 2008). This implies a statistical interaction between defined genotypes and differing environmental exposures—molecular G × E interaction, or more accurately, genotype-environment interaction. Such interactions would tend to dilute genetic "main effects" if exposure to a predisposing environment is limited in a study population and if the genetic variation examined has little effect outside that environment. Conversely, genetic effects might be detected more readily if sought in samples enriched for key environmental exposures. Although often mentioned only briefly in commentaries on missing heritability, the idea that genetic influences vary over diverse environments is not new and has been studied in animal models for many years (Plomin et al. 2008).

The earliest prominent behavioral studies of human G × E interactions were rooted conceptually in the diathesis-stress model of disease risk, which dates from the early 1960s. This model hypothesizes genetic vulnerabilities to mental disorders that are expressed when susceptible individuals encounter life adversities. G × E interactions have attracted interest elsewhere as well, as in agricultural genetics, where their experimental study informs the commercial viability of new genetic strains under varying soil and climate conditions (Crossa 2012), as well as in cancer genetics, where heritable variation and lifestyle are likely entwined in the origins of most common cancers (Hunter 2005), and in environmental genetics, where exposure rates for major toxins (pollution, chemical exposures) vary across populations (e.g., Thomas 2010a). Thus, in addition to their possible contribution to gene discovery, G × E interactions may be pursued with a variety of aims—to test conceptual models of development and disease risk, define boundaries of genetic and environmental influences, and identify individuals most susceptible to risk exposures or most amenable to preventive and therapeutic interventions.

Another reason to posit G × E interaction is suggested by Uher (2009), who notes that common psychopathologies, such as major depression and anxiety disorders, confer a small reproductive disadvantage. Even a slight reduction in fertility would ordinarily suffice to remove a harmful genetic variant through negative selection, so that the persistence of such alleles and their associated disorders presents a paradox. The pressure of selection will be relaxed, but not eliminated, if many persons carrying a risk allele do not experience the disorder, as would happen if the disorder's occurrence requires both the risk allele and exposure to a predisposing, and possibly infrequent, environmental "pathogen." Moreover, if the same genotype bestows a benefit in other environments or in circumstances prevailing at other times, and if this confers reproductive advantage, the implicated allele could persist in the population indefinitely. Such G × E interactions would be consistent, too, with evidence of strong environmental risk factors and with observed regional and temporal differences in incidence rates of these disorders.

The same is not likely to explain persistence of more severe mental disorders, however, such as schizophrenia, bipolar disorder, and autism, which are far less prevalent, have very high heritability, and profoundly depress reproductive fitness (Power et al. 2013). Instead, these disorders may

reflect a chance aggregation of deleterious alleles that are of recent origin, rare, and subject to strong negative selection. The rate at which new mutations arise may be sufficient to offset the rate at which existing ones are selected against (termed mutation-selection balance), so that these disorders endure at stable, but low, frequencies over time. That these disorders show limited variation in incidence across geographic regions and cultures and are more likely to occur with a later paternal age (which increases risk of acquiring new mutations) are consistent with this hypothesis, as are the related discoveries of several rare structural variants (e.g., copy number variants), some of which appear to have arisen de novo in affected individuals (Sullivan et al. 2012, Visscher et al. 2012b). Altogether, the foregoing arguments suggest different pathways to different psychopathologies and anticipate that G × E interactions will figure prominently in the most common of these disorders (Uher 2009).

## LATENT VARIABLE G × E INTERACTION

Heritability estimates reflect the proportion of phenotypic variation due to genetic differences among individuals of a given population, as seen at a particular time and in a particular environment or range of environments. Elsewhere, or in a different mix of environments, a trait's heritability may be either greater or smaller, and even if the same, whatever genetic variation predicts trait variability in one environment might differ in another. In a twin study of stress-elicited physiological responses, for instance, several cardiovascular measurements (e.g., heart rate, blood pressure) were obtained while study participants sat at rest and during performance of frustrating cognitive and psychomotor tasks (De Geus et al. 2007). The twin analyses revealed two kinds of genetic effects: those common to cardiovascular measurements obtained both at rest and under stress, and new genetic variation that emerged only during stress. The latter indicates a gene × stress (G × E) interaction in which some genes modulate cardiovascular reactions under stress but do not affect variation in the same parameters at rest. This finding suggests, too, that discovering specific genes contributing to cardiovascular regulation will benefit from observations made in multiple environments, including those that perturb resting-state functioning. The same may be anticipated for other phenotypes as well, when genetic variances are imperfectly correlated across different environments (De Geus et al. 2007).

The preceding example involved behavioral testing in two distinct settings, whereas most biometric family studies are blind to the environments participants experience. Instead, effects of heredity and environment are inferred alone from phenotypic differences and similarities among persons who vary in genetic relatedness or rearing background (Plomin et al. 2008). The correlation of a trait (phenotype) among identical twins reared in different families, for instance, sets an upper limit on heritability, since they share all genetic variation and are raised in unrelated (uncorrelated) environments. Conversely, any difference between the phenotypic correlation and unity (i.e., the difference from a coefficient of 1.0) reflects dissimilarity between identical cotwins resulting from their individual, or unique, experiences (termed nonshared environment), plus any error of measurement. In another comparison, phenotypic correlations among paired siblings reared in the same family, but where one or both were adopted (genetically unrelated), denote similarities of phenotype attributable to their shared family environments. Since the latter inference does not rely on measuring actual attributes of the shared environment, though, these effects could reflect any factor on which families differ, such as parenting styles, socioeconomic status, diet, or neighborhood characteristics.

The logic underlying these inferences is less obvious when extended to the bulk of reported twin studies, where cotwins share genetic variation and are also raised in the same family. Yet because identical and fraternal (dizygotic) twins differ in their genetic relatedness by an average

of 50% (and assuming that identical and fraternal twins experience their shared environments equally), the total phenotypic variance can be partitioned algebraically into genetic and environmental components. In these analyses, structural equations are commonly used to relate observed phenotypes to latent (unobserved) genetic and environmental determinants and to test competing models in which additive and nonadditive genetic components, and shared and nonshared environmental parameters, are added or removed to identify a best-fitting model. These analyses are insensitive, however, to any differences in genetic effects that might occur over an unmeasured gradient of shared environmental experience (e.g., warm or harsh parenting), as these will be concealed in the estimate of additive genetic variance. Recognizing this limitation, advances in twin structural modeling have been introduced recently that permit the incorporation of measured environmental variables, thus allowing estimation of environmentally moderated genetic influences (Purcell 2002). Such latent variable G × E interaction has now been shown for several behavioral phenotypes.

In one example, the heritability of trait positive and negative emotionality among late adolescents varied by quality of parental relationships, namely the degree of positive regard experienced by study participants (Krueger et al. 2008). The proportion of trait variation due to genetic influences differed about twofold over a range of ±2 standard deviations in parental positive regard, from strong genetic effects at the high end of positive regard to much weaker effects at the low end of this distribution. Likewise, heritable differences in childhood IQ have been found to vary from ∼10% to 70% over a gradient of low to high childhood socioeconomic status in the United States (Turkheimer et al. 2003). This finding has replicated in most other US studies of childhood IQ but not in studies of European cohorts or of predominantly postadolescent samples (reviewed in Hanscombe et al. 2012). These discrepancies await elucidation but may reflect national differences in educational and family support services affecting disadvantaged youth and, in relation to older study cohorts, further moderation by known age-related changes in genetic effects on cognitive abilities.

Cultural and institutional factors that proscribe or channel personal conduct, such as social norms, regulations, or legal restrictions and prohibitions, might also act to restrict genetic influences on behavior, whereas their absence may allow for a wider expression of genetic differences among individuals (Shanahan & Hofer 2005). Variation in such social control might explain why patterns of alcohol use appear to be less heritable in persons with a religious upbringing (Koopmans et al. 1999) and among those living in rural or more stable communities (Dick et al. 2001, Rose et al. 2001) and why stronger genetic effects on adolescent drinking are seen where peer substance use is prevalent or parental monitoring deficient (Dick et al. 2007a,b). Similarly with respect to cigarette smoking, the heritability of daily smoking among adolescents and young adults is lowest where cigarette taxes are high, tobacco products are not easily obtained, and cigarette advertising is restricted (Boardman 2009).

A third health-related behavior, physical activity, also interacts with latent genetic variation in predicting adiposity, with stronger genetic effects on BMI in sedentary individuals than among the more physically active (e.g., McCaffery et al. 2009, Mustelin et al. 2009). These findings, and other literatures showing genetic effects to vary by environment, suggest that some or much associated molecular variation will likewise interact with environmental factors (Dick 2011). For instance, shortly after discovery of the BMI-associated *FTO* gene, *FTO* susceptibility alleles were found related to adiposity more strongly in persons of sedentary (versus active) lifestyle (e.g., Andreasen et al. 2008, Kilpelainen et al. 2011). Although the earliest of these studies preceded evidence of activity-dependent variation in the heritability of BMI, other latent variable G × E findings would also suggest the likelihood of interactions involving specific genotypes and environmental moderators (Dick et al. 2009, Latendresse et al. 2011).

## CHALLENGES OF G × E RESEARCH

Having good reason to posit G × E interactions doesn't assure their discovery, and investigators differ on how best to pursue G × E research with measured genotypes and in their interpretations of existing evidence. Like candidate gene studies generally, G × E findings have been challenged for limited replication and vulnerability to publication bias. In addition, tests of interactions are susceptible to scaling artifacts, and inadequate statistical power may undermine the reliability of many reported G × E results. In discussing several of these concerns, we suggest that some seemingly contentious issues in this field may partly reflect differences of approach between two disciplines with a shared interest in G × E research, statistical genetics and psychology.

### A "Main Effect" Predicate for G × E Research?

Some disagreement surrounds what prior evidence is needed to advance a G × E hypothesis, and particularly, whether a polymorphism suggested for G × E must already demonstrate association with the outcome of interest (that is, exert a main effect on the study phenotype). Consider two examples. The first is the aforementioned interaction of *FTO* with level of physical activity, in which effects of *FTO* genotype on adiposity are greatest among people who are least physically active (Kilpelainen et al. 2011). In the second, a variant of the gene encoding brain-derived neurotrophic factor (*BDNF*) was recently associated with poorer working memory performance among midlife men and women, and here too, only among those who are least physically active (Erickson et al. 2013). These two interactions are analogous but forwarded on different grounds. *FTO* was selected as a candidate for G × E after GWA studies found it related to adiposity, and physical activity was selected as a moderator because it is known to variably affect body weight. In the second example, Erickson et al. (2013) cite several observations in nominating *BDNF* as a candidate for G × E research on cognition. These include widespread expression of BDNF in the brain, which supports neuronal and synaptic function; polymorphic variation in the *BDNF* gene, encoding substitution of a methionine (Met) for valine (Val) amino acid in the BDNF protein; and an inconsistent literature associating the *BDNF* Met allele with deficits in episodic and working memory performance, in which heterogeneity of effect sizes suggested possible stratification by unmeasured moderators (Mandelman & Grigorenko 2012). Additionally, extended exercise improves cognitive function and increases serum BDNF levels in humans, and physical activity improves learning and memory in rodent models, mediated by enhanced BDNF production and secretion (summarized in Erickson et al. 2013). Together, these observations suggested that physical activity may benefit cognitive functioning through a BDNF mechanism, and to that extent, such effects might differ in magnitude with functional variation in the *BDNF* gene.

Thus, in the example of *BDNF*, the rationale for positing a G × E interaction draws on multiple streams of evidence—from neurogenetics, experimental neuroscience, and studies in physical training—to postulate a common pathway linking genotype, activity level, and cognition. It is theoretically grounded and hypothesis driven in a way many psychologists would find familiar. In this instance, justification is also undeterred by the equivocal literature on *BDNF* main effects and thus differs from the GWA-based G × E approach exemplified by the interaction of *FTO* and physical activity. When the first of the *FTO* G × E studies were published, little was known about the function of *FTO* or how it might affect relevant metabolic processes, so that only the fact that *FTO* exerted a main effect on obesity risk nominated it for G × E interaction. Understandably so, since GWA is an atheoretical approach to gene discovery that is meant to find phenotype-associated genetic variation without regard to known functionality or prior biological plausibility. But beyond that, some statistical geneticists elevate the gene "main effect" to a predicate for G × E

investigation, arguing that only genetic variants of "compelling association" in GWA studies most warrant interrogation for interaction with environmental exposures (Psychiatr. GWAS Consort. Steer. Comm. 2009). Others invoke the lack of a marginal main effect as well to critique candidate gene G × E studies, which often exploit polymorphisms of absent or checkered main effect histories (Risch et al. 2009). Of course, this reasoning also negates a key argument for G × E studies, that gene associations may be amplified, and therefore more readily detected, when examined in the context of predisposing environments (Caspi et al. 2010, Dick 2011, Moffitt et al. 2006). Moffitt et al. (2006) aptly framed this negation as a logical paradox, where a G × E interaction impedes its own discovery by weakening the genetic main effect on which its investigation is dependent.

Our point is not to discount direct effects of genetic variation but instead to suggest limitations imposed when insisting that they precede G × E consideration. Another limitation is the paucity of "compelling" associations found for behavioral phenotypes in GWA studies, which generates few candidates to probe for G × E interaction. On the other hand, GWA-inspired G × E interactions, when found, are as cogent as hypothesis-driven findings, and like GWA studies generally, have the added potential to identify novel biological mechanisms. GWA-derived multilocus composites can be exploited in G × E research as well. For instance, high parental negativity and a chaotic home environment were found recently to accentuate effects of a ten-SNP genetic risk score on children's mathematical abilities (Docherty et al. 2011). And finally, many genetic epidemiologists do not adhere dogmatically to the marginal genetic main effect as a predicate for G × E research but embrace G × E interaction as a possible aid in gene discovery and to elucidate variability in responses to common environmental risk factors (Thomas 2010b).

## Scaling and Models

In an early G × E experiment, Krafka (1920) reported that the number of facets in the compound eye of *Drosophila* varied inversely with manipulated rearing temperature and that temperature affected facet number more strongly in one genetic strain than in another. Some years later, this experiment became the subject of a controversy between the statistician, Ronald Fisher, and embryologist, Lancelot Hogben. To puncture Hogben's enthusiasm for G × E effects on development, Fisher argued that interactions can be artifacts of the metrics used in their analysis and showed that expressing facet number logarithmically removed the interaction from Krafka's data. As interpreted by Tabery (2008), Fisher was motivated to dismiss G × E interactions from prior studies of strain and soil effects on crop variation, where such interactions were not prominent, and perhaps also by the eugenic social biology he espoused, where conditional genetic effects would impede eugenic selection to improve human "stock." Notwithstanding that Fisher made his case by transforming a variable of absolute scale (a counted object, no less), the proper scale of measurement for many behavioral variables is unknown. Can we confidently assume, for instance, that twice the score on a trait anxiety scale denotes twice the level of an anxious disposition or that severity of a mental disorder tracks with a simple count of symptoms? Sensitivity of a G × E interaction to scaling effects will vary by phenotype and moderator and may be greatest for ordinal interactions in which the influence of one predictor (e.g., an environmental exposure) varies by degree, but not direction, with the level of another (e.g., genotype) (Thomas 2010a). Whatever the prevalence of scale-dependent effects, though, confidence in a G × E interaction will be enhanced if shown for measurements having different metric properties as well as for different indicators of the same construct (Dick 2011, Hyde et al. 2011, Moffitt et al. 2006).

In addition to scaling artifacts, how an interaction is tested for deviation from main effects can affect the likelihood of its detection. For instance, if an interaction is modeled as the product of relative risks conferred by two predisposing factors, as commonly done in predicting diagnostic

status for a disorder, the bar on claiming an interaction is set higher than if it is modeled as a departure from additive risks. Which is the more appropriate model for testing interactions cannot be adjudicated on statistical grounds and is a perennial source of controversy in epidemiology (Rothman et al. 2008). Another complicating factor is the potential for erroneous G × E findings when logistic regression is used for analysis of categorical outcomes (Kendler 2011). This was shown by Eaves (2006), for instance, when dichotomizing variables of continuous distribution for analysis as binary outcomes in G × E simulations produced a high rate of spurious interactions. On the other hand, model-dependent differences also may be overstated, as G × E interactions on the multiplicative and additive models are similar when one or both predictors are independently weak, which has generally been true for genetic main effects (Uher 2008, 2011).

## Power, Replication, and Publication Bias

Statistical power and replication woes stalk G × E interaction as aggressively as they do GWA and candidate-gene association studies (Munafo & Flint 2009). Rules of thumb abound, as that G × E interactions require samples four times larger than are needed to find genetic main effects or that G × E research requires samples in the thousands (for candidate genes) or tens of thousands (for GWA studies) (Thomas 2010b). Power to detect a G × E interaction can vary by a number of factors, including effect size, distribution of genotypes, quality of measurement, proximity of the phenotype to biological actions of the implicated gene, and rates of exposure to the environmental moderator. With respect to the latter, if a risk allele affects a study phenotype in environment A and not in environment B, an associated G × E interaction will be most readily observed when samples are drawn equally from the two environments. If sampled from A or B alone, however, the interaction cannot be seen at all for lack of variance in the moderating environments. Thus, an underlying biological interaction that involves a causal genetic variant with environmentally modulated phenotypic effects may or may not be observed as a statistical interaction at the population level, depending on the distribution of environmental exposures sampled (Rutter 2010; Uher 2008, 2011; Uher & McGuffin 2008).

Nor is a genetic main effect necessarily easier to detect than an interaction. Caspi et al. (2010) modeled power to identify an ordinal G × E of moderate effect size in simulations involving samples of 1,000 individuals, with genotypes of equal frequency and varying exposure rates for a nominal environmental moderator. With very low exposure, neither a genetic main effect nor the G × E interaction is readily detected. Power to identify the main effect exceeds that of the interaction when a majority of individuals are exposed to the "predisposing" environment, and yet the reverse holds at lesser, but nontrivial, exposure rates. Power is also qualified by variation in the distribution of genotypes and recedes as minor alleles become less common. Of course, observational studies are necessarily constrained by the population frequencies of genetic variants and by naturally occurring variability in environmental exposures. Experimental studies, such as laboratory-based paradigms or randomized clinical trials, offer enhanced power to test G × E hypotheses and allow causal inferences not permitted in correlational designs (Thomas 2010a,b; Uher 2011; van IJzendoorn et al. 2011). Here, exposure rate is controlled by random assignment to study conditions and, if participants are selected from a pool of previously genotyped individuals, distribution of genotypes can be equalized as well (Caspi et al. 2010). Finally, power to detect G × E interactions should increase when either the phenotype or environmental moderator is measured with heightened precision (van der Sluis et al. 2010) or, as in neuroimaging and psychophysiological protocols, when dependent variables reflect intermediate behavioral or biological processes that genetic differences may influence more directly than distal phenotypes, such as complex traits and disorders (Hariri 2009, Hyde et al. 2011).

Inadequate statistical power is one reason a true G × E interaction might not be observed or a previously reported G × E may fail to replicate. Obviously, replication is essential to the credibility of any finding, although the aims of successor studies may vary and do not always conduce to exact replication. At present, meta-analysis is our preferred arbiter of valid findings, requiring multiple studies of comparable method and outcome that claim to test the same hypothesis. Comparability can be ambiguous, though, in the sense that two measured variables might be equivalent in one frame of reference, but not another. Consider that there are many adversities of early childhood, such as material privation, family discord, emotional neglect, or physical and sexual abuse. If early adversity is indexed by childhood abuse in an initial G × E study predicting a later psychopathology, a subsequent study using a different indicator of adversity (e.g., insensitive parenting) might be represented variously as a direct replication, a replication attempt of trivial difference (e.g., due to working from a different set of available measurements), or a deliberate attempt to probe the boundaries of childhood experiences pertinent to this G × E interaction. How it is framed will inform our interpretation of the second study's positive or negative outcome. And from the perspective of G × E hypotheses grounded in a theoretical framework, the interpretation of a particular interaction will also draw on a consilience of observations by other methodologies that more broadly confirm predictions from an underlying construct (Caspi et al. 2010).

That said, the essential importance of replication cannot be gainsaid, and it is sobering that a recent survey of G × E studies in psychiatric research found only about one-quarter of studies following up 10 original G × E findings to have replicated successfully (Duncan & Keller 2011). These authors interpreted the poor replication rate as indicative of editorial biases favoring publication of novel G × E findings and cited other ways in which publication bias may generate a skewed literature. These include less frequent replication among later studies; instances of cryptic G × E replication, in which an analogous, but previously untested, G × E finding is reported beside a failure to confirm the original interaction; and a preponderance of smaller, poorly powered studies among "successful" replications. These are not unique to G × E studies, of course, nor definitive, as the enhanced power of larger studies, for instance, can be offset if accompanied by weaker measurements of environment or outcome. Still, the centrality of replication means that finding robust G × E interactions requires meeting the challenge of their repeated observation.

## PSYCHOLOGICAL MODELS OF G × E INTERACTION

Psychology got a head start on G × E interaction when, 50 years ago, Meehl (1962) hypothesized a genetic vulnerability to schizophrenia, a single "schizogene" that predisposed individuals to the fully expressed disorder when co-occurring with ambivalent and inconsistent maternal parenting. Later theorizing posited multiple genetic influences, different environmental risk factors, and extension of the framework to other mental disorders to form the diathesis-stress model of psychopathology (Monroe & Simons 1991, Zuckerman 1999). Until recently, support rested on family studies, as when "latent" genetic liability is inferred among twins from differences in twin-pair zygosity and in cotwin diagnostic status along a continuum from low (fraternal cotwin, unaffected) to high (identical cotwin, affected) risk. High genetic risk defined in this manner, for instance, was shown to magnify effects of maltreatment on children's risk for conduct problems (Jaffee et al. 2005) and of stressful life events on women's risk for major depression (Kendler et al. 1995). Now the same G × E hypotheses are routinely tested on the molecular level as interactions between specific genotypes and the same environmental moderators (Caspi et al. 2002, 2003).

The diathesis-stress (or vulnerability) model reflects a predominant interest in disorders of functioning and their etiologies, yet genetic variation is potentially just as relevant to positive outcomes, beneficial traits, and responses to interventions intended to enhance competent

functioning. We have labeled as vantage sensitivity a form of G × E interaction in which benefits accrued in a favorable environment are likewise modulated by genetic variation (Sweitzer et al. 2013), and this model is formalized in further treatment by Pluess & Belsky (2013). On a third model, now commonly referred to as differential susceptibility, some genetic variation is thought to portend both greater vulnerability to adversity and an increased responsiveness to advantage, rather than valenced sensitivity to environments that are either, and specifically, adverse or propitious. This potential for disordinal (or cross-over) interactions has been wedded to theoretical frameworks in developmental psychology that posit variability in individuals' responsiveness to environmental influences that can be either positive or negative (Belsky & Pluess 2009, Boyce & Ellis 2005). In the following sections, we discuss some considerations pertinent to each of the three models.



## Diathesis-Stress (Vulnerability) Model

The bulk of G × E research comports with this model, if only because most investigators have focused on genetic influences moderated by adversities. The range of studied phenotypes is broad, including major psychopathologies and personality traits; children's cognitive and social development; physiological responses to naturally occurring stressors, life events, or trauma; and, in experimental studies, behavioral, autonomic, or neuroendocrine reactions to acute psychological challenges, as well as neural responses to threat-related cues in brain circuitries of emotion processing (Hariri 2009, Hyde et al. 2011, Manuck & McCaffery 2010). Much of this research, particularly that addressed to distal behavioral traits and disorders, has so far produced only small literatures, often of just a few studies. Thus, it is difficult presently to gauge the strength of individual findings, and given the diversity of study outcomes, problematic to aggregate over topical literatures that share only a common interpretive framework. Notable exceptions are two studies describing genotype-dependent environmental influences on risk for antisocial behavior and depression, respectively, in a longitudinally studied birth cohort (Caspi et al. 2002, 2003). Now cited over 8,000 times, these two studies largely kick started the current era of psychological research on G × E interactions, and the literatures they generated now include over 80 replication attempts or attempted extensions of the initial studies as well as ancillary literatures of mechanistic interest.

**Monoamine oxidase-A, childhood adversity, and antisocial behavior.** In the first study, exposure to maltreatment in childhood, such as physical or sexual abuse, maternal rejection, or harsh physical punishment, predicted later male aggressive and antisocial behaviors, and this association varied by genotype of a promoter polymorphism in the gene encoding the degradative enzyme monoamine oxidase-A (*MAOA*) (Caspi et al. 2002). Effects of maltreatment on boys' later conduct problems, antisocial disposition, and violent offending were greater in individuals with an *MAOA* variant of lesser transcriptional efficiency (low-activity *MAOA* genotype) than among those carrying an alternate (high-activity) allele. The interaction was corroborated in a majority of initial replication reports involving other male samples recruited from nonpatient populations and was confirmed in an early meta-analysis of eight studies (Taylor & Kim-Cohen 2007). Since then many additional reports have been published, including further studies of early maltreatment, studies examining other environmental moderators (e.g., socioeconomic disadvantage, peer deviance, parenting styles, maternal prenatal smoking), and studies of females. In a recent meta-analysis of 27 independent studies, childhood maltreatment was again found to presage antisocial outcomes more strongly in males of low-activity, relative to high-activity, *MAOA* genotype ($P = 0.0000008$) (Byrd & Manuck 2013). The interaction did not extend to the aggregate of other early-life adversities, and in females, high-activity *MAOA* genotype predicted greater antisocial

behavior in those who were also maltreated, but only weakly and inconsistently. In sum, *MAOA* variation appears to moderate effects of childhood adversity on males' aggressive and antisocial behaviors, specifically among studies that, like the initial report, targeted boys' early experiences of abuse, neglect, or other ill treatment.

**The serotonin transporter gene, life stress, and depression.** In the second influential study, both recent stressful life events and childhood maltreatment predicted later depression more strongly in young adults carrying the short (S) variant of a length polymorphism in the regulatory region of the serotonin transporter gene (5-HTTLPR) relative to individuals homozygous for the long (L) allele (Caspi et al. 2003). As with the prior study on *MAOA* variation and antisocial behavior, many investigators quickly attempted replication of this key early G × E finding, and several narrative and meta-analytic reviews followed. Two prominently reported meta-analyses, published in 2009, failed to confirm the interaction of 5-HTTLPR and life events on depression (Munafo et al. 2009a, Risch et al. 2009). Subsequent commentaries pointed to several limitations of these analyses, noting that they included only a small number of relevant investigations, oversampled from studies of negative outcome, excluded maltreatment studies and those exploiting exposures to a common stressor, and with respect to studies of enumerated life events, relied disproportionately on self-report inventories (which are subject to recall biases and other reporting inaccuracies) rather than contextually sensitive interviews or objective indicators of stress (Rutter et al. 2009, Uher & McGuffin 2010). In a further meta-analysis that included all available literature, Karg et al. (2011) confirmed the interaction of 5-HTTLPR genotype and life stress exposures on depression and depressive symptomatology across 54 published studies ($P = 0.00002$). Consistent with the critiques of earlier reviews, stratified analyses showed variation across studies of differing methodology. The interaction was robust in studies of childhood maltreatment, in cohorts exposed to a common stressor, and in studies with objective measures of stress exposure or assessing life events by structured interview. In contrast, 5-HTTLPR genotype interacted only marginally with self-reported life events.

As replicable examples of environmentally moderated genetic vulnerability (diathesis stress), it is not surprising that these two seminal studies have continued to inspire wide interest in G × E interactions. Their interpretation is further informed by related literatures studying the same genetic variation via other methodologies. For instance, persons of low-activity *MAOA* genotype may perform more poorly on tests of executive processing (e.g., working memory, attentional control) with diminished engagement of frontal brain regions supporting these processes, indicating a possible deficit in inhibitory control underlying the restraint of aggressive and antisocial impulses (e.g., Byrd & Manuck 2013, Cerasa et al. 2008, Enge et al. 2011, Fan et al. 2003, Meyer-Lindenberg et al. 2006). With respect to 5-HTTLPR, a variety of evidence suggests that the S-allele heightens sensitivity to stress. This is seen in cognition, as an increased vigilance, or attentional bias, toward negative emotional stimuli (Pergamin-Hight et al. 2012); in peripheral physiology, as heightened cortisol reactivity to acute psychological stressors (Miller et al. 2013); and on neuroimaging, as enhanced reactivity to threat-related stimuli in the amygdala, accompanied by altered neural coupling with prefrontal regulatory regions (Drabant et al. 2012, Hariri et al. 2005, Munafo et al. 2008a). These and other observations from human and animal research are consistent with the hypothesis that these polymorphisms provide a genetic substrate for individual differences in sensitivity to life adversities.

## Vantage Sensitivity

The notion that genetic variation might also moderate positive effects of exposure to salutary environments is not so much a novel concept as a logical complement to the diathesis-stress

(vulnerability) framework. And although observational studies of naturally occurring adversities dominate G × E research on mental disorders and other problematic behaviors, intervention studies and studies of health-promoting behaviors more commonly illustrate vantage sensitivity. As an example, nicotinic receptor gene variations associated with frequency of smoking in a community sample were recently found to predict successful abstinence among individuals assigned to active treatment arms of a smoking cessation trial, relative to placebo-treated controls (Chen et al. 2012). Similarly, several developmental studies have found benefits of favorable environmental exposures moderated by variation in *DRD4*. Children carrying the 7-repeat variant of a common *DRD4* length polymorphism were more likely to exhibit prosocial behaviors, such as donating to a charity or sharing with others, when prompted experimentally or with increasing maternal positivity than were those of alternate *DRD4* genotype (Bakermans-Kranenburg & van IJzendoorn 2011, Knafo 2009, Knafo et al. 2011). Likewise, treatment to enhance maternal sensitivity and effective parenting preferentially reduced oppositional behavior in children with externalizing problems among those carrying the 7-repeat allele (Bakermans-Kranenburg & van IJzendoorn 2008). Although these studies offer evidence consistent with vantage sensitivity, it is noteworthy that some of the same genes that moderate positive outcomes in positive environments, like *DRD4*, are likewise prominent among G × E studies of risk incurred in adverse environments and thus also contribute to evidence for the differential susceptibility hypothesis (Pluess & Belsky 2013).

## Differential Susceptibility

Some authors have found it peculiar that reported G × E interactions for mental disorders seldom involve genetic variants for which reliable main effects are found, either in the G × E studies themselves or in very large GWA investigations, and while acknowledging that cross-over interactions could accommodate the absence of a genetic main effect, view this possibility as unlikely (Boffetta et al. 2012, Risch et al. 2009). Conversely, we have noted Uher's argument that an allele conferring risk for a disorder associated with even a small reproductive disadvantage will tend to be removed by negative selection, so that persistence of the risk allele would seem to require compensating benefit at other times or in other circumstances (Uher 2009). This implies a disordinal interaction between the gene polymorphism and whatever environmental factors condition its cost and benefit. This is also the pattern of interaction defining differential susceptibility, which grew out of theorizing on individual differences in developmental plasticity. Belsky and colleagues (1991) proposed a theory of socialization that identified differences in developmental outcomes as conditional adaptations to rearing environments containing cues to either good or poor future life prospects and, at the same time, allowed for heritable variation in individuals' sensitivity to these cues. By this account, behavioral outcomes may differ most appreciably ("for better or for worse") across a gradient of favorable to unfavorable environments in persons who are genetically most susceptible to such influences (i.e., differential susceptibility) (Belsky & Pluess 2009). In related theorizing, Boyce & Ellis (2005) independently postulated individual differences in children's responsiveness to varying environmental "contexts" but were less explicit regarding a genetic origin of these differences (Ellis et al. 2011).

Consistent with its provenance in developmental psychology, the differential susceptibility framework has sought support from child and adolescent studies. Across multiple cohorts, for instance, youth carrying the 5-HTTLPR S-allele showed greater positive affect when experiencing supportive parenting and less positive affect with unsupportive parenting than did counterparts of alternate genotype (Hankin et al. 2011). This finding is reminiscent of the first clear demonstration of differential susceptibility, in which young adults who were homozygous for the 5-HTTLPR S-allele reported greater depressive symptomatology if reared in an adverse family environment or

experiencing recent stressful life events and less depressive symptomatology if raised in supportive families or experiencing positive events, relative to those carrying the L-allele (Taylor et al. 2006). In another example, adults with the *DRD4* 7-repeat allele discounted future rewards more steeply if raised in socioeconomically stressed families and less steeply if reared in more advantaged circumstances, compared to like-reared study participants lacking the 7-repeat variant (Sweitzer et al. 2013).

These and other recent studies illustrate differential susceptibility as a reversal of allelic association across an environmental gradient in individuals of the same cohort. A second source of evidence comes from literatures testing G × E interactions separately on vulnerability and vantage sensitivity models for the same genetic variation. In the preceding section, we cited studies in which children exposed to positive parenting or prosocial experimental manipulations experienced more favorable outcomes if carrying the *DRD4* 7-repeat allele. In other studies and against a variety of developmental adversities (e.g., parenting deficiencies, maternal insensitivity, low socioeconomic status), the 7-repeat allele was associated with unfavorable child outcomes, such as disorganized infant attachment, heightened sensation seeking, and various externalizing behaviors (Bakermans-Kranenburg & van IJzendoorn 2006, Nobile et al. 2007, Sheese et al. 2007, Van IJzendoorn & Bakermans-Kranenburg 2006). In a meta-analysis of these and other child studies of dopamine system polymorphisms, genotype-dependent positive outcomes proved significant in positive environments, as did negative outcomes in adverse environments (Bakermans-Kranenburg & van IJzendoorn 2011). A similar conclusion was supported (albeit limited to white participants) on a meta-analysis of interactions involving 5-HTTLPR variation, as seen across 30 child and adolescent studies of behavioral and psychiatric outcomes, when effect sizes were again combined separately among investigations of either positive or negative environmental exposures (van IJzendoorn et al. 2012).

A challenge for the differential susceptibility model is to explain how a reversal of allelic association across favorable and unfavorable environments might occur. One obvious possibility would involve genetic influences on fundamental psychological processes that target no particular outcome but may be exploited to disparate effects in differing environments. For instance, the attentional bias toward negative emotional stimuli predicted by the 5-HTTLPR S-allele has been shown for positive stimuli as well (Fox et al. 2011). Thus, 5-HTTLPR variation might contribute to differences in individuals' sensitivity to external stimuli generally rather than vigilance directed toward the detection of threat alone (Pluess & Belsky 2013). Alternatively, a genetic variant could have multiple phenotypic effects (termed pleiotropy) that dispose to outcomes of differing valence, with environmental factors promoting the dominance of one over the other. Here, too, the 5-HTTLPR might serve as an example, as the S-allele has been related not only to indicators of heightened emotionality but also to better performance on certain cognitive tasks, such as reversal learning and attentional set-shifting (reviewed in Homberg & Lesch 2011). Conceivably, the first of these might be expressed preferentially in adverse environments and the second in circumstances advantaging competent cognitive functioning. A similar argument is offered by Sweitzer et al. (2013) with respect to *DRD4* variation, in which pleiotropic effects of the 7-repeat allele on both reward sensitivity and higher executive processes differentially affect risk-related decision making, modulated by early environmental influences on developing brain circuitries of regulatory control.

Despite positive evidence, the generality of differential susceptibility remains uncertain. Because few investigators have explicitly hypothesized disordinal G × E effects, some cited findings are supported only by visual inspection of plotted interaction terms rather than formal testing for bidirectional allelic associations. Recent papers have drawn attention to this deficiency and offered recommendations for distinguishing differential susceptibility from other forms of interaction, as

by examining "regions of significance" or calculating the proportion of the interaction explained on either side of the crosspoint on the environmental axis (Roisman et al. 2012). A related risk in claiming evidence of differential susceptibility is the greater power to detect crossover interactions in standard regression models, owing to reduced, or absent, main effect variance. This suggests that spurious G × E interactions in underpowered samples are more likely to be attributed to differential susceptibility than to G × E models positing ordinal interactions (Dick 2011). Other limitations of current work on differential susceptibility include a restricted focus on just a few monoamine-regulating genes, principally in the serotonin and dopamine systems, and a paucity of literature outside of developmental research.

## Plasticity Alleles?

One danger of framing G × E findings in psychological terms is the temptation to attribute purpose to genetic variants whose only actions are biological and distant from predicted phenotypes. Terms like vulnerability and vantage sensitivity are more accurately evaluative characterizations that label G × E interactions by the valence of their outcomes and environmental moderators, and even then require a consensual frame of reference. Many other such models might be conceived as well. For instance, the same pattern of interaction that comports with diathesis-stress (vulnerability) could also define a resilience model, in which persons possessing a protective genotype are spared undesired outcomes commonly occasioned by an adverse environmental exposure (Pluess & Belsky 2013). A related difficulty, also of terminology, attends a distinction now often made between so-called vulnerability alleles and alleles implicated in differential susceptibility, which are said to confer plasticity (e.g., Belsky et al. 2009). We suggest this distinction may be misleading, since all G × E interactions reflect genotype-dependent variation in phenotypic response to varying environmental conditions, or plasticity. Interpreting G × E interactions from a "reaction norm" perspective, which unites the several G × E models within a familiar biological framework, demonstrates this point (Manuck 2010).

A reaction norm refers to the range of phenotypic variation observable across different environments in individuals of the same genotype. For illustration, the lines drawn in **Figure 1** depict the reaction norms of three genotypes, *a*, *b*, and *c*. Each reaction norm denotes variation in an unnamed phenotype (on the ordinate) as a function of a hypothetical environmental variable (on the abscissa). Genotype *a* exhibits greater plasticity than either *b* or *c* because it produces a broader range of phenotype values across the gradient of environmental variation. The reaction norms of genotypes *b* and *c* are equivalently shallow and thus parallel, but *b* is displaced upward along the ordinate to yield a higher average phenotype than genotype *c*; this difference reflects a genetic main effect (G). Finally, a G × E interaction exists when two or more reaction norms differ in slope, indicating that their respective genotypes occasion different phenotypic responses over an identical range of environments (Stearns 1992). If the environmental factor in the figure were an index of good to poor parenting and the phenotype a measure of poor psychosocial adjustment, the interaction of *a* and *c* would exemplify the diathesis-stress (vulnerability) model and that of *a* and *b*, differential susceptibility.

What then distinguishes the psychological models of G × E interaction? It cannot be that differential susceptibility requires an allele of a particular quality, plasticity, that is lacking in the diathesis-stress model, since the reaction norm of genotype *a* is both constant and compatible with interactions involving either *b* or *c*. And if plasticity (great or small) is a property possessed of all genotypes, and all G × E interactions entail allele-specific differences in phenotypic plasticity, it is also true that the magnitude of such differences need not differ between the various interaction models. Rather, what distinguishes the disordinal interactions of differential susceptibility from

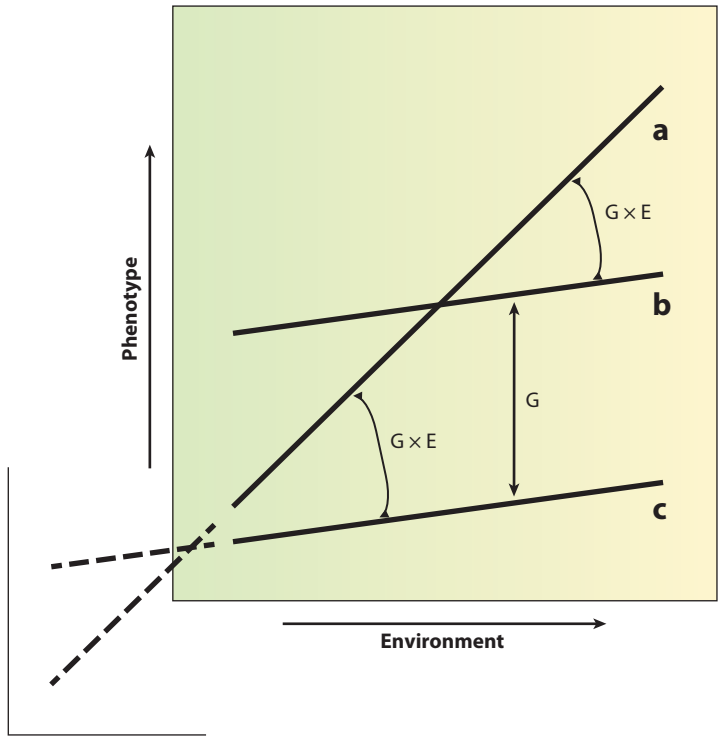


**Figure 1**

Reaction norms of three hypothetical genotypes: *a*, *b*, and *c*. Dashed lines depict hypothetical extension of reaction norms *a* and *c*. Abbreviations: G, genetic main effect; G × E, gene-environment interaction. Adapted from Manuck (2010).

ordinal interactions of the diathesis-stress (vulnerability) model is simply that, in differential susceptibility, different genotypes produce identical phenotypes at an intermediate location along an environmental gradient. If a phenotype of the same value is produced instead at either end of the gradient, the interaction is one of diathesis-stress or vantage sensitivity. Nonetheless, the form of the interaction is not the same as the conditions that give rise to it, and true disordinal interactions may well be overlooked in studies sampling from restricted ranges of phenotype or environment (Belsky & Pluess 2009). If the axes depicted in **Figure 1** capture only a portion of their natural ranges and could be extended meaningfully (dashed lines), for instance, the reaction norms of genotypes *a* and *c* would ultimately cross over to reveal an otherwise unrecognized instance of differential susceptibility.

## THE ENVIRONMENT IN G × E INTERACTION

In this article, we have briefly reviewed the recent—and to some, frustrating—history of attempts to identify genetic variants underlying heritable variation in behavior; outlined some of the reasons offered in explanation of the "missing heritability," and among these, highlighted the possibility of prevalent G × E interactions; summarized points of common critique to which G × E research is vulnerable; and overviewed various conceptual frameworks that inform the interpretation of G × E interactions from a psychological perspective. Most of our discussion has focused on the genetic component of G × E interaction and has taken at face value whatever environmental

parameter partnered in a given G × E finding or literature. In this concluding section, we turn to the environmental component explicitly, with two questions in mind: What does the environment do, and how truly "environmental" is the E in G × E interaction?

## What Does the Environment Do?

In the most prosaic sense and perhaps also the most common, environments may simply afford (or impede) opportunities for the expression of behavioral propensities to which genotypes conduce. This was implicit, for instance, in several examples of latent variable G × E interactions cited previously, where heritable influences on smoking or alcohol use varied by religious upbringing (Koopmans et al. 1999), community attributes (e.g., urban/rural) (Dick et al. 2001, Rose et al. 2001), legal restrictions (Boardman 2009), peer substance use, or parental monitoring (Dick et al. 2007a,b). Some of these environmental variables have also been shown to moderate effects of individual polymorphisms on behavior (e.g., Dick et al. 2009, Latendresse et al. 2011). Other environmental factors prominently implicated in G × E interactions involve impactful experiences, like childhood abuse, that evoke strong emotional and physiological reactions. Recent evidence suggests that such responses affect biological pathways that intersect with genetic influences, acting even to affect the expression of genes themselves. These effects can either be transitory and contemporaneous with environmental exposures or, via certain genomic modifications, persist over much, or all, of the life span.

The first step in the expression of a gene (i.e., the transcription of DNA into RNA) happens when various transcription factors bind to gene regulatory sequences. In a behavioral context, this may occur when experiences are transduced into patterns of centrally mediated neuroendocrine or neural output (e.g., hormone release, neurotransmission) that then activate receptors and intracellular signaling cascades culminating in the transcriptional control of genes. The protein produced by a targeted gene might also vary in amino acid sequence owing to polymorphic variation in a coding region, in which case a G × E interaction could result when an environmental event first promotes gene transcription (by activating transcription factors) and the transcribed gene then yields a protein of varying structure due to a difference in genotype. DNA variation can also occur in regulatory sequences, suggesting that effects of a transcription factor on gene expression may itself vary by genotype of a polymorphism in the gene's regulatory region. An interesting example is a functionally active regulatory SNP in the gene encoding the inflammatory cytokine, interleukin-6 (IL-6). IL-6 is a marker of risk for diseases linked to inflammation, and levels of IL-6 are elevated in association with a variety of psychosocial and sociodemographic adversities (Miller et al. 2009). In a study of older adults, recently widowed individuals showed higher plasma IL-6 levels than nonbereaved counterparts if homozygous for a variant (the G-allele) of an upstream regulatory SNP labeled *IL6* -174G/C (Schultze-Florey et al. 2012). Among those carrying the alternate C-allele, bereavement did not increase IL-6 levels. Additionally, the stress-sensitive neurotransmitter, norepinephrine, is known to enhance *IL6* expression by activating a proximal transcription factor (GATA1), and like the effect of bereavement on IL-6 levels, the ability of norepinephrine to stimulate GATA1-mediated *IL6* transcription is mitigated in the presence of the *IL6* -174C allele (Cole et al. 2010). Thus, "stress" may augment *IL6* expression through activation of a transcription factor that is itself modulated by polymorphic variation in the *IL6* gene, which suggests a mechanism for genotype-dependent stressor effects on inflammatory responses. More generally, these experiments illustrate how neurotransmitters, hormones, and genetic variation might converge to influence gene expression and give rise to G × E interactions.

A gene can be expressed only if it is accessible to the transcription apparatus of the cell, and accessibility of the DNA is regulated by a number of biochemical processes. Collectively, these

processes define the epigenome, a term meaning "above the genome" and referring to various chemical modifiers that inhibit or allow gene transcription without altering the DNA's nucleotide sequence. The study of variation in gene expression caused by these mechanisms is called epigenetics, and epigenetic mechanisms have attracted interest in part because the ways in which they regulate transcriptional control can persist through successive cycles of cell replication to affect gene expression over protracted periods. One type of epigenetic modification, methylation, occurs when a methyl group (a carbon and three hydrogen atoms) attaches to a cytosine nucleotide of DNA. An effect of this addition is to interfere with the binding of transcription factors to regulatory sequences and thus usually to repress or silence gene expression. In contrast, low levels of methylation ordinarily permit gene transcription. A second epigenetic mechanism involves modifications of chromatin structure. Chromatin is a complex of DNA and histone proteins, in which DNA is wrapped tightly around the histones and, in this conformation, is inaccessible to transcription factors. Conversely, transcriptional activity is enabled when, by acetylation, histones are bound less tightly to DNA. These and other epigenetic modifications of DNA play critical roles in developing organisms, providing a mechanism for the differentiation and maintenance of tissue-specific cells. That some epigenetic changes to DNA can be induced (or even reversed) during life, as catalyzed by various enzymes such as DNA methyltransferase and demethyltransferase, suggests that environmental exposures such as those experienced in early development can exert long-lasting biological and behavioral influences through an epigenetic mechanism.

Elegant experimental studies have shown deficiencies of early rearing to effect lifelong behavioral alterations in laboratory animals via epigenetic modifications of the hypothalamic-pituitary-adrenal system (Champagne & Mashoodh 2009, Meaney 2010), although relatively little research has yet been done in humans or in relation to G × E. One exception is recent work relevant to posttraumatic stress disorder (PTSD), which was previously predicted by an interaction of early childhood trauma with polymorphic variation in *FKBP5*, a protein involved in the regulation of glucocorticoid receptor binding and function (Binder et al. 2008, Xie et al. 2010). In follow-up work, Klengel and colleagues (2013) found exposure to trauma in early life to be associated with demethylation of DNA proximal to a glucocorticoid response element in *FKBP5*, an effect that was specific to persons carrying one of the *FKBP5* variants previously linked to risk of PTSD. The associated demethylation increases *FKBP5* expression, thereby suppressing responses to cortisol in glucocorticoid-sensitive tissues and increasing glucocorticoid resistance in individuals with the *FKBP5* risk allele. These findings may be relevant to the pathophysiology of PTSD, and in this instance, corroborative studies in hippocampal cells suggest that patterns of methylation in the brain parallel those first observed in peripheral blood cells. Other work will surely follow on epigenetic mechanisms of environmental influences and their potential interaction with genetic variation; already, commercial arrays are available to simultaneously assess the methylation status of hundreds of thousands of genes (Pan et al. 2012). How pervasive behaviorally relevant epigenetic effects may eventually turn out and, given expected heterogeneity of epigenetic modifications across tissues, how generalizable findings may prove elsewhere when based on cells conveniently sampled from blood will largely determine the explanatory scope of these newly recognized mechanisms. Until then, the limited current work in this area may be best seen as promissory.

## The E in G × E Research

It is reassuring that new biological understandings may bring gene and environment together in a swirl of molecular interplay to undergird statistical G × E associations at the population level, however few examples we have at hand. At the same time, there is a conundrum at the heart of much G × E literature that obscures interpretation. If the boundary between heredity

and environment can seem to erode when environments act, in part, to affect gene expression (even of the genes that convey heritable variation), it is weakened in a more fundamental sense if environmental exposures are themselves subject to genetic influence. And there is abundant evidence of such gene-environment correlations (rGEs). These may occur when individuals select environmental experiences guided by their heritable dispositions (active rGE) or create aspects of the environments they experience, as through the reactions they elicit in others (evocative rGE). And in a family context, phenotype and environment may be correlated due to shared genetic variation among related individuals (passive rGE) (Plomin et al. 2008). Importantly, twin studies document genetic influences on nearly all categories of environmental exposures, including stressful life events; traumatic (life-threatening) events; divorce; adverse parenting environments; socioeconomic position; peer group relations; work and classroom environments; and exposures to smoking, drugs, and alcohol; as well as protective resources such as the availability of confidants and engagement in social networks (reviewed in Kendler & Baker 2007, Manuck & McCaffery 2010). Effect sizes are generally modest to moderate but may be underestimated due to arbitrary reporting intervals that imperfectly capture stable individual differences in exposure rates. When measured on just two occasions, for example, genetic factors accounted for over 60% of variability in reported life events and social integration—two sentinel markers of environmental adversity and resources in G × E research (Foley et al. 1996, Kendler 1997).

To the extent rGE is present, an ostensible G × E interaction may partly reflect an interaction of measured genotypes with unrecognized genetic variation in the environmental moderator (G × G interaction). It also occasions the peculiar circumstance in which one scientist's environment (e.g., smoking, parenting, social support) is another's heritable phenotype. And although G × E investigators often document a null association between study genotypes and key environmental exposures, this alone cannot exclude potential confounding by rGE, since other genetic variation not included in the analysis may associate with the environmental factor. As a consequence, much G × E research undoubtedly harbors cryptic rGE and, when unacknowledged, suggests tacit acceptance of variables that are not explicitly genetic as environmental—a sort of methodological environmentalism. Obviously, these interpretive problems do not apply to studies of experimentally manipulated environmental exposures, such as randomized clinical trials and studies of responses to laboratory challenges (Uher 2008, van IJzendoorn et al. 2011). And to be sure, some investigators have employed creative methods to address rGE confounding. For instance, Caspi et al. (2003) found depression to be predicted by the interaction of 5-HTTLPR genotype with stressful life events that were experienced before, but not after, outcome assessment. This suggests an absence of rGE confounding, on the assumption that genetic effects on event exposures should be constant over time. In addition, quantitative (twin) genetic studies can potentially distinguish environmental effects that are causal from those associated with correlated genetic variation (Kendler et al. 1999). Yet, analogous claims cannot be made for the bulk of G × E studies, which typically enroll population or case-control samples of unrelated participants and employ measurement protocols precluding causal inference.

Maybe the more interesting question is not whether the environments studied in G × E research are purely environmental in origin, but why this seems to matter. G × E interaction was born, in part, as a rhetorical truce in the nature/nurture debate of the early- and mid-twentieth century (Cravens 1988). It was not generally expressed then in terms of statistical interaction among codependent processes, as treated here, but as an inchoate sense of coacting factors that, once acknowledged, allowed proponents of each side to go their separate ways (albeit with occasional flare-ups). And perhaps behavioral genetics itself, with its heritability and two kinds of environmentality (shared, nonshared), inadvertently reinforces popular notions of the essential separateness of gene and environment. Against this background, an interaction confounded by

rGE might well seem to lack the implications of a true G × E finding. Yet what is the implication, if not confirming a proposition predicated on a frayed dichotomy? If heritable influences contribute to interindividual variability in as many categories of experience as rGE literature documents, finding the pure environment (and hence pure G × E interaction) in a natural population may be akin to verifying Newton's first law of motion from everyday experiences in a world possessed of atmosphere, friction, and gravity. As a practical matter, too, genetic variance in environmental exposures does not preclude environmental interventions to alleviate their ill consequences. And recognizing that, for instance, adversities of early rearing may have a heritable component is no more an argument against interventions to redress such circumstances than is the observation that, by genotype, some children may be protected from adversity. In view of the extent of demonstrated rGE, it seems reasonable to assume that most dimensions of measured experience will have both environmental and genetic determinants, and most G × E studies will not be able to partition genetic and environmental influences on their environmental moderators. With this in mind, we think it useful to acknowledge the interpretive limitations of most nonexperimental G × E interactions and recommend adopting a slightly different terminology, one that refers more modestly to interactions between genes and environmental exposures, where exposures denote experiences that may be attributable to a variety of undetermined causes. Finally, relinquishing pure G × E interaction as the grail of G × E research may encourage interest in a broader expanse of potential gene-exposure ($G \times E_{exp}$) interactions affecting behavior, such as those moderated by complexly determined experiences, dispositions, abilities, attitudes, and affective states.



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The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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