Strategy for Investigating Interactions Between Measured Genes and Measured Environments

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The purpose of this article is to promote research that tests hypotheses of measured gene-environment interaction (GxE). A GxE occurs when the effect of exposure to an environmental pathogen on health is conditional on a person's genotype (or conversely, when environmental experience moderates genes' effects on health). Gene-environment interactions were thought to be rare in psychiatry, but empirical findings of measured GxEs are now emerging. However, the current high level of curiosity about GxE is accompanied by uncertainty about the feasibility of GxE research and by pragmatic questions about how to carry out good GxE studies. First, we summarize emerging evidence about GxE in psychiatric disorders. Second, we describe 7 strategic steps that may be used to organize further hypothesis-driven studies of GxE. Third, we explain the potential benefits of the measured-GxE approach for basic neuroscience and for gene hunting. We suggest that in psychiatric genetics, ignoring nurture handicaps the field's capacity to make new discoveries about nature.

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Gene-environment interaction (GxE) has a long scientific history.[1] However, only recently has behavioral science begun to grapple empirically with GxE involving measured genes. It has been said that GxEs are so infrequent that they can safely be ignored in behavioral genetic analyses.[2-4] This long-standing dogma from quantitative behavioral genetics seems to have transferred unchallenged into the younger field of psychiatric molecular genetics, which tacitly adopted the assumption that genes' connections to disorders will be direct and additive. Hundreds of studies seeking direct measured-gene-to-disorder connections contrast against a handful of studies testing measured GxE. Despite the voluminous evidence base about environmental causation of mental disorders, most measured-gene research into mental disorders has ignored nongenetic environmental factors that contribute to these disorders. It seems reasonable to suggest that wherever there is variation among humans' psychological reactions to a major environmental pathogen for mental disorder, GxE must be expected to some degree.[5-7] This article aims to encourage empirical work on measured GxE in behavioral science.

EMERGING GxE FINDINGS

Our research team recently reported measured GxE in 3 mental disorders. Findings for other disorders are appearing.[8] We describe our 3 studies herein because they provide proof of principle that GxE occurs in relation to psychopathology outcomes, and they illustrate the feasibility of the GxE 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 would moderate the effect of child maltreatment in the cycle of violence. Results showed maltreated children whose genotype conferred low levels of monoamine oxidase A expression more often de-

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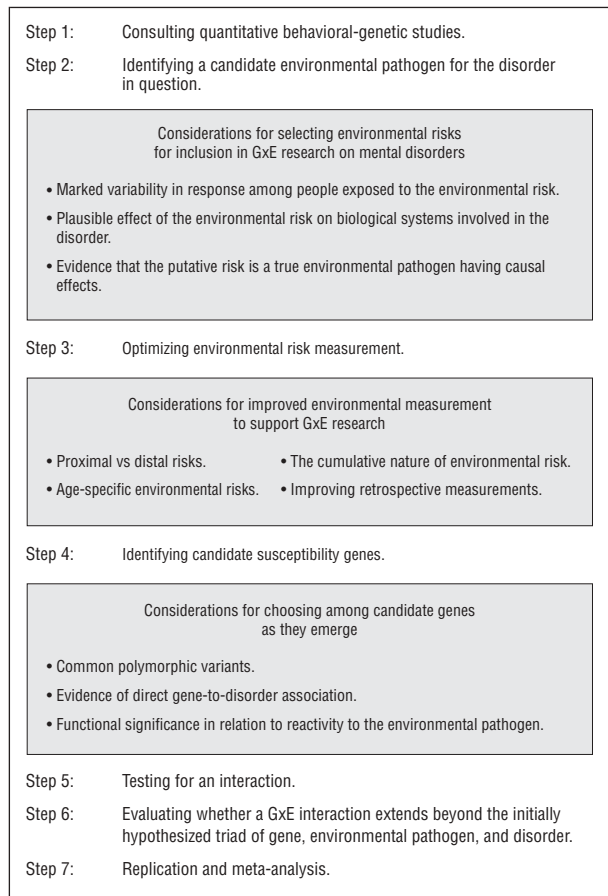
Step 1:   Consulting quantitative behavioral-genetic studies.

Step 2:   Identifying a candidate environmental pathogen for the disorder in question.

> **Considerations for selecting environmental risks for inclusion in GxE research on mental disorders**
>
> • Marked variability in response among people exposed to the environmental risk.
> • Plausible effect of the environmental risk on biological systems involved in the disorder.
> • Evidence that the putative risk is a true environmental pathogen having causal effects.

Step 3:   Optimizing environmental risk measurement.

> **Considerations for improved environmental measurement to support GxE research**
>
> • Proximal vs distal risks.   • The cumulative nature of environmental risk.
> • Age-specific environmental risks.   • Improving retrospective measurements.

Step 4:   Identifying candidate susceptibility genes.

> **Considerations for choosing among candidate genes as they emerge**
>
> • Common polymorphic variants.
> • Evidence of direct gene-to-disorder association.
> • Functional significance in relation to reactivity to the environmental pathogen.

Step 5:   Testing for an interaction.

Step 6:   Evaluating whether a GxE interaction extends beyond the initially hypothesized triad of gene, environmental pathogen, and disorder.

Step 7:   Replication and meta-analysis.

Figure. Seven strategic steps for research into measured gene-environment interaction (GxE).

veloped conduct disorder, antisocial personality, and adult violent crime than children with a high-activity monoamine oxidase A genotype.[9] A replication of this study has been published.[10]

In a second study, we hypothesized that a functional polymorphism in the promoter region of the serotonin transporter (*5-HTT*) gene would moderate the influence of stressful life events on depression. Individuals with 1 or 2 copies of the *5-HTT* short allele exhibited more depressive symptoms, diagnosable depression, and suicidality following stressful life events than individuals homozygous for the long allele.[11] This study has published replications[12-15] and 1 failure to replicate.[16]

In a third study, we demonstrated that GxE 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 gene (*COMT* Val158Met) would moderate the risk from adolescent cannabis use for developing adult psychosis. Cannabis users carrying the *COMT* valine allele were likely to exhibit psychotic symptoms and to develop schizophreniform disorder, but cannabis use had no such adverse influence on individuals with 2 copies of the *COMT* methionine allele.[17]

Beyond psychiatric genetics, in other branches of medicine, large-scale projects are under way to build infrastructure for GxE research,[18-21] and some GxE effects are already being reported. An exhaustive review is beyond the scope of this article, but some examples are illustrative. In the study of cardiovascular disease, some subjects who had high dietary fat intake developed abnormal high-density lipoprotein cholesterol concentrations and some did not, depending on their genotype on the polymorphic hepatic lipase gene promoter.[22] This hepatic lipase GxE has been replicated.[23] A separate study showed that tobacco smokers developed coronary heart disease, or did not, depending on their lipoprotein lipase genotype[24] and their apolipoprotein E4 (*APOE4*) genotype.[25] The *APOE4* GxE has been replicated.[26] In the study of dental disease, heavy tobacco smokers developed gum disease, or did not, depending on their genotype on the polymorphic interleukin 1 (*IL1*) gene.[27] This *IL1* GxE has been replicated.[28] Research into cancer and infectious diseases such as malaria, human immunodeficiency virus and AIDS, leprosy, and tuberculosis are yielding similar replicated patterns of measured GxE.[29]

Three notable patterns emerge across these initial reports. First, several of the initial GxE 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 GxE approach each gene's connection to illness would have been negated in error. Later in this article, we will revisit the possibility that unrecognized GxE can foster false-negative findings in genetic research. These emerging examples of GxE are prompting new interest among behavioral scientists in the GxE phenomenon.[30] However, the current high level of curiosity about GxE is accompanied by uncertainty about the feasibility of GxE research[31] and by pragmatic questions about how to carry out good GxE studies. This article aims to address these questions.

A PROGRAM OF RESEARCH INTO MEASURED GxE: 7 STRATEGIC STEPS

We aim to encourage careful, deliberate GxE hypothesis testing. Such testing begins with specifying theoretically plausible triads of a gene, an environmental pathogen, and a behavioral phenotype. Toward this aim, this section presents strategic steps for GxE tests using measured variables (**Figure**). Information about working with genetic data is widely available. Accordingly, this article emphasizes working with environmental data.

Step 1: Consulting Quantitative Behavioral-Genetic Models

Quantitative models of data from twins and adoptions may offer clues to whether GxE is likely to play a part in the etiology of a disorder. The heritability coefficient from quantitative models indexes not only the direct effects of genes but also the effects of interactions between genes and environments.[32-34] Therefore, "high heritability" for a disorder should not discourage constructing hypoth-

eses of GxE. To the contrary, a high heritability estimate can encourage hypotheses about measured GxE (although it does not guarantee GxE is acting). It is also possible to model a variance term for GxE.[35-40] Significance for such a latent GxE term would strongly encourage constructing hypotheses about measured GxE. However, the absence of latent GxE would not rule out the existence of measured GxE because the significance tests rely on the assumption that there ought to be a single unified interaction between all of the anonymous genes and all of the anonymous environments related to a disorder.[41] This hypothesis is biologically implausible, and therefore, it is not surprising (and perhaps reassuring) that data seldom support it.

More specific support for pursuing GxE can come from evidence that an indicator of latent genetic risk is involved in interaction with a measured environmental risk for a disorder. Though the genes remain anonymous, variation in participants' genetic risk is inferred, based on the diagnosis of a first-degree, biological relative. This can be achieved using both adoption and twin designs.[42,43] In such studies, it has been shown that the likelihood of disorder was greatest among participants at genetic risk if they also experienced adverse family environments.[44-47] Incidentally, when studies document GxE between a measured environment and anonymous genetic risk in relation to a disorder, that environment becomes an obvious candidate for further GxE research with measured genes.

Step 2: Identifying the Candidate Environmental Pathogen

Pools of candidate environmental risk factors are available for outcomes such as substance abuse,[33] the antisocial disorders,[48] depression,[49] and even schizophrenia-spectrum disorders.[50,51] The pools of candidate environmental risks for disorders such as autism, Alzheimer-type dementia, or attention-deficit/hyperactivity disorder are more limited. Nonetheless, the concordance of monozygotic twins for even these highly heritable disorders is less than perfect, indicating nongenetic contributing causes exist. 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 considerations in selecting candidate environmental risks for GxE research (Figure).

Variability in Response Among People Exposed to the Environmental Risk. One feature of a good candidate environmental risk factor is obvious but bears noting: it should not perfectly predict the disorder outcome. Evidence of marked variability in outcome of people exposed to the same level of environmental risk implies that individual differences in genetic susceptibility might be at work (ie, GxE).

Plausible Effect of the Environmental Risk on Biological Systems Involved in the Disorder. Logically, genes that influence mental disorders must do so via neurobiological pathways. Thus, to be a good candidate for in-

teraction with genes, an environmental risk ought to have evidence that it affects a neurobiological pathway to disorder. Consider that dietary fat was an ideal environmental candidate for the study of the hepatic lipase gene and cholesterol[22] because the pathophysiologic processes of how dietary fat is metabolized by the liver and converted to high-density lipoprotein cholesterol were already understood. Although this kind of evidence is highly desirable for framing GxE hypotheses, it is not easily achievable because so little is known yet about the impact of environmental factors on brain pathophysiologic features.[52-54] Nevertheless, this model of logic can be followed for developing hypotheses of GxE that are at a minimum biologically plausible. For example, cannabis was a good environmental candidate for our GxE study of *COMT* and psychosis because cannabis affects the same neuroanatomical sites, dopaminergic indicators, and memory deficits that have been implicated in studies of schizophrenia and of *COMT* functionality.[17]

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, but variables become risk factors if they merely have a documented predictive statistical association with disorder outcomes, whether or not the association is causal.[55,56] For GxE studies, a variable must be more than a risk factor; evidence is also required that it is a true environmental pathogen.

Why must GxE researchers prove that a risk factor has environmentally mediated causal effects on a 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. 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.[34] To illustrate, the association between child maltreatment and children's aggression could be genetically mediated because aggressive parents might transmit an aggressive disposition to their offspring and also treat offspring harshly (passive rGE) or because aggression-prone offspring might provoke harsh treatment by adults (active rGE).[57] If an alleged environmental risk factor's association with disorder behavior is wholly genetically mediated, then a putative GxE 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 GxE finding.

At least 3 methods can be harnessed to control for genetic mediation while testing a risk factor for environmental mediation.[58] First, treatment experiments rule out genetic influence on the environmental factor by randomly assigning subjects to environmental treatment conditions.[59] Second, longitudinal studies showing behavior has changed from a prior baseline level after an environmental experience rule out genetic influence on the environmental factor by using participants as their own controls.[60,61] Third, twin and adoption designs can

control for genetic contributions to phenotypic variation while testing if a measured environmental variable makes an additional contribution.[44,45,62-65] Each of these 3 methods is fallible, and thus, the most compelling evidence for an environmental risk factor's causal role comes from studies reporting a combination of them.[66-69] Some measured-GxE studies have included analyses that ruled out the potential confound of rGE.[10,11,17]

Step 3: Optimizing Environmental Risk Measurement

Presuming that an environmental risk factor has been converted to the exalted status of an environmental pathogen by appropriate studies, the GxE researcher must set about to measure it. Many geneticists are put off measuring environments because of the expense of collecting environmental data. However, measuring environmental pathogen exposure precisely and reliably can hugely enhance a study's power. Needed sample size depends on allele frequency and the magnitude of the interaction term but also on the strength of the association between the environmental exposure and the outcome. This is a function (in part) of the precision with which both are measured. Simulations reveal that the difference between unreliable (correlation with true score=0.4) vs reliable (0.7) measurements corresponds to a 20-fold difference in sample size. Thus, although measuring environmental exposure is costly, doing it well can pay for itself by reducing sample size.[70,71] Furthermore, any cost of measuring environments needs to be weighed against the potential cost of not doing GxE research, which is overlooking genes that might be important in disease causation.

Proximal Measures of Environmental Pathogens. It is critical to differentiate between distal and proximal risk factors.[72] Distal environmental influences include historical, socioeconomic, demographic, and geographic characteristics. In contrast, proximal environmental influences are specific social and physical exposures that impinge directly on the individual. For example, distal effects of low socioeconomic status on childhood disorder appear to operate through proximal parent-child relationships.[60] Proximal environmental risk factors are more relevant for GxE research because they are more likely to meet criteria for pathogen status and they lend themselves to biologically plausible hypotheses about their impact on neurobiological systems that mediate psychiatric symptoms. Unfortunately, many existing genotyped samples have only distal measures, such as participants' occupation or education, while lacking good proximal measures.

Age-Specific Environmental Pathogens. It is important to take developmental considerations into account when interpreting environmental effects because environmental pathogens can be differentially salient in different age groups. 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.[50] Some environmental pathogens' effects may be limited to sensitive periods of genetically influenced vulnerability.

The Cumulative Nature of Environmental Influences. Studies of the temporal nature of environmental risk processes yield 4 important findings. First, although the effects of 1 pathogen may be quite weak, the accumulated effect of multiple pathogens can be large.[73,74] Second, although the effects of a pathogen measured at a single point may be weak, the cumulative effects of extended or repeated exposure to that pathogen are often strong. Third, most risks derive from long-standing situations rather than acute events. Fourth, many of the most powerful effects involve chains of related events rather than a single factor at 1 point.[49] For GxE research, cumulative, repeated measures are better than snapshot measures because they provide more precise, sensitive, and reliable measurement of the environmental pathogen.[75]

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 is necessary in psychopathology research because many important exposures occur years before the disorder (eg, childhood sexual abuse) or gradually over a period leading up to the disorder (eg, sustained, heavy alcohol consumption). The dangers of retrospective data are known: normal forgetting, revisionist recall, bias by respondents' knowledge of subsequent disease outcome, bias from patients' cognitive dysfunction or low mood, and forward telescoping of recalled events.[76,77] A specific difficulty for retrospective recall in GxE studies is evidence that memories of events (eg, parental treatment) are under the influence of genes and that the same genes influence personality and behavior.[78] This implies that some retrospective environmental risk measures are confounded with disorder-relevant genes and cannot pass the test of environmental mediation.

There are solutions to the problems of retrospective data. Clearly, the best antidote is collecting data prospectively in a longitudinal study. 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.[18] Fortunately, DNA can be collected at any point in the life course, and as a result, genotyping can be added to the variety of ongoing longitudinal cohort studies having established data sets of prospective, repeated, cumulative measures of exposure to environmental pathogens relevant to psychopathology.

However valuable existing cohort studies may be, they cannot supply prospective measures of an environmental pathogen that is only discovered to be important for psychopathology after a study has been under way for some years. 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 reliable and valid retrospective reports of a variety of pathogenic life events,[79,80] including exposure to domestic violence[81] and spells of substance abuse.[82] Life history calendars can also generate reliable histories of onset, duration, and recurrence of disorder,[79,83] which are essential for assessing the timing of pathogen exposure relative to disorder onset and course.

Step 4: Identifying Candidate Susceptibility Genes

The obvious challenge for hypothesis-driven GxE studies is how one chooses genes to test. We propose the following guidelines.

Common Polymorphic Variants. Good candidate genes for GxE 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 does not guarantee) that natural selection has not been able to eliminate the variant because its effects on the phenotype are only expressed under particular environmental conditions, or perhaps even because it confers advantage under particular environmental conditions.[29,84-86] From a pragmatic point of view, common allelic variants confer advantages of statistical power when testing interaction effects.[87]

A Direct Gene-to-Disorder Association. If a gene has already been shown to have a replicated association with the psychiatric disorder, it is an easy choice. However, it is vital to appreciate that the GxE endeavor cannot rely on such associations because of the following paradox: logically, if a gene's connection to disorder is conditional on the environment, this will have the natural consequence of diminishing researchers' capacity to detect the association between the gene and disorder. Thus, a known association between gene and disorder can nominate a gene for a GxE hypothesis, but the absence of such an association does not disqualify a gene.

Functional Significance in Relation to the Environmental Pathogen. Candidate genes have empirical evidence of functional physiological significance in brain systems relevant to the disorder.[88] However, this is not enough to frame hypotheses in GxE research. The soundest logical basis for selecting a candidate gene for GxE is evidence that the gene is related to organisms' reactivity to the environmental pathogen, which is completely different from the gene being associated with any disorder. This evidence is necessary to frame a biologically plausible hypothesis that the gene moderates responses to an environmental pathogen (ie, GxE). For example, we elected to focus on the *5-HTT* gene in our GxE research into life events and depression, despite the fact that there was no robust association between this gene and depression,[89] because the *5-HTT* gene had been shown to predict individual differences in physiological responsiveness to stress conditions in knockout mice,[90] stress-reared rhesus macaques,[91] and a human functional-neuroimaging paradigm.[92]

To date, most evidence of connections between genes and pathogen responsiveness emerges from studies of rodents and nonhuman primates having known human-relevant genotypes.[91,93,94] As yet, there is relatively little information about genes associated with environmental pathogen responsiveness among humans. We look toward a new wave of experimental investigations asking if genotypes influence human participants' responsiveness to emotion-eliciting stimuli, laboratory stress paradigms, toxic exposures, or other pathogens. These human GxE experimental studies will use as phenotypes neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, emotional, or neuropsychological measures.[92,95-98] Until now, researchers have put most of their efforts into the search for connections between genes and disorders, whereas the search is only beginning for connections between genes and pathogen responsiveness.

Step 5: Testing for an Interaction

Recommendations have been published elsewhere about research designs and statistical approaches for studying measured GxE, and those need not be repeated herein.[99-103] Measured GxE can be approached using a variety of conventional statistical methods.[104-107] The most informative design for testing GxE begins with a cohort sample, to represent as accurately as possible population variation in genotype, environmental pathogen exposure, and a variety of disorders (as well as representing variation in healthy outcomes).[18] The epidemiological cohort design is desirable because it contains population information needed to evaluate a finding's potential clinical utility. It allows accurate estimation of sensitivity, specificity, positive and negative predictive values for clinical outcome, and attributable risk (which implies how much disorder could be reduced in the population if the GxE could be disrupted). Although concerns about clinical utility may seem premature today, systematic evidence of utility from epidemiological designs will be necessary before any GxE finding can be translated into application of measured genes in diagnostics and therapeutics.[108,109]

Despite the clear advantages of testing GxE in longitudinal cohort studies, cheaper and quicker designs have been advocated.[110] The recommended strategy is to add information about environmental exposure to conventional genetic association designs (case-control comparisons, affected relative pair designs, etc).[101] We mention an additional possibility: testing GxE 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 genotype-risk individuals develop psychopathology but genotype controls do not. Exposed samples might also be used to uncover new genes, by testing whether disorder cases differ on any genetic markers from controls without a disorder. The logic of this design is that (1) the environmental pathogen's main effect on the disorder is already documented and (2) participants' genotypes are unassociated with exposure to the pathogen. Therefore, any variation in who develops a disorder that can be attributed to genotype is evidence that the effect of exposure is dependent on (moderated by) genetic susceptibility. As an example of this approach, 1 study began with hospital patients exposed to streptococcal infection[111] and found that variation in leukocyte antigen class II haplotypes associated with histocompatibility explained which patients developed severe toxic systemic syndrome, as opposed to mere sore throat.

Step 6: Evaluating Whether a GxE Extends Beyond the Initially Hypothesized Triad of Gene, Environmental Pathogen, and Disorder

Step 6 ensues if, and only if, the hypothesized GxE is obtained. Analysis at this step systematically replaces 1 variable in the triad while holding the other 2 constant to ascertain whether the interaction holds when the gene is replaced with other relevant genes, when the environmental pathogen is replaced with the disorder's other known risk factors, and when the disorder is replaced with other related disorders. This step may be revealing because neither genes, environmental pathogens, nor disorders are likely to operate in isolation. Step 6 is exploratory but is distinguished from fishing about in a data set, which risks chance faux findings from multiple tests.[112] Once the initial hypothesis has been tested in the affirmative, epidemiological data sets offering more than 1 disorder group, more than 1 environmental risk, and more than 1 gene can provide added value by carrying out planned tests to ascertain how far beyond the original hypothesis the GxE might extend.[113] This strategy has proved beneficial in 2 of our GxE studies.[11,17]

Step 7: Replication and Meta-analysis

Psychiatric genetics has been "mired in nonreplications."[114(p616)] Some of the first GxE findings have been replicated, but it is early days to assess the overall track record. On the one hand, GxE studies need not necessarily be tarred with the same brush as studies seeking direct main effects of genes on disorders for the simple reason that interactions are statistically independent of main effects. The GxE studies may fail to replicate, but for their own unique reasons, such as the known difficulty of detecting interactions in behavioral science.[115,116] Interestingly, tests of measured GxE have not been hampered statistically by rGE to date, as no GxE study has detected a correlation between a polymorphism and an environmental exposure. On the other hand, until the reasons behind failed replication in gene-association studies are understood, it is impossible to say whether those reasons ought also to apply to GxE findings. In the meantime, we recommend that replication checks be carried out within each single study to ensure that a GxE applies to psychopathology measured through independent data sources.[9,11,17] The erratic record of association studies teaches the wisdom of awaiting the meta-analysis, while not overreacting to any single study, whether or not it replicates the original.

POTENTIAL BENEFITS OF TESTING MEASURED GxES

Hypotheses of GxEs are worth testing because where measured GxEs are found, both specific genes and specific environmental risks can conceivably have much stronger connections with a disorder than previously thought, within vulnerable groups. Although a GxE finding is too crude to be an answer by itself, it has useful implications for basic neuroscience and for future gene hunting.

POTENTIAL IMPLICATIONS FOR BASIC NEUROSCIENCE

The special gift from a reliable GxE finding is clear evidence that there must be a pathway of causal process connecting the 3 disparate end points forming a GxE triad: gene, pathogen, and disorder. The pathway may initially be hidden from scientific view but knowing 3 end points enhances the likelihood of finding paths that unite them.[117-119] As noted earlier in this article, one of the major gaps in knowledge in the study of mental disorders concerns how an environmental pathogen external to the person gets under the skin to result in a mental disorder.[53,54] The insight that the result depends on the person's genotype with respect to a specific functional gene offers clues for tracing the causal pathway in the laboratory. Furthermore, 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 pathogen-to-disorder pathways are expected to differ for each disorder, but there is precious little evidence about this. Genes may offer clues to this perennial riddle of disorder-specific causal mechanisms.

POTENTIAL IMPLICATIONS FOR GENE HUNTERS

The expectation that simple direct paths will be found from gene to disease has not proven markedly fruitful for complex psychiatric disorders; few linkage studies detect genes, many candidate gene–association studies fail consistent replication, and genes that replicate account for little variation in the phenotype.[120] Several explanations have been invoked to explain failures to find psychiatric genes that replicate, including publication bias, misclassification of outcome, phenotypic heterogeneity, allelic heterogeneity, weak prior probabilities of association, multiple testing, population stratification, and inadequate sample size.[112,121-124] Gene-environment interaction research is suggesting another reason. Ignoring nurture may have handicapped the field's ability to understand nature.

A finding from several initial measured GxE studies may be relevant to the slow progress in gene replication. Genotype was statistically unrelated to outcomes in the full cohorts of these studies; genotypes' effects on disorder, apart from their role in the GxE, were virtually nil and statistically undetectable.[8-12,15,22,28,125] In these studies, genotype effects were only revealed among individuals exposed to an environmental pathogen. This pattern could be more widespread, and if so, it suggests 4 implications for future measured-gene research.

First, a major challenge in linkage pedigrees is the gene whose effect occasionally skips a generation, leaving a family member carrying the gene phenotypically healthy. In mendelian disorders this is referred to as incomplete penetrance, whereas in multifactorial disorders it could arise for several reasons. Gene-environment interaction findings suggest one reason: if the gene's effects are expressed only among pedigree members exposed to environmental risk then unexposed carriers might escape disorder.[102] Previously unproductive linkage pedigrees

might be revived to evaluate whether ascertaining pedigree members' environmental pathogen exposure might shed new light.

Second, candidate gene–association studies may not replicate each other if GxE is operating and research samples differ on risk exposure. A sample having many exposed subjects will report association, whereas a sample having few exposed subjects will not, and if exposure is not ascertained, the source of nonreplication will remain a mystery. Where possible, candidate gene–association studies should take into account samples' environmental risk exposure.

Third, the aforementioned GxE studies showed that when GxE operates and environmental pathogen exposure differs among participants within a sample gene, it 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 psychiatric disorders must arise from many genes, each having a small effect detectable only with large samples.[126] In our GxE studies, the GxE accounted for a sufficient proportion of the cohorts' psychiatric outcome to suggest a provocative hypothesis that some multifactorial disorders, instead of resulting from very many genes of small effect, might result from relatively fewer 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 GxE research.

Fourth, genome-wide scans for new disease genes, like most psychiatric genetics designs, aim to uncover genes having direct main effects (ie, genes that show associations with behavior regardless 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 aforementioned GxE studies, genes showing no direct connection to disorder in genome-wide scans might nevertheless be connected to disorder through hidden GxE. Scans might be more powerful if gene hunters deliberately recruit samples selected for known exposure to an environmental pathogen for the disorder under study and then scan for genetic variants that characterize participants who did or did not develop the disorder.

The GxE 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, 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.

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