Measured Gene-Environment Interactions in Psychopathology

Concepts, Research Strategies, and Implications for Research, Intervention, and Public Understanding of Genetics

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ABSTRACT—There is much curiosity about interactions between genes and environmental risk factors for psychopathology, but this interest is accompanied by uncertainty. This article aims to address this uncertainty. First, we explain what is and is not meant by gene-environment interaction. Second, we discuss reasons why such interactions were thought to be rare in psychopathology, and argue instead that they ought to be common. Third, we summarize emerging evidence about gene-environment interactions in mental disorders. Fourth, we argue that research on gene-environment interactions should be hypothesis driven, and we put forward strategies to guide future studies. Fifth, we describe potential benefits of studying measured gene-environment interactions for basic neuroscience, gene hunting, intervention, and public understanding of genetics. We suggest that information about nurture might be harnessed to make new discoveries about the nature of psychopathology.

A gene-environment interaction occurs when the effect of exposure to an environmental factor on health and behavior is conditional upon a person's genotype (or conversely, when the genotype's effect is moderated by the environment). In defining what gene-environment interaction is, it is useful to contrast gene-environment interaction against what it is not.

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GENE-ENVIRONMENT INTERPLAY VERSUS BIOLOGICAL INTERACTION

Increasingly, psychologists have come to appreciate that co-action between genetic risk and environmental risk influences behavior in many ways. Frequently, this co-action, or interplay, is referred to imprecisely as gene-environment interaction. However, interplay and interaction are not synonyms. In reality, gene-environment interplay comprises several different concepts and bodies of research findings, only one of which is the topic of this article: measured gene-environment interaction, which we refer to here as G × E. This section briefly defines four different forms of gene-environment interplay, to delimit what is particular about G × E. (We discuss the other three forms of interplay in greater depth in Rutter, Moffitt, & Caspi, in press.)

One type of gene-environment interplay, demonstrated in studies of twins, comprises quantitative models of *heritability-environment interaction*, in which the balance of heritable versus environmental influence on a phenotype's variation is shown to differ across subsegments of the population (Rowe, Jacobson, & van den Oord, 1999; Turkheimer, Haley, Waldron, D'Onofrio, & Gottesman, 2003). Findings from these twin models constitute a very important reminder that heritability estimates are population-specific. The models do involve statistical interaction. However, they do not address biological G × E because they focus on latent omnibus genetic effects in population variation, not on effects of a specific identified genotype in individuals. Moreover, these models do not indicate that sensitivity to the environment is moderated by variation in the DNA sequence. Heritability-environment interaction is clearly interesting, but it is not addressed in this article.

A second type of gene-environment interplay is *epigenetic programming*, in which environmental effects on an outcome

such as health or behavior are mediated through altered gene expression (Cameron et al., in press; Levenson & Sweatt, 2005; Pray, 2004; Waterland & Jirtle, 2003) or even altered chromosomal structure (Epel et al., 2004; Sapolsky, 2004a). Experimental studies with rodents have shown that early-life rearing experiences can alter gene expression, and that this expression is linked to later behavior (Francis, Szegda, Campbell, Martin, & Insel, 2003; Meaney, 2001). This programming is clearly a biological process, and it involves specific measured genes, as well as specific environments. However, the effects do not involve variation in the DNA sequence, and they do not indicate that sensitivity to the environment is moderated by measured genetic variation. Rather, the environmental effects are *mediated* through gene expression. Epigenetic programming is important, but it is not addressed in this article.

A third type of gene-environment interplay is the familiar *gene-environment correlation*, in which a person's genotype influences his or her probability of exposure to environmental risks (Plomin, DeFries, & Loehlin, 1977; Rutter & Silberg, 2002). Gene-environment correlations are often discussed as if the genes have direct biological effects on an environmental risk factor (e.g., the tendency to experience stressful life events is partly heritable). This shorthand is misleading, as inevitably the genetic effect is mediated through some behaviors (in the case of life events, personality traits) that in turn bring about the environmental risk. This is an important indirect route of gene action, and it warrants more investigation than it has received, but it is not the topic of this article.

Finally, there is the topic of this article, behavioral effects due to interdependence between a specific identified variation in the DNA sequence and a specific measured environment: G × E. G × E has a long scientific history (Haldane, 1946). It has become an empirical essential in agricultural research (animals' and crops' genotypes moderate resistance to pests and disease) and infectious-disease research (hosts' genotypes moderate susceptibility to diseases such as malaria and tuberculosis). In the behavioral sciences, too, G × E has long been a useful theoretical concept. It plays a central role in developmental psychology's resilience theories about children who have good mental health despite adversity, and in psychopathology's diathesis-stress theories of mental illness. However, only recently has behavioral science begun to grapple empirically with G × E, particularly with G × E involving measured genes.

G × E: RARE OR COMMON?

Behind this empirical neglect of G × E in behavioral science, we find two prior assumptions imported from quantitative behavioral genetics research. The first assumption was that an additive effect for genetic and environmental influences would be the norm. Quantitative behavioral genetic models thus tacitly misattributed any phenotypic variation generated by G × E to additive genetic effects (Boomsma & Martin, 2002; Rutter &

Silberg, 2002). Of course, it could happen that the environmental causes of behavior disorders operate independently alongside genetic causes, each making an additive contribution that operates separately from the other's, but there is no evidence that this assumption is generally true.

The second assumption, deriving directly from the first, was that G × E effects must be so infrequent or so trivial that they can safely be ignored in behavioral genetic analyses (Bergeman, Plomin, McClearn, Pedersen, & Friberg, 1988; Caspi, 1998; Scarr, 1992). A few reports of G × E between measured environments and indicators of genetic risk appeared in the psychopathology literature (Cadoret, Yates, Troughton, Woodworth, & Stewart, 1995; Kendler et al., 1995; Wahlberg et al., 1997), but the field as a whole tended to view those studies' results as fascinating but isolated incidents of G × E, and put the findings to one side, because of a more general belief that G × E effects rarely occur.

These two long-standing assumptions from quantitative behavioral genetics seem to have transferred unchallenged into psychiatric molecular genetics. This younger research field has tacitly adopted the dogmas that genes' connections to disorders are direct and additive, and that G × E must be rare and atypical. Acceptance of the predominance of additive effects leads to the conviction that "a so-called reductionist strategy of studying genes one at a time should yield useful results, even when gene-environment effects are not being modeled" (Colhoun, McKeigue, & Davey Smith, 2003, p. 865). As a result, the possibility of interactions between measured genes and environments in the origins of behavioral disorders was neglected empirically until recently. Contrast the hundreds of studies seeking direct measured gene-to-disorder connections versus the handful of studies testing measured G × E in psychopathology. If G × E does operate only in rare, isolated instances, then this neglect has been benign, and investing more scientific resources into G × E research would seem unwise. But if G × E effects are common, they should be researched.

One purpose of this article is to challenge prior assumptions and to encourage more empirical attention to G × E in behavioral science. There are at least three theoretical reasons to reject the assumptions that G × E effects are uncommon and inconsequential for mental health. First, the underlying concepts of natural selection dictate that genes are involved in organisms' adaptation to the environment, that all organisms in a species will not respond to environmental change in the same way, and that this within-species variation in response involves individual differences in genetic endowment. Genetic variation in response to the environment is the raw material for natural selection (Ridley, 2003). Second, biological development at the level of the individual involves adaptations to prevailing environmental conditions (Gottlieb, 2003). The literature on biological programming by early experience provides relevant examples (Bateson & Martin, 2000; Rutter, O'Connor, & the English and Romanian Adoptees Study Team, 2004). Given that

human development is an environment-dependent process, it is implausible that genetic factors do not play a role in moderating the process (Johnston & Edwards, 2002). It is even more implausible that the process does not include mental health among its outcomes. Third, both human and animal studies consistently reveal great variability in individuals' behavioral responses to a variety of environmental hazards. Heterogeneity in response characterizes even the most overwhelming of traumas, including all known environmental risk factors for psychopathology. To argue that such response heterogeneity is not under genetic influence would require the assumption that although genes influence all other areas of biological and psychological function, responsiveness to the environment is uniquely outside the sphere of genetic influence. In opposition to any such assumption, research guided by diathesis-stress and resilience theories shows that individual variation in response to environmental hazards is associated with preexisting individual differences in temperament, personality, cognition, and psychophysiology, all of which are known to be under genetic influence (Plomin, DeFries, McClearn, & McGuffin, 2001; Rutter, in press).

In addition to theoretical reasons to expect G × E, there are reasons to reject empirical claims that G × E effects are uncommon and inconsequential for mental health. Although it is often claimed that reports of significant G × E effects on behavior are uncommon in the published literature, this claim does not constitute evidence that G × E effects on behavior are uncommon in nature, for two methodological reasons. First, the claim is not relevant because quantitative tests for G × E, which test for interactions between latent genetic and environmental variance components (instead of interactions between measured genes and measured environments), are limited to testing the implicit hypothesis that there ought to be a single unified interaction between all or most of the anonymous genes related to a disorder and all or most of the anonymous environments related to it (Rutter & Pickles, 1991). This hypothesis is biologically implausible, and therefore it is not surprising (and perhaps reassuring) that data seldom support it, and few omnibus G × E effects are found.

The second methodological reason to reject empirical claims that G × E effects are uncommon is that statistical testing for them in behavioral genetics has been intent on detecting statistically significant interaction terms that are multiplicative. As Heath and Nelson (2002) pointed out, this multiplicative assumption gave us the "×" in G × E. However, this narrow statistical operationalization does not necessarily map onto the ways that genes and environments interact in nature (Rutter, 1983; Rutter & Pickles, 1991; Yang & Khoury, 1997). That is because multiplicative interaction requires variation in both genotype and environment. If the environment that creates risk is all-pervasive, there cannot be a multiplicative interaction even if the reality is that the effects of genotype are wholly contingent on environment (Rutter, 1983). The best-known examples of G × E in medicine involve pervasive environmental

risk, and therefore would not pass the test of multiplicative interaction. We refer to genetically moderated susceptibility to malaria in regions where infection is endemic, genetically moderated allergic reactivity to airborne spring pollens, and genetically determined phenylketonuria in response to the ordinary diet. In these examples of G × E, genes moderate humans' capacity to resist the health-damaging effects of a pathogenic environment. However, lack of variation in the environment within the population under study precludes a test of multiplicative interaction with genotype, so other statistical tests are more appropriate.

The larger point is that synergistic interdependency between genotype and environment is a theoretical biological concept, not a statistical concept. The essential feature of this concept is its thesis that genotype moderates the effect of exposure to an environmental pathogen on health. This moderation concept can be empirically operationalized through a variety of study designs and tested by more than one statistical tool (Hunter, 2005). A multiplicative interaction test is not the only tool for testing G × E; it is one among several, and thus G × E should not be viewed as synonymous with multiplicative statistical interaction. A too-narrow focus on multiplicative statistical interaction terms has given behavioral geneticists the impression that G × E effects are seldom found.

On the basis of this analysis, we suggest that there is little support for the expectation that G × E effects ought to be rare or trivial in mental health. Evolutionary, developmental, and diathesis-stress theories suggest the opposite. Empirical claims that G × E findings are rare derive from flawed methodological assumptions. Of course, it would be wholly unreasonable to suggest that all genetic effects on mental health operate through the environment. However, like other noncommunicable diseases that have common prevalence in the population and complex multifactorial etiology, most mental disorders have known nongenetic, environmental risk factors and causes. It is reasonable to suggest that wherever there is variation among humans' psychological reactions to the major environmental pathogens for mental disorders, G × E must be expected to operate to some degree.

EMERGING G × E FINDINGS

Our research team recently reported measured G × E in three mental disorders. G × E findings for other mental disorders are appearing as well (e.g., Kahn, Khoury, Nichols, & Lanphear, 2003), and of course the new field of psycho-pharmacogenetics operates on the G × E premise that patients' genotype determines variation in the efficacy of psychiatric drugs, which are in essence manipulated environments (Basu, Tsapakis, & Aitchison, 2004; W.E. Evans & Johnson, 2001; Goldstein, Tate, & Sisodiya, 2003). We describe our three studies here because they provide proof in principle that G × E effects occur in

relation to psychopathology outcomes, and they illustrate the feasibility of the G × E research strategy.

In our first study, we hypothesized that a functional polymorphism in the promoter region of the gene encoding the neurotransmitter-metabolizing enzyme monoamine oxidase A (MAOA) moderates the effect of child maltreatment in the cycle of violence. Results showed maltreated children whose genotype conferred low levels of MAOA expression more often developed conduct disorder and antisocial personality, and were more likely to commit violent crimes as adults, than children with a high-activity MAOA genotype (Caspi et al., 2002). A replication of this study has been published (Foley et al., 2004), as has a (partial) failure to replicate (Haberstick et al., 2005).

In a second study, we hypothesized that a functional polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) moderates the influence of stressful life events on depression. Individuals with one or two copies of the 5-HTTLPR short allele exhibited more depressive symptoms, diagnosable depression, and suicidality following stressful life events than individuals homozygous for the long allele (Caspi et al., 2003). Replications of this study have been published (Eley et al., 2004; Grabe et al., 2005; Kaufman et al., 2004; Kendler, Kuhn, Vittum, Prescott, & Riley, 2005; Wilhelm et al., in press; Zalsman et al., in press), as has one failure to replicate (Gillespie, Whitfield, Williams, Heath, & Martin, 2005).

In a third study, we demonstrated that G × E applies to environmental pathogens apart from psychosocial risks, by asking why exposure to cannabis leads to psychosis in some users but not others. We hypothesized that a functional polymorphism in the catechol-O-methyltransferase (COMT) gene moderates the risk from adolescent cannabis use for developing adult psychosis (Semple, McIntosh, & Lawrie, 2005). Cannabis users carrying the COMT valine allele were likely to subsequently exhibit psychotic symptoms and to develop schizophreniform disorder, but cannabis use had no such adverse influence on individuals with two copies of the COMT methionine allele (Caspi et al., 2005).

Beyond psychiatric genetics, in other branches of medicine, large-scale data-collection initiatives are being planned or launched to build infrastructure for G × E research (Collins, 2004; Kaiser, 2003; Radda & Viney, 2004; U.S. National Children's Study, 2004; Wright, Carothers, & Campbell, 2002), and some G × E effects are already being reported. An exhaustive review is beyond the scope of this article, but a few examples are illustrative. In the area of bacterial infection, patients infected with invasive streptococci did or did not develop severe systemic disease depending on their genotype on polymorphisms in human leukocyte antigen class II haplotypes (Kotb et al., 2002). The G × E approach is also being taken in studies of other infectious diseases, such as malaria, HIV-AIDS, leprosy, and tuberculosis (Hill, 1999; Hoffjan et al., 2005).

In the field of cardiovascular disease, subjects in the Framingham Heart Study who had high dietary fat intake did or did not develop abnormal high-density lipoprotein (HDL) concentrations depending on their genotype on the polymorphic hepatic lipase (HL) gene promoter (Ordovas et al., 2002). This HL G × E has been replicated (Tai et al., 2003). Reports from a different study showed that tobacco smokers did or did not develop coronary heart disease depending on their lipoprotein lipase genotype (Talmud, Bujac, & Hall, 2000) and their apolipoprotein E4 (APOE4) genotype (Humphries et al., 2001). The APOE4 G × E effect has been replicated (Talmud, 2004). In the study of stroke-prone hypertension, rats exposed to a high-salt diet did or did not develop elevated systolic blood pressure depending on their genotype on the polymorphic angiotensin-converting enzyme (ACE) gene (Yamori et al., 1992). The G × E approach is also being taken in the study of other exposure-related diseases such as asthma, lung cancer, and type 2 diabetes (Kleeberger & Peden, 2005; O'Rahilly, Barroso, & Wareham, 2005). A good replication record is building (Hunter, 2005).

In a study of low infant birth weight, women who smoked tobacco during pregnancy did or did not give birth to underweight infants depending on their genotype on two polymorphic metabolic genes, CYP1A1 and GSTT1 (Wang et al., 2002). In studies of dementing illnesses, patients with a history of head injury did or did not develop Alzheimer's dementia, and increased beta-amyloid deposition in the brain, depending on their genotype on the polymorphic apolipoprotein (APOE) gene (Mayeux et al., 1995; Nicholl, Roberts, & Graham, 1995). A G × E pattern was also found when instead of head injury, the environmental influence on cognitive decline was estrogen therapy (Yaffe, Haan, Byers, Tangen, & Kuller, 2000). In a study of dental disease, heavy tobacco smokers did or did not develop gum disease depending on their genotype on the polymorphic interleukin 1 (IL1) gene (Meisel et al., 2002). This G × E effect has been replicated (Meisel et al., 2004).

Three notable patterns emerge across these initial reports of G × E effects. First, several of the initial findings have already been replicated. Second, every study took as its starting point a known environmental pathogen for the health outcome in question. Third, in many of the reports, the gene studied bore no significant relation to health outcome in the absence of exposure to the environmental pathogen. Thus, although there was a biologically plausible rationale for considering each gene as a candidate gene, without the G × E approach each gene's connection to illness would have been negated in error. Later in this article, we revisit the unsettling possibility that unrecognized G × E can foster false negative findings in genetic research.

These emerging examples of G × E are prompting new interest in the G × E phenomenon among behavioral scientists: "The identification of gene-environment interactions will be one of the most important future goals of genetic epidemiology" (Merikangas & Risch, 2003b, p. 631). However, this interest has met with a lack of pragmatic information: "No aspect of human behavioral genetics has caused more confusion and generated more obscurantism than the analysis and interpretation of the

various types of non-additivity and non-independence of gene and environmental action and interaction" (Eaves, Last, Martin, & Jinks, 1977, p. 1), an observation that "is as true today as when it was written" (Boomsma & Martin, 2002, p. 185). Moreover, many researchers remain skeptical about the feasibility of studying measured G × E:

> Despite the theoretical value of characterizing both intrinsic and extrinsic components of the causal process in the development of disease, . . . gene-environment interactions are likely to remain a conceptual framework for health research rather than a practical goal for the foreseeable future. (Cooper, 2003, p. 437)

Thus, the current high level of curiosity about G × E is accompanied by uncertainty about the feasibility of G × E research, and by pragmatic questions about how to carry out good G × E studies. In this article, we aim to address these issues.

STRATEGIES FOR PROGRAMMATIC RESEARCH INTO MEASURED G × E

We aim to encourage careful, deliberate G × E hypothesis testing. Such testing begins with specifying theoretically plausible triads of a gene, an environmental pathogen, and a behavioral phenotype. This section puts forward principles to guide G × E tests using measured variables. Information about working with genetic data is widely available; accordingly, we give more emphasis to information about working with environmental data.

Step 1: Consulting Quantitative Behavioral Genetic Models of the Disorder

Quantitative models may offer clues to whether or not G × E is likely to play a part in the etiology of a disorder. Such quantitative models are derived from twin and adoption designs that have been used to disentangle genetic and environmental effects on disorder (Plomin et al., 2001). In most quantitative genetic research, measured genes and environments are not available, and therefore structural equation modeling of phenotypic variation is used to estimate the probable contribution of unmeasured latent variables to individual differences in an outcome. Phenotypic variance is decomposed into three basic latent variables: a genetic variance component called A (to denote additive genetic variance), an environmental variance component called C (denoting "common" or family-wide environmental variance), and another environmental component called E (denoting person-specific environmental variance, including measurement error). In this framework, it is also possible to model and test a variance term for G × E (Eaves et al., 1977; Eaves, Silberg, & Erkanli, 2003; Heath et al., 2002; Kendler & Eaves, 1986; Purcell, 2002; Sham, 1997). Significance for such a latent G × E term would strongly encourage constructing hypotheses about measured G × E. (However, the absence of a significant G × E term would not rule out the possible existence of measured G × E, because the significance tests rely on the two assumptions of multiplicative interaction and unitary interaction across all genes and environments. These two assumptions are not always true, as we noted earlier.)

In the vast majority of published twin and adoption analyses of behavioral phenotypes, G × E has not been explicitly modeled. In this existing quantitative literature, any interactions between genes and environments would be confounded with the other terms in the model and, as a result, would generate upwardly biased estimates of the A and E parameters. For example, if the effects of family salt intake depended on the genetic predisposition of the individual, this effect would register in most analyses as a pure genetic effect on blood pressure. (If one monozygotic, MZ, twin's salt intake exceeded his or her co-twin's salt intake, this same effect would register as E, person-specific environment.) Thus, the heritability coefficient A indexes not only the direct effects of genes, but also effects of interactions between genes and environments (Boomsma & Martin, 2002; Heath & Nelson, 2002; Rutter & Silberg, 2002). For this reason, a large estimate of A for a disorder, sometimes referred to as "high heritability," should not discourage constructing hypotheses of G × E for the disorder. To the contrary, moderate to large quantitative estimates of heritability for a disorder should encourage constructing hypotheses about measured G × E (although they do not guarantee G × E). This logic also applies to E, person-specific environment.

Additional, more specific, support for pursuing G × E can come from evidence that an indicator of latent genetic risk is involved in interaction with a known environmental risk for a disorder. In research designs providing such evidence, the environmental pathogen is measured. Even though the actual genes remain anonymous, variation in participants' genetic risk is inferred on the basis of the diagnosis of a first-degree biological relative. This can be achieved using both adoption and twin designs. In an adoption study, an individual's genetic risk is high if his or her biological parent had a diagnosis of disorder, and low if not. This information about an adoptee's latent genetic risk can be brought together with measures of the adoptee's rearing experience in order to estimate the joint, and possibly interactive, contribution of genetic and environmental risks to disorder. In one study using this design, it was shown that the likelihood of developing conduct disorder was greatest among adoptees with a genetic background of antisocial personality if they were brought up in adverse adoptive family environments (Cadoret, Yates, Troughton, Woodworth, & Stewart, 1995). Another study using this design showed that schizophrenia spectrum disorder was more likely if high-risk adoptees had been brought up in an adoptive home environment characterized by dysfunctional communication than if they were brought up in an environment with better communication (Tienari et al., 2004).

When data are collected on twins, an individual's genetic risk for disorder can be estimated as a function of his or her co-twin's

diagnostic status and the pair's zygosity (Andrieu & Goldstein, 1998; Ottman, 1994). An individual's genetic risk is deemed high if his or her MZ twin has been diagnosed for the disorder in question, and low if not. In one study using this design, the likelihood of becoming depressed following a major life stress was greatest for individuals who had the most genetic liability (Kendler et al., 1995). In another study using this design, the experience of maltreatment was associated with a 24% increase in diagnosable conduct disorder among children at high genetic risk, but an increase of only 2% among children at low genetic risk (Jaffee et al., 2005). Note that when studies document an interactive effect of measured environment and anonymous genetic risk for susceptibility to a disorder, then that measured environment becomes an obvious candidate environment for further G × E research with measured genes. The next section turns to choosing candidate environments.

Step 2: Identifying the Candidate Environmental Pathogen for the Disorder

It is necessary to glean from the literature the candidate environmental risk factors already known to predict each disorder (Rutter, 2005). A pool of candidate environmental risk factors is available for outcomes such as substance abuse (Heath & Nelson, 2002), the antisocial disorders (Loeber & Farrington, 1998), depression (Kendler, Gardner, & Prescott, 2002), and even schizophrenia spectrum disorders (Tsuang, Stone, & Faraone, 2001; van Os, Krabbendam, Myin-Germeys, & Delespaul, 2005). The pool of candidate environmental risks for disorders such as autism, Alzheimer-type dementia, or attention-deficit/hyperactivity disorder is currently more limited. Nonetheless, the concordance of MZ twins for even these highly heritable disorders is less than perfect, indicating the existence of nongenetic contributing causes. Moreover, conceptualizing environmental risk for mental disorders should not be restricted to psychosocial experiences, but should extend to perinatal, infectious, and toxic pathogens associated with elevated rates of mental disorder. We now turn our attention to three considerations in selecting candidate environmental risks for inclusion in G × E research.

Variability in Response Among People Exposed to the Same Environmental Risk

One feature of a good candidate environmental risk factor is obvious, but nevertheless bears noting: It should not perfectly predict the disorder. Thus, for our G × E studies, child maltreatment was a good environmental candidate because not all maltreated children turn out to be violent, stressful life events was a good candidate because not all people experiencing them become depressed, and cannabis use was a good candidate because there is huge variation in people's response to cannabis, ranging from no response whatsoever to psychosis. Evidence of marked variability in the outcome of people exposed to the same

level of an environmental risk implies that individual differences in genetic susceptibility (i.e., G × E) might be at work.

Plausible Effect of the Environmental Risk on Biological Systems Involved in the Disorder

Genes that influence mental disorders must logically exert their effects via the brain's neurobiological pathways. To be a good candidate for interaction with genes, an environmental risk ought to have evidence that it affects a neurobiological pathway to disorder. Although this kind of evidence is highly desirable for framing G × E hypotheses, we accept that it is not easily achievable at the moment, because so little is known about the impact of environmental factors on biological brain systems. Consider that dietary fat was an ideal environmental candidate for the study of the HL gene and cholesterol in the Framingham Heart Study (Ordovas et al., 2002) because the pathophysiology of how dietary fat is metabolized by the liver and converted to HDL cholesterol was already well understood.

Behavioral science is only beginning to understand some of the pathophysiological processes that convert environmental pathogens to mental disorders (Adolphs, 2003; Charney, 2004; de Kloet, Joels, & Holsboer, 2005; Nemeroff, 2004). Nevertheless, this model of logic can be followed for developing hypotheses of G × E that are at a minimum biologically plausible. For example, child maltreatment was a good environmental candidate for our G × E study of MAOA and aggression because neurotransmitter systems having connections to both MAOA and aggression are known to be altered by maltreatment in early life, in ways that persist into adulthood (DeBellis, 2001; Flugge, van Kampen, & Mijnster, 2004). Likewise, cannabis use was a good environmental candidate for our G × E study of COMT and psychosis because cannabis affects the same neuroanatomical sites, dopaminergic indicators, and memory deficits that have been implicated in studies of COMT functionality and studies of schizophrenia (Caspi et al., 2005).

Evidence That the Putative Risk Is a True Environmental Pathogen Having Causal Effects

Once a candidate risk factor has been identified, it is important to go a step further to test whether it has causal effects that are actually environmentally mediated. In general, there is no shortage of candidate environmental risk factors; decades of research have contributed this information. Proven environmental causes are in shorter supply, however. Variables become "risk factors" if they merely have a documented predictive statistical association with disorder outcomes, whether or not the association is causal. But in many cases it is unknown whether these environmental risk factors are true environmental pathogens having causal effects (Kraemer, 2003; Kraemer et al., 1997). For G × E studies, a variable must be more than a risk factor; evidence that it is a true environmental pathogen is also required.

Why must G × E researchers prove that a risk factor has environmentally mediated causal effects on disorder? An association between an alleged environmental risk factor and a disorder cannot be presumed to represent a cause-effect association because some unknown third variable may account for the association, and if the environmental risk factor is correlated with heritable risk, then that third variable may well be genes. Correlation between environmental risk and genetic susceptibility is denoted as rGE (Rutter & Silberg, 2002). For example, the association between maltreatment during childhood and subsequent aggression could be genetically mediated through two forms of rGE (DiLalla & Gottesman, 1991): First, aggressive parents could transmit an aggressive disposition to their offspring and also treat them harshly (passive rGE). Second, aggression-prone offspring could provoke harsh treatment by adults (active rGE). If an environmental risk is found to be under genetic influence, some or all of the observed association between environmental risk and disorder may nevertheless represent true environmental causation. However, if an alleged environmental risk factor's association with psychopathology is wholly genetically mediated, then a putative G × E is really only an interaction between one specific gene and other unidentified anonymous genes. That could be interesting in its own right, but it would lack the implications of a G × E finding.

How can researchers test whether a risk factor is causal? It is, of course, unethical to assign participants to experimental conditions expected to induce psychopathology. However, at least three methodologies can be harnessed to test a risk factor for environmental mediation (Rutter, 2005; Rutter, Pickles, Murray, & Eaves, 2001). First, causation can be documented through a treatment experiment, by implementing a randomized clinical trial to show that an intervention in the environmental risk factor can alter the course or reduce the prevalence of disorder (Howe, Reiss, & Yuh, 2002; Olds et al., 1998). Treatment experiments rule out genetic influence on the environmental risk factor by randomly assigning subjects to the treatment condition. Second, causation can be documented by capitalizing on a naturally occurring experiment of nature that involves an exogenous shock (e.g., combat exposure). Here, the longitudinal method can be used to show that an experience of an environmental factor brings about a change in behavior from a prior baseline level, within individuals (for examples of within-individual change in such natural experiments, see Cicchetti, 2003; Costello, Compton, Keeler, & Angold, 2003; Duyme, Dumaret, & Tomkiewicz, 1999). Natural experiments rule out genetic influence on the environmental risk factor by using the subjects as their own controls.

Third, causation can be documented using twin and adoption designs to control for and rule out genetic influences on the phenotype, while highlighting in bas-relief the influence of a measured environmental variable (Moffitt, 2005). For example, adoptions can be studied to test if an environmental factor alters adoptees' disorder outcomes, by influencing outcome over and above the genetic liability from their biological parents' disorder (Cadoret et al., 1995). Similarly, twins can be studied to test if an environmental risk factor increases twins' disorder outcomes, over and above genetic contributions to their similarity. For example, MZ twin pairs who are discordant for an environmental risk factor can be studied, to test if differences between siblings in their exposure explain their discordant status on behavioral disorder (Caspi et al., 2004; Orr et al., 2003; Toomey et al., 2003). A promising method studies the families of adult MZ twins who are mothers. In this twin-mothers design, the MZ sisters are equivalent genetic mothers to each other's birth children, and therefore genetic influence on the children is matched. In this design, if the environment provided by an MZ mother predicts her children's behavior no better than does the MZ aunt's environment, this would be evidence against an environmental effect (D'Onofrio et al., 2003; Silberg & Eaves, 2004).

Each of these methods is fallible, and thus the most compelling evidence for environmental causation would come from a combination of them (Caspi et al., 2004; Kim-Cohen, Moffitt, Taylor, Pawlby, & Caspi, 2005). For example, whether college attendance has an environmentally mediated effect promoting alcohol abuse among young people has been ascertained using two methods: first, by asking if students' abuse had increased from precollege levels and decreased again after graduation (a natural experiment), and second, by asking if within MZ twin pairs discordant for college attendance, the student twin was more likely to abuse alcohol than the nonstudent co-twin (an MZ-twin-control design; Slutske et al., 2004).

In most cases, the required evidence that a candidate environment has pathogenic effects will come from research conducted outside the G × E study. For example, maltreatment can be considered an environmental pathogen in our G × E study with MAOA because separate research in a twin sample has established that much of maltreatment's effect on children's aggression is environmentally mediated (i.e., the effect does not arise because a child's genetic characteristics provoke maltreatment or because maltreatment-prone parents transmit aggression-prone genes; Jaffee, Caspi, Moffitt, & Taylor, 2004). In some cases, even when dealing with an environmental pathogen for which there is evidence of environmental mediation in the literature, it will be necessary to undertake further checks within the G × E study. For example, in our G × E study of 5-HTTLPR and life events predicting depression, the G × E effect applied only to life events occurring in years just prior to the target depression episode; if life events occurring after the depression episode were substituted, the G × E effect dropped to nil (Caspi et al., 2003). This established that the role of life events in the observed G × E was not an artifact of any inherited tendency to have stressful life events.

Step 3: Optimizing Measurement of Environmental Risk

Once an environmental risk factor has been converted to the exalted status of an environmental pathogen by experimental or genetically sensitive studies, the G × E researcher must set

about to measure it. Much attention has been paid to precise and reliable ascertainment of mental-disorder outcomes, but less has been paid to precise and reliable measurement of environmental pathogens. Many geneticists are reluctant to measure environments because they think it is expensive to collect environmental data. However, measuring exposure to an environmental pathogen precisely and reliably can enhance a study's power enormously. The needed sample size depends on allele frequency and the magnitude of the interaction term, but also critically on the strength of the association between the environmental exposure and the outcome, which is a function (in part) of the precision with which both are measured. In fact, simulations reveal that the difference between unreliable (correlation with true score = .4) versus reliable (correlation = .7) measurements corresponds to a 20-fold difference in sample size, indicating that although measuring environmental exposure might seem costly, doing it well can pay for itself by substantially reducing the need for a large sample (Wong, Day, Luan, & Wareham, 2003). For detecting G × E, smaller samples with expensive but more precisely measured exposures compare favorably against very large samples with necessarily imprecise but inexpensive measurement of exposure (Luan, Wong, Day, & Wareham, 2001). Furthermore, any cost of measuring environments needs to be weighed against the potential cost of not doing G × E research, which is overlooking genes that might be important in disease causation. Next, we offer four considerations for improved environmental measurement in the context of G × E research.

Proximal Measures of Environmental Pathogens
It is critical to differentiate between distal and proximal risk factors (Wachs, 2000). Proximal environmental influences are specific social and physical experiences that directly impinge on the individual. In contrast, distal environmental influences include historical, cultural, demographic, and geographic characteristics whose effects are mediated by more proximal factors. A distal risk factor is important only because it increases the likelihood of occurrence of a proximal pathogen. For example, a large literature shows statistical associations between low family socioeconomic status and mental disorder in children, but more focused analyses reveal that the effect of low socioeconomic status is mediated by parent-child relationships, rather than directly by lack of money (Conger & Elder, 1994; Costello et al., 2003). Proximal environmental risk factors are more relevant than distal factors for G × E research because they are more likely to meet criteria for pathogen status, and they lend themselves to biologically plausible hypotheses about their impact on specific neurobiological systems that mediate psychopathology symptoms. Unfortunately, for many existing genotyped samples, only a few distal variables (such as participants' occupation or education) have been measured, and good measures of proximal environmental pathogens are lacking.

Age-Specific Environmental Pathogens
Some environmental pathogens' effects may be limited to sensitive periods of genetically influenced vulnerability. In some cases, this is common sense. For example, a mother's tobacco smoking is a risk factor for cognitive development of her offspring if their exposure occurs prenatally during fetal brain growth, but that pathogenic effect is unlikely to apply to offspring exposed to their mother's smoking later during childhood. Other developmentally limited effects may not be as obvious. For example, the deleterious brain consequences of drug use appear to be more pronounced on adolescents than adults, a difference that has been linked to brain maturation stage in rodent models (Chambers, Taylor, & Potenza, 2003). Some disorders may have a succession of environmental risks, each relevant at a different stage of the life course. For schizophrenia, infectious exposure is relevant prenatally, hypoxia is relevant at birth, drug use is relevant during early adolescence, and demanding life stress can precipitate deterioration in adulthood (Tsuang et al., 2001). It is important to take developmental considerations into account when interpreting environmental effects because the impact of specific environmental influences will be differentially salient at different ages.

The Cumulative Nature of Environmental Influences
Studies of the temporal nature of environmental risk processes associated with psychopathology yield four important findings. First, although the effects of a single pathogen may be quite small, the cumulative effect of multiple pathogens may be quite large (G.W. Evans, 2004; Rutter & Quinton, 1977; Sameroff, Seifer, & Bartko, 1997). Second, many of the most powerful effects involve chains of related events rather than a single factor at just one point in time. Such a developmental cascade of experiences has been documented as leading to women's depression (Kendler et al., 2002). Third, although the effects of a pathogen measured at a single point in time may be very small, the cumulative effects of extended exposure or repeated exposure are often quite strong. Fourth, most risks derive from long-standing situations rather than acute events.

For G × E research, cumulative measures are better than snapshot measures because they provide more precise, sensitive, and reliable measurement of the environmental pathogen (Wolfe, Havemen, Ginther, & An, 1996). For example, bone lead burden ascertains cumulative lead exposure over time, whereas acute blood lead concentration does not. Likewise, a measure of a person's cumulative months of unemployment over recent years is more useful than whether he or she happens to be unemployed on the date of a research interview. Both bone lead burden and long-term unemployment will have stronger associations with mental-disorder outcomes than their acute, short-term counterparts (Caspi, Wright, Moffitt, & Silva, 1998; Needleman, McFarland, Ness, Fienberg, & Tobin, 2002). In G × E studies, an accumulation of multiple negative life events (such as job loss, divorce, or being the victim of an assault) interacted

more strongly with genetic risk than did a single life event (Caspi et al., 2003), even if the single event was extremely traumatic (Kendler et al., 2005). In many cases, cumulative measurement can be attained by taking repeated measurements over time, which markedly enhances power to detect G × E (Wong et al., 2003).

Retrospective Measures of Environmental Pathogens
Most measurement of environmental pathogens is likely to involve collecting and dating people's retrospective reports of their exposure. Retrospective assessment of exposure is necessary in mental health research because many important exposures occur years before the disorder appears (e.g., childhood sexual abuse) or gradually over a period of time leading up to disorder (e.g., sustained heavy alcohol consumption). The several dangers of retrospective data in psychopathology research are well known: normal forgetting, revisionist recall, bias by the respondents' knowledge of subsequent disease outcome, bias by patients' cognitive dysfunction or low mood, and forward telescoping of recalled events (Hardt & Rutter, 2004; Simon & VonKorff, 1995). A specific difficulty for retrospective recall of psychosocial risks in G × E studies is evidence that memories of past events (e.g., parental treatment) are under partial genetic influence, and that the same genetic factors influence personality and behavior (Krueger, Markon, & Bouchard, 2003). This implies that some retrospective measures of environmental risk are confounded with outcome-relevant genes and will probably not pass the test of environmental mediation.

Fortunately, there are solutions to the problems of retrospective data. Clearly, the best antidote to the ills of retrospective data is collecting data prospectively in a longitudinal study. Repeated prospective measurement of environmental pathogens and mental health status enhances the reliability and precision of measurement (and increases power to detect G × E), and augments scientific inference. But for geneticists accustomed to their field's rapid pace, the prospect of starting up a prospective study and waiting years for outcomes may lack appeal (Collins, 2004). Fortunately, DNA can be collected at any point in the life course, and as a result, genotyping can be added to the large variety of excellent ongoing longitudinal cohort studies having established data on prospective, repeated, cumulative measures of exposure to environmental pathogens relevant to mental health.

However valuable existing cohort studies may be, they cannot supply prospective measures of an environmental pathogen that is discovered to be important for mental health only after a study has been under way for some years. Exposure to domestic violence comes to mind, as it was not prospectively assessed for children in those cohort studies begun in the 1970s that are now yielding adult mental-disorder outcomes; domestic violence was virtually unheard of in the literature then and was assumed to be too rare to warrant measurement in cohort samples. Even when no prospective data exist, it is possible to improve the quality of retrospective reports by using the life-history-calendar method. Life-history calendars have been proven to generate highly reliable and valid retrospective reports of a variety of pathogenic life events (Belli, Shay, & Stafford, 2001; Caspi et al., 1996), including exposure to domestic violence (Ehrensaft, Moffitt, & Caspi, 2004) and spells of substance abuse (Horney, Osgood, & Marshall, 1995). Life-history calendars can also generate reliable histories of onset, duration, and recurrence of illness (Belli et al., 2001; Lyketsos, Nestadt, Cwi, Heithoff, & Eaton, 1994), which are essential for assessing the timing of pathogen exposure relative to onset and course of the disorder. This fundamental principle can be illustrated by our finding of a G × E effect involving the 5-HTTLPR polymorphism and life events; a study that could not date life events relative to episodes of disorder would not have identified the effect, because life events occurring before disorder onset generated a G × E, but life events occurring after disorder onset did not.

Step 4: Identifying Candidate Susceptibility Genes
So far, tests of G × E hypotheses have not hunted for new genes; they have exploited candidate genes already identified, to ascertain whether they are involved in G × E as hypothesized. The obvious challenge for such hypothesis-driven studies is how to choose genes to test. We propose the following three guidelines for choosing among candidate genes as they emerge.

Common Polymorphic Variants
Good candidate genes for G × E will be those whose polymorphic variants are relatively common in the population. If a potentially disadvantageous variant is maintained at a high prevalence rate, this might imply (although it certainly does not guarantee) that natural selection has not been able to eliminate the variant because its deleterious effects on the phenotype are expressed only under particular environmental conditions, or perhaps even because it confers a selective advantage under particular environmental conditions (Aldoo et al., 2002; Hill, 1999; Schork, Cardon, & Xu, 1998; Searle & Blackwell, 1999). In other words, the gene involved in G × E can be hidden from the forces of natural selection, just as it is hidden from gene hunters. From a more pragmatic point of view, common allelic variants confer advantages of statistical power when testing interaction effects (Hwang, Beaty, Liang, Coresh, & Khoury, 1994).

A Direct Gene-to-Disorder Association
If the gene has already been shown to have a replicated main-effect association with the mental disorder, it will be an easy candidate choice. However, it is vital to appreciate that G × E research cannot rely on such replicated main-effect associations, because of the following paradox: Logically, if a gene's effects are conditional on the environment, this will have the natural consequence of diminishing researchers' capacity to

detect a main-effect association between the gene and a disorder. Thus, a known association between gene and disorder can nominate a gene for a G × E hypothesis, but the absence of such an association does not in any way disqualify a gene.

There is hope that gene associations will be found more successfully with endophenotypes than has been the case with diagnosed disorders. Endophenotypes are heritable neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological correlate constituents of disorders (Gottesman & Gould, 2003). Because they are thought to have simpler genetic underpinnings than disorders themselves, endophenotypes may assist with identifying candidate genes for G × E hypotheses. As a caution, it must be noted that to the extent that endophenotype studies look only for main effects, they too will probably overlook genes whose effects are conditional on the environment. For instance, the connection between the HL gene and cholesterol, an endophenotype for heart disease, remained hidden until it was revealed in a G × E study involving dietary fat (Ordovas et al., 2002).

Functional Significance in Relation to Reactivity to the Environmental Pathogen

Candidate genes are those for which there is empirical evidence of a functional physiological significance in brain systems with known connections to psychopathology (Tabor, Risch, & Meyers, 2002). However, such evidence is not enough to frame hypotheses in G × E research. The soundest logical basis for selecting a candidate gene for G × E is evidence that the gene is related to organisms' reactivity to the environmental pathogen. This evidence is necessary to frame a biologically plausible hypothesis that the gene moderates responses to an environmental pathogen (i.e., G × E). This association is completely different from the gene being associated with the disorder itself. For example, we elected to focus on the 5-HTTLPR gene in our G × E research on life events and depression, despite the fact that there was no robust association between the gene and depression (Lesch, 2003), because the gene had been shown to predict individual differences in physiological responsiveness to stress conditions in three different experimental paradigms, knockout mice (Murphy et al., 2001), stress-reared rhesus macaques (Bennett et al., 2002), and a human functional neuroimaging paradigm (Hariri et al., 2002).

To date, most evidence of connections between genes and pathogen responsiveness has emerged from studies of rodents and nonhuman primates having known human-relevant genotypes. In nonhuman animals, both genotype and exposure to an environmental pathogen can be manipulated under experimental control (Crabbe, 2003; Flint, 2003; Maxson, 2000; Suomi, 2001). Studying nonhuman subjects is an advantage because they can be assigned to detrimental risk conditions that are unethical in human studies (e.g., deprivation of maternal rearing). These experiments use genetically modified animals, or animals having known human-relevant polymorphisms, and

they measure responsiveness through a variety of physiological and behavioral phenotypes. For example, two groups of rhesus macaques differing in their serotonin genotype reacted differently to stressful maternal deprivation during infancy, as indicated by measures of serotonin metabolites in cerebrospinal fluid (Bennett et al., 2002), adrenocorticotropic hormone (Barr et al., 2004), and visual orientation to stimuli (Champoux et al., 2002). We have emphasized the value of animal models of pathogen reactivity, rather than animal models of disorder per se. Animal models of disorder have been criticized because they cannot faithfully represent core cognitive symptoms of human mental disorders, whereas animal models of pathogen reactivity offer a valuable window for understanding the neurobiological effects of environmental pathogens (Carola, Frazzetto, & Gross, 2005; Holmes, Murphy, & Crawley, 2003).

As yet, there is relatively little information available about genes associated with reactivity to environmental pathogens among humans. We look toward a new wave of experimental research investigating whether or not genotypes influence human participants' responsiveness to emotion-eliciting stimuli, laboratory stress paradigms, toxic exposures, or other pathogens. Some such studies have already been conducted. For example, humans with one or two copies of the short 5-HTTLPR allele exhibited greater amygdala reactivity to fearful visual stimuli compared with individuals homozygous for the long allele (Hariri et al., 2002, 2005; Heinz et al., 2005). Also, humans with one or two copies of a dopamine receptor polymorphism allele, the DRD4 7-repeat (or longer), exhibited more craving and arousal when looking at smoking cues (a lit cigarette) than did individuals not carrying the 7-repeat allele (Hutchison, La Chance, Naiura, Bryan, & Smolen, 2002). Random assignment of human subjects to experimental environmental-risk stimuli, as done in the aforementioned studies, rules out the possibility of any confounding gene-environment correlation.

Future human G × E investigations of the influence of genotype on reactivity to environmental pathogens will use neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, emotional, and neuropsychological phenotypes as measures of pathogen reactivity. (Note that these are the same domains that other researchers have proposed for study as endophenotypes, but endophenotypes are defined as stable, state-independent traits, whereas reactivity measures by definition must be state dependent.) Likely examples might include peripheral psychophysiological measures such as electrodermal or heart rate reactivity (Battaglia et al., 2005; Finley et al., 2004), adrenocortical reactivity (Wust et al., 2004), and reactivity of the brain as measured by functional neuroimaging tools (Egan et al., 2001, 2003; Hariri et al., 2002, 2005; Heinz et al., 2005). The results of more reactivity studies will provide an evidence base to nominate candidate genes for G × E hypotheses predicting disorders.

This fourth step, nominating candidate genes for G × E hypotheses, is going to require patience. Good candidate genes will probably not pile up rapidly because the many pragmatic barriers to detecting reliable connections between genes and disorders (Merikangas & Risch, 2003b; Sullivan, Eaves, Kendler, & Neale, 2001) will also bedevil research designed to detect connections between genes and responsiveness to environmental pathogens. Moreover, until now, researchers have put most of their efforts into the search for direct connections between genes and disorders, whereas the search is only beginning for connections between genes and responsiveness to stress or other pathogens.

Step 5: Testing for an Interaction

Each G × E study will involve key pragmatic decisions, such as how to characterize the genotype of interest, how to reduce genotyping measurement error, what sample size is needed for statistical power, or how to handle the study sample's ethnic mix. In this article, we do not offer instruction about such decisions, because the decisions must be made according to the specifics of a study's hypothesis. Detailed recommendations about studying measured G × E have been published elsewhere (see Hunter, 2005; Ottman, 1990, 1996; van den Oord, 1999; van Os & Sham, 2003; Yang & Khoury, 1997), and new methodological advice is constantly published. This section addresses general issues of research design.

Study Sampling Designs

The most informative design for testing G × E begins with a cohort sample, to represent as accurately as possible population variation in genotype, exposure to environmental pathogens, and a variety of disorders (as well as to represent variation in healthy outcomes). This design is enhanced if the cohort can be enlisted prospectively in early life and followed longitudinally, with repeated assessments to obtain unbiased measures of cumulative exposure to environmental pathogens, and to ascertain psychiatric history relative to timing of exposure (Collins, 2004; Hunter, 2005). As a very simple illustration, in the case of dichotomous genotypic and environmental variables, four cells of participants can be compared. First, a cell having low genotypic risk and low environmental risk establishes the baseline level of psychopathology outcome associated with factors apart from the G × E hypothesis. Second, a cell having high genotypic risk but low environmental risk ascertains any effect of the gene in isolation on psychopathology outcome. Third, a cell having high environmental risk but low genotypic risk ascertains any effect of risk environment in isolation. The key test of G × E compares information from these three cells against information from a fourth cell having both high genotypic risk and high environmental risk, to ascertain whether the joint association of the two risk factors with psychopathology outcome is additive or multiplicative. As this example makes obvious, measured G × E can

be approached using a variety of familiar statistical methods (Cohen, Cohen, West, & Aiken, 2003; Greenland & Rothman, 1998; Rosenthal, Rosnow, & Rubin, 2002; Rutter & Pickles, 1991).

The epidemiological cohort design is desirable for health research because it contains population information needed to evaluate a finding's potential clinical utility, and this advantage applies equally to G × E research. Although concerns about the clinical utility of G × E findings may seem premature today, systematic evidence of utility from epidemiological designs will be necessary before any G × E finding can be translated into applied use of measured genes in diagnostics and therapeutics (Haga, Khoury, & Burke, 2003; Merikangas & Risch, 2003a). The epidemiological design allows accurate estimation of sensitivity, specificity, positive and negative predictive values for clinical outcome, and attributable risk (which implies how much the disorder could be reduced in the population if the G × E could be disrupted). The interaction between the COMT polymorphism (valine vs. methionine alleles) and cannabis use provides an illustration. The prevalence of schizophrenia spectrum psychosis in the population is about 1 in 100; in adolescent cannabis users, this risk multiplies to about 4 in 100, and in studied adolescent cannabis users with the COMT valine genotype, this risk multiplied to 15 in 100 (yielding a significant G × E). However, 85% of the study cohort's adolescent cannabis users had no untoward psychotic effects even if they had a homozygous valine genotype, and further, only a small fraction of psychosis cases could be attributed to the G × E (Caspi et al., 2005). Thus, testing in a birth cohort revealed that clinical diagnostic prediction from this G × E would be unwarranted, although the G × E may prove useful for understanding etiological processes in psychosis.

Despite the clear advantages of testing G × E in longitudinal cohort studies, cheaper and quicker designs have been put forward (Clayton & McKeigue, 2001). The recommended strategy is to add information about environmental exposure to conventional genetic association designs (case-control comparisons, affected-relative pair designs, etc.; Yang & Khoury, 1997). Even a case-only design to screen for G × E has been described (J. Khoury & Flanders, 1996). We mention an additional possibility: testing G × E within a pool of individuals exposed to a known environmental pathogen. If a good candidate gene is available, such an exposed sample could be used to test the hypothesis that individuals with that gene develop psychopathology, but individuals without that gene do not. Exposed samples might also be used to uncover new genes, by testing whether individuals with a disorder differ on any genetic markers from those without the disorder. The logic of this design is that (a) the environmental pathogen's main effect on disorder is already documented, and (b) participants' genotype is not associated with exposure to the pathogen (or all participants are matched for exposure). Therefore, any outcome variation that can be attributed to genotype is evidence that the effect of exposure depends on (is

moderated by) genetic susceptibility. This is the essence of the concept of G × E. (Note that a statistical test for multiplicative G × E would be irrelevant in this design, as study samples lack variation on E.)

An example of this latter approach is the previously mentioned study of hospital patients exposed to streptococcal infection (Kotb et al., 2002). The researchers tested the G × E hypothesis that variation in genotypes associated with histocompatibility might explain which patients would develop severe toxic systemic syndrome (as opposed to mere sore throat). Another study focused on toddlers exposed to contagions at daycare facilities and tested links between candidate polymorphisms and individual differences in immune tolerance (Hoffjan et al., 2005). The complement of this design is also possible, beginning with a pool of individuals at known genotypic risk and ascertaining whether those exposed to an environmental pathogen develop psychopathology more than those who are unexposed (we found no studies using this design).

Ascertaining the Validity of a G × E Finding
A key methodological challenge is how to decide when a G × E finding is real, rather than artificial. For example, we noted earlier in this article the possibility that, because of gene-environment correlations, what at first appears to be a G × E might in reality be a gene-gene interaction. Moreover, statisticians have long been aware of the fact that statistically significant interactions are sensitive to alterations in both the definition of the variables being examined and the way they are scaled. Artifactual interactions can be produced by altering scaling, and different conclusions can be reached depending on the specific link function used for testing interaction (Greenland & Rothman, 1998; Rutter, 1983; Rutter & Pickles, 1991). Several strategies, used in combination, can inform researchers whether confidence in a G × E finding appears to be warranted. In some way or another, all of these strategies involve the use of theory.

First, potential scaling artifact can be attacked by substituting for the genotype of interest a similarly distributed polymorphism that bears no theoretical relation to the hypothesis. In our study of MAOA and conduct problems (Caspi et al., 2002), we reasoned that if the interaction between MAOA and maltreatment was a consequence of scaling artifact, a random single nucleotide polymorphism with similar allele frequencies ought to show the same interaction. It did not. We further reasoned that if this interaction was a scaling artifact, it ought to predict an outcome that had no relation to the hypothesis but had the same prevalence as conduct disorder—gum disease. It did not. Along these same lines, if the G × E reflects a valid biological process, then it ought to robustly predict the same disorder outcome measured in different ways, each having its own metric properties. For this reason, it is useful to carry out what econometricians call sensitivity analyses, that is, to test whether the G × E can predict different measures that share construct validity for the disorder of interest, such as a categorical diagnostic measure (e.g.,

conduct disorder), a scale of symptoms (e.g., number of conduct problems), a personality trait scale (e.g., aggressive personality), an informant's rating (e.g., antisocial lifestyle), or an official record (e.g., criminal conviction). The choice of measures must be guided by theory. If a G × E is observed for only one in such a set of measures of a phenotype, the finding may be nothing more than a scaling artifact or a chance product of multiple testing. But if a G × E is observed for most or all of a set of measures of a phenotype, this defies chance, and also assuages concerns about scaling artifact.

Second, it is important to achieve a good match between the predictions derived from the G × E hypothesis and the statistical approach used to operationalize it. In some cases, the least satisfactory approach is to rely on putting an interaction term into an overall multivariate analysis (Rutter & Pickles, 1991). Consider a data set in which a main effect of genotype on disorder is statistically significant in the full sample, but this apparent main effect in reality arises from an underlying pattern of moderation. In this pattern, genotype is associated with disorder in the environmentally exposed group, but genotype is not associated with disorder in the nonexposed group. In such data, the obtained main effect of genotype is not statistically equivalent to an effect in all study participants who carry the at-risk genotype. Testing this data set in the usual way would allow the (false) statistical main effect of genotype to absorb part of the variance of the interaction. In contrast, planned group comparisons may be the best choice of analysis, if researchers have enough a priori theoretical information about the genotype and environment to break down the G × E hypothesis to predict the precise pattern of psychopathology it predicts. This approach can circumvent much of the uncertainty of scaling in omnibus multiplicative tests.

Third, the best protection against a chance G × E finding is a sound nomological network of evidence to support a biologically plausible theoretical rationale behind the hypothesis. We have already mentioned the importance of evidence that the environmental risk factor influences biological systems involved in the disorder, evidence that the putative risk factor has true environmental causal effects on the disorder, and evidence that the candidate gene is associated with animals' and humans' reactivity to the environmental pathogen. At present, such information is limited, but it is rapidly expanding for many genes already implicated in G × E findings, such as MAOA, 5-HTTLPR, COMT, APOE4, and DAT1 (a dopamine transporter). Efforts to summarize and integrate the evidence are emerging (e.g., Madras, Miller, & Fischman, 2005).

Step 6: Evaluating Whether a G × E Extends Beyond the Initially Hypothesized Triad of Gene, Environmental Pathogen, and Disorder
Step 6 ensues if and only if the hypothesized G × E is obtained. Analysis at this step systematically replaces one variable in the

triad while holding the other two constant. Restated, this step ascertains whether the interaction holds when the gene is replaced with other disorder-relevant candidate genes, when the environmental risk is replaced with the disorders' other known risk factors, and when the disorder is replaced with other related disorder phenotypes. This step is exploratory, but it may be revealing because neither genes, environmental pathogens, nor disorders are likely to operate in isolation. Step 6 is to be distinguished from fishing about in a data set of genes, environments, and disorders, which entails inherent risk of a chance faux finding from multiple statistical tests (van den Oord & Sullivan, 2003). One purpose of this article is to increase theory-guided hypothesis testing in G × E research, and thereby to decrease data dredging. However, once the initial hypothesis has been tested and supported, it is also responsible scientific practice to ascertain how far beyond the original hypothesis the G × E may extend (Licinio, 2003). In this way, large epidemiological data sets offering more than one gene, more than one environmental risk, and more than one disorder group can provide added value per grant dollar by being used in planned tests to uncover (or rule out) a potentially wider nomological net surrounding the original finding. Of course, researchers must be cautious about interpreting any exploratory findings until they are replicated.

This Step 6 post hoc strategy proved beneficial in two of our G × E studies. In the study of the 5-HTTLPR polymorphism, life events, and depression, the G × E applied when childhood maltreatment was substituted for adult life events, suggesting that the 5-HTTLPR genotype moderates the depressogenic influence of stress that occurs not just in adulthood, but also earlier. However, the G × E between 5-HTTLPR status and stressful life events did not extend to anxiety disorders (Caspi, 2003; Kendler et al., 2005). In the study of COMT, cannabis, and psychosis, we found that the G × E predicted not only psychosis, but also depression (even after comorbid psychosis was ruled out). This result suggests that the explanation behind this G × E may involve neurobiological processes shared by affective and psychotic disorders.

Step 7: Replication and Meta-Analysis

Some of the first G × E findings have been replicated, but it is early to assess the overall track record. Replication is the "sine qua non for accepting a hypothesis" (Merikangas & Risch, 2003b, p. 627), yet psychiatric genetics' association studies are "mired in nonreplications" (Insel & Collins, 2003, p. 618). On the one hand, G × E studies need not necessarily be tarred with the same brush as association studies seeking direct main effects of genes on disorders, for the simple reason that interactions are statistically independent of main effects. G × E studies may fail to be replicated, but this failure could be for reasons other than those that bedevil association studies. For example, there is the known difficulty of detecting interactions between

any two factors in behavioral science, let alone genes and environment (McCall, 1991; McClelland & Judd, 1993). On the other hand, until scientists understand the reasons behind failed replication in gene-association studies, it is impossible to say whether those reasons ought also to apply to G × E findings.

In the meantime, we reiterate guidelines applicable to all replication studies. Findings can fail to be replicated because the initial study yielded a false positive result, or because the subsequent studies yield a false negative result. Earlier, we discussed avoiding a false positive result in the initial study, and replication studies should likewise address those concerns (scaling artifact, the right statistical test, plausible theory). In addition, it is well established that replication samples should be substantially larger than the sample that yielded the original finding, so as to avoid a false negative finding.

False negative results may arise if correlation between the two elements in an interaction term prevents detecting their interaction (McClelland & Judd, 1993). Thus, gene-environment correlation could prevent detecting G × E, but interestingly, no G × E study to date has detected any correlation between its measured gene and its environmental pathogen. This consistent absence of correlation between a measured gene and an environmental risk across studies is not too surprising; it is more likely that many genes act in concert to influence individual differences that, in turn, increase the probability of exposure to environments. Nevertheless, the possibility of correlation between a measured gene and environmental pathogen should always be tested. Further, to aid replication efforts, the report of the original study must be as specific as possible about the effect claimed: Does it apply to one age group, one sex, one type of polymorphism, one subset of environmental pathogen, or some particular manifestation of the disorder? That said, there is no need to insist on exact duplication of the initial study reporting a G × E, because a finding that is robust in nature ought to hold up despite differences between studies in particulars of design and measurement. Overall, the record of gene-association studies teaches the wisdom of not overreacting to any single study, whether it replicates the original or not. Cumulative science patiently awaits the meta-analysis.

POTENTIAL IMPLICATIONS OF MEASURED G × E EFFECTS

Hypotheses of G × E are worth testing because if measured G × E effects are found for mental disorders, both specific genes and specific environmental risks can conceivably have much stronger connections with disorders than previously thought, within vulnerable groups. However, a G × E finding is too crude to be an answer in and of itself. As we describe next, G × E is interesting because of its potential to stimulate progress in basic neuroscience, in future gene hunting, in intervention research, and in public understanding of genetics.

Potential Implications for Basic Neuroscience

Once a G × E is documented to be robust, this new knowledge should stimulate fresh research into how the mechanisms behind the G × E might work, and what it means for understanding, and hence potentially for reducing, psychopathology. The very special gift from a reliable G × E finding is clear evidence that there must be a pathway of causal process connecting the three disparate "end points" forming the gene-pathogen-disorder triad. The pathway may initially be hidden from scientific view, but knowing three end points enhances the likelihood of finding paths that unite them. As we noted earlier, one of the major gaps in knowledge about mental disorders concerns the exact nature of environmental pathogens' effects on the organism (Charney, 2004; Nemeroff, 2004). Clearly, because pathogens can result in disorders years after the immediate period of risk exposure, some mechanisms must mediate the persistence. How does an environmental factor external to the person get under the skin to result in a mental disorder? The insight that the result depends on the person's genotype with respect to a specific functional gene offers clues for unraveling the causal pathway in the laboratory.

Further, most pathogens constitute nonspecific risk for many disorders (smoking influences cancer, osteoporosis, lung disease, and heart disease; maltreatment influences aggression and depression; birth complications influence aggression and schizophrenia). The pathophysiological pathways connecting a pathogen to disorder are expected to differ from one disorder to the next, but there is precious little evidence about this variation. Genes may offer clues to this perennial riddle of disorder-specific pathophysiology. Already, G × E findings have been key in leading to elaboration of the physiological causal processes linking environmental pathogens, via genes, to cardiovascular disease (Lifton, Gharavi, & Geller, 2001; Talmud & Humphries, 2001; Yamori et al., 1992).

Potential Implications for Gene Hunters

High heritability estimates for many mental disorders have implied that these disorders are good targets for molecular genetic research (Martin, Boomsma, & Machin, 1997; McGuffin, Riley, & Plomin, 2002). However, psychiatric geneticists have been frustrated because progress in finding genes reliably associated with mental disorders has been slow. The expectation that simple direct paths from gene to disease will be found has not proven markedly fruitful for complex mental disorders: Few linkage studies detect genes, many gene-association studies fail consistent replication, and gene findings that are replicated account for little variation in the phenotype (Hamer, 2002). Several explanations have been invoked to explain some of the failures to find mental-disorder genes for which initial significant results can be replicated over time. These explanations include, but are not limited to, publication bias, misclassification of outcome, phenotypic heterogeneity, allelic heterogeneity,

weak prior probabilities of association, multiple testing, population stratification, and inadequate sample size (Cardon & Palmer, 2003; Colhoun et al., 2003; Lohmueller, Pearce, Pike, Lander, & Hirschhorn, 2003; Sullivan et al., 2001; van den Oord & Sullivan, 2003). G × E research is suggesting another, different, reason for the slow progress in finding genes for mental disorders. Ignoring nurture may have handicapped the field's ability to understand nature.

A finding from several initial G × E studies of measured genes may be relevant to the slow progress in replication of gene findings. In these studies, although particular genes had marked effects on outcome within environmentally exposed subgroups, the effects of these genes on disorder apart from their role in G × E were virtually nil, and statistically undetectable (Caspi et al., 2002, 2003, 2005; Eley et al., 2004; Foley et al., 2004; Grabe et al., 2005; Kahn et al., 2003; Kendler et al., 2005; Meisel et al., 2004; Ordovas et al., 2002; Wang et al., 2002). Genotype was statistically unrelated to outcomes in the full cohorts of these studies; its effects were revealed only among individuals exposed to an environmental pathogen. This pattern of nil to small main effects for measured genes could be more widespread, and if so, it will have a conceptual implication for gene hunters: If a gene-to-disorder connection is apparent only among individuals exposed to specific environmental pathogens, then the connection will be diluted by other individuals in the sample who carry the genotypic risk but have no exposure. This pattern of findings also suggests four methodological implications for future measured-gene research, as follows.

First, a major challenge in linkage pedigrees is the gene whose effect occasionally "skips a generation"; that is, a family member carrying the gene appears phenotypically healthy. In Mendelian single-gene disorders, this effect is referred to as incomplete gene penetrance, whereas in complex multifactorial disorders, the effect could arise for several reasons. G × E findings suggest one reason: If a gene's effects are expressed only among pedigree members exposed to environmental risk, then unexposed carriers of the gene might escape disorder (van Os & Sham, 2003). It might be possible to revive some previously unproductive linkage pedigrees, to evaluate whether ascertaining pedigree members' exposure to environmental pathogens might shed new light.

Second, a finding of association between a candidate gene and a given outcome may not be replicated if G × E is operating and there are differences in risk exposure between the research samples. A sample having many exposed subjects will show an association, whereas a sample having few exposed subjects will not, and if exposure is not ascertained, the source of nonreplication will remain a mystery. When possible, gene-association studies should measure and take into account samples' exposure to environmental risks.

Third, when G × E operates and exposure to environmental pathogens differs among participants within a sample, genes will account for little phenotypic variation, and their effect sizes will

be small to nil. Quantitative models of continuously distributed complex disorder phenotypes have been interpreted to imply that mental disorders must arise from many genes, each with a very small effect (Plomin & Crabbe, 2000). This small effect size has been invoked to explain the poor success of genetic studies, and to call for extremely large samples. However, in the initial G × E studies cited in this article, the G × E accounted for a sufficient proportion of outcome to suggest a provocative hypothesis—that some multifactorial disorders, instead of resulting from very many genes of small effect, might result from relatively few genes whose effect sizes are conditional on exposure to environmental pathogens. For understanding the influence of such conditional-effect genes, large samples may be less necessary than strategic G × E research. Large samples are undoubtedly essential to study genes having main effects on disorder, but if large-sample studies collect data on environmental risks, they can also examine genes involved in G × E, thus reaping enormous added value.

Fourth, genome-wide scans intended to find new genes linked to disease, like most psychiatric genetics designs, aim to uncover genes having direct main effects (i.e., genes that show associations with behavior irrespective of participants' environments). However, this main-effects approach is inefficient for detecting new genes whose effects are conditional on environmental risk. As illustrated by the initial G × E studies cited here, main effects of factors are not prerequisite for interactions between them. Interactions are statistically independent of main effects. As a result, genes showing no direct connection to disorder in genome-wide scans may nevertheless be connected to disorder through hidden G × E. Genome-wide scans might be more powerful if gene hunters deliberately recruited samples selected for known exposure to an environmental pathogen for the disorder they wish to study and then scanned for genetic variants characterizing participants who did versus did not develop the disorder.

We are suggesting that the G × E approach can be of practical benefit as a tool in the hunt for genes connected with mental disorders. Known environmental pathogens might be profitably exploited as research tools, by being applied like a magnifying glass to reveal some genes' connections to disorder. Of course, this magnifying glass will be useful only for genes whose connection to disorder operates via susceptibility to an environmental pathogen, and it is unknown how many of these genes exist. However, there are undoubtedly more than the handful already found.

Potential Implications for Environmental Researchers and Interventionists

Many environmental researchers have become discouraged in recent years because high estimates of heritability from quantitative behavioral genetic studies were understood to imply that nongenetic factors are of little importance in the causal origins

of mental disorders (Plomin & Bergeman, 1991; Rowe, 1994; Turkheimer & Waldron, 2000). In contrast, recent demonstrations of G × E reveal that potentiated effects of environmental risks can be unexpectedly large, in the specific context of genetic vulnerability. Thus, findings of G × E reframe the scientific question for environmental researchers. The question is not "Is there any effect of environmental risk?" or "How big is the average effect of an environmental pathogen across all people exposed to it?" but rather "Who is at the greatest risk from an environmental pathogen?"

This "who" question implies potential benefits of G × E information for interventionists. Because it is difficult to alter genes in humans, the outcome of G × E research that is most likely to be relevant for application is new information about which environmental risks to modify (Guttmacher & Collins, 2003). First, G × E findings can help to refine understanding of the heterogeneity in humans' responses to environmental pathogens, which would allow for greater precision and less measurement error in basic-science studies of environmental risk processes. Such precision would increase knowledge of how environmental pathogens bring about mental illness. Second, when a gene's association with disorder is revealed to be increased in the presence of environmental risk, this information may direct strategic priorities toward research into that gene's expression and function. New genetic diagnostics and new treatments may emerge (W.E. Evans & Johnson, 2001; Guttmacher & Collins, 2002; Radda & Viney, 2004). Third, G × E findings can help to categorize genetic heterogeneity in response to environmental interventions, which may eventually facilitate individualized treatments for mental disorders. Fourth, G × E findings suggest the possibility that scarce public-health resources could be directed toward population segments most vulnerable to environmental pathogens. Most environmental risk factors have only modest predictive value for disease outcome averaged across the population. However, a person who is aware that his or her genetic health profile suggests susceptibility to an environmental pathogen might be particularly receptive to environmental-risk education (M.J. Khoury, 1996). Before any intervention application, G × E must be tested in epidemiological cohort designs so that aspects of clinical validity, such as specificity and attributable risk, can be evaluated (Collins, 2004; Haga et al., 2003). Undoubtedly, any translations from G × E research to intervention will involve fundamental ethical considerations, and those should continue to be an integral part of the research process (Haga et al., 2003; Nuffield Council on Bioethics, 2002; Parens, 2004; Sankar, 2003).

Potential Implications for Public Understanding of Genetics

The public's understanding of genetics in psychopathology is naively deterministic, and the public's feeling about genetics is fearful, but G × E findings may help to improve this situation. To

understand how G × E findings can help, it is relevant to take note of the public's views about genetic research. The Hastings Center's working group on behavioral genetics concluded, "Few issues inspire as much feeling [as genetic research does]" (Parens, 2004, p. S5). Vocal protestors a few years ago demanded a ban on genetic research into behavior in the United States (Roush, 1995). A public consultation carried out by the Nuffield Council on Bioethics (2002) revealed that although few British respondents recommended a total ban on behavioral genetics research, the majority expressed strong fears about the research, believed application of genetic findings about behavior would be morally unacceptable, felt that the research should be given low funding priority, and favored strict regulatory controls. Public demands for legislation to control the use of genetic information have been voiced in the United States and elsewhere (Sankar, 2003).

It is useful to analyze why members of the public view DNA-based information as exceptional and dangerous, compared with other similar personal information (Sankar, 2003). Is genetics threatening because it is reductionistic? Neuroscience studies are showing how humans' highest mental activities can be reduced to biological processes, which could be subject to deliberate manipulation, but there is no widespread public clamor to ban the work of neuroscientists (Moreno, 2003). Is genetics threatening because it is associated with the risk of discrimination? Other medical tests forecast future health and can entail risk of stigma, but such tests are not generally the subject of great public anxiety. Many genetically influenced human features, such as appearance, abilities, personality, and even mental health, can be readily assessed or observed by other people and have been the basis for eugenic policies, but information on these features is not generally considered highly sensitive. Is genetics information threatening because it carries risks for personal privacy? Records of family medical history also reflect genetic information, but these are not generally considered as so sensitive to warrant exceptional laws to preserve privacy (beyond those covering medical confidentiality in general). Concerns about reductionism, discrimination, and privacy do not fully account for the exceptional public fears about genetics research and practice.

Ethicists attribute the root of the public's concern about genes to a pervasive belief in the power of genetic determinism (Parens, 2004; Sankar, 2003): "Genetic determinism is the belief that genetic contributions to behavior and personality are more important than other factors such as environments . . . genetic determinism implies that knowing a person's genetic makeup is tantamount to knowing his or her future" (Sankar, 2003, p. 398). In part, the public's acceptance of genetic determinism has its origins in public understanding of disorders caused by chromosomal or single-gene defects; these rare illnesses provide compelling illustrations of genetic determinism. In everyday speech, "genetic" and "hardwired" are used as synonyms. Kendler (in press) illustrated that genetic determinism has

become endemic in public culture by asking his readers to envisage saying aloud, "the gene for . . ." and then "the environment for . . . ." The former phrase feels comfortable, but the latter phrase feels awkward, if not ridiculous. In relation to complex psychopathology arising from multifactorial genetic and environmental causes, the two phrases are equally ridiculous, but they do not seem so. In the past, the popular press ignored or disparaged geneticists who attempted to explain that environmental causes of behavior are important:

> This point [that environmental causes are important] is so firmly embedded in the repertoire of cautious human-genome types that they have developed pet metaphors to express it . . . 'the brain is hardware, education is software' . . . This all sounds nice—and for the most part it is true. But this doesn't mean that it is impossible to alter behavior by manipulating the genes. (Saletan, 1989, p. 19)

Thus, metaphors about the contribution of the environment have not been sufficiently reassuring to persuade the public to abandon genetic determinism. The cautious geneticists rebuked by Saletan have tried to persuade the public against genetic determinism by using metaphors, but metaphors have not worked. Evidence from data is needed.

Concrete data needed to counter genetic determinism are provided by new G × E findings (and by new findings about the responsiveness of gene expression to environmental input; Pray, 2004). For example, recall that in the study of 5-HTTLPR and depression (Caspi et al., 2003), cohort members carrying the homozygous short 5-HTTLPR genotype had no elevated risk of depression, unless they also had stressful lives—not a good track record for genetic determinism. G × E findings are now being disseminated through television, radio, newspapers, popular science writings, and Web sites ("The Long and the Short," 2003; "Nurturing Nature," 2002; Parens, 2004; Ridley, 2003; Sapolsky, 2004b; Sinha, 2004; Underwood & Adler, 2005). These efforts promote public understanding of the conditional nature of genes' links to behavior and psychopathology. Such understanding should make eugenics and other misuses of genetic information much more difficult.

RESEARCH NEEDS

In this article, we have pointed to several types of studies required to support and extend G × E research into mental health and behavior. Psychologists are well situated to play a central role in all of them.

First, research is needed to identify good candidate genes for G × E hypotheses. Particular emphasis should be placed on identifying genes associated with variation in biological or psychological reactivity to environmental pathogens. Much of this work will involve animal models, to reap the advantages of experimentation. But because of the uniquely human cognitive and emotional features of mental disorders, human studies of genetic variation in environmental reactivity are badly needed.

Second, more research is needed to identify good candidate environmental risk factors for G × E hypotheses about mental disorders. Research is needed both to uncover new environmental risk factors and to better characterize the environmental risk factors that are already known. New, better, and cheaper normed and standardized methods for measuring environmental exposure precisely and accurately would be helpful. Special attention should be paid to study designs that can evaluate whether a risk factor is a true pathogen having environmentally mediated causal effects on disorder. Once an environmental pathogen becomes known, research is needed to uncover which brain systems it influences, and how. Again, both animal and human models of environmental impact on the brain will be vital.

Third, there is a need for more studies that frame biologically plausible G × E hypotheses and test them, in the context of longitudinal cohort studies when possible. For this purpose, we encourage researchers (and funding agencies) to collect DNA from individuals participating in existing longitudinal cohort studies with well-characterized environmental histories.

Fourth, we put forward here the hypothesis that unrecognized G × E may undermine the efficiency of conventional measured-gene designs, and could in part account for the nonrobust status of many findings in psychiatric genetics to date. If this hypothesis is true, linkage pedigree studies, association studies, and genomic scans could enhance their performance by importing environmental data, perhaps to reveal larger-than-expected effects of genes or even to uncover new genes conveying susceptibility to mental disorders. Studies attempting this are needed, to see if the hypothesis is correct.

Fifth, there is a need for research that integrates G × E processes with all the other forms of gene-environment interplay. We began this article by distinguishing G × E from gene-environment correlation, heritability-environment interaction, and epigenetic programming. Eventually, research must integrate these different mechanisms to achieve a fuller understanding of psychopathology's origins.

Sixth, research is needed to find out whether G × E applies to individual differences apart from mental disorders. In this article, we have focused exclusively on psychopathology, as opposed to other behaviors that interest psychologists, because the requisite evidence base to support biologically plausible hypotheses is more developed for mental disorders than for other behaviors. Whether or not the G × E approach extends equally well to other behaviors, such as self-esteem, well-being, conscientiousness in the workplace, or school achievement, will depend on whether information about biological pathways and environmental causes is reported for individual differences in these domains.

Despite the voluminous evidence base about environmental causation of mental disorders, it is safe to say that so far most measured-gene research into mental disorders has ignored the nongenetic environmental factors that contribute to them. We hope this article encourages more theory-guided research into measured G × E effects in mental health genetics.

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