Mind the Gap

Why Many Geneticists and Psychological Scientists Have Discrepant Views About Gene–Environment Interaction (G×E) Research

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As our field seeks to elucidate the biopsychosocial etiologies of mental health disorders, many traditional psychological and social science researchers have added, or plan to add, genetic components to their programs of research. An understanding of the history, methods, and perspectives of the psychiatric genetics community is useful in this pursuit. In this article we provide a brief overview of psychiatric genetic methods and findings. This overview lays the groundwork for a more thorough review of gene–environment interaction (G×E) research and the candidate gene approach to G×E research that remains popular among many psychologists and social scientists. We describe the differences in perspective between psychiatric geneticists and psychological scientists that have contributed to a growing divide between the research cited and conducted by these two related disciplines. Finally, we outline a strategy for the future of research on gene–environment interactions that capitalizes on the relative strengths of each discipline.

Keywords: gene–environment interaction (G×E), genetics, depression, 5-HTTLPR, publication bias

Psychiatric genetics is a field in which quantitative and molecular methods are used to identify genetic contributions to mental health outcomes. To the mainstream psychology and social science community, this field may appear enigmatic at first glance. However, the outcomes (phenotypes) under discussion and the basic statistical techniques used to examine them are largely familiar to traditional psychological scientists. Like many psychological scientists, psychiatric geneticists explore variables that are hypothesized to predict mental health outcomes. Like psychological scientists, they control for known confounders and grapple with correlated predictor and outcome variables. However, there are some broad differences between these two fields as well. For example, in addition to their more frequent use of genetic predictors, psychiatric geneticists are increasingly focused on larger datasets and genomic confounders, while psychological scientists have often employed more sophisticated modeling of phenotypic and environmental variables.

Historically, psychiatric genetics began with twin and family studies, which can be used to quantify the contributions of genetic and environmental variables to disorders without directly examining DNA. When technological advances made it possible to directly measure individuals' genotypes, many sought to find "the gene" causing each psychiatric disorder. However, genetic influences on psychiatric disorders are much more complex. Notably, there is no single genetic variant that reliably predicts any psychiatric disorder; rather, each psychiatric disorder is likely influenced by thousands of genetic variants that are found within and *often outside* of the 20,000 or so human protein coding genes (Hindorff et al., 2009). The ways in which genetic and environmental factors interact to influence psychiatric outcomes are also largely unclear.

Consistent with these complexities, in this article we differentiate two ways in which genetic influences may impact psychiatric phenotypes. First, genetic influences on phenotypes may be direct; the presence of a particular genetic variant may increase (or decrease) the likelihood of

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developing a disorder, independent of environmental conditions. Like other factors that influence outcome variables, the effects of genetic variants on phenotypes can be linear, quadratic, and so forth. Alternatively, genetic influences on phenotypes may be interactive; the effects of genetic variants may vary according to the level of an environmental variable (or another genetic variable). The particular case of an interaction between a genetic variable and an environmental variable is referred to as gene–environment interaction (G×E, pronounced "G-by-E").[1]

Gene–Environment Interactions

G×E implies that the effect of an environmental exposure on the outcome depends on one's genotype, or alternatively, that the effect of the genotype on outcome depends on an environmental exposure. For example, we might wonder whether the relationship between severity of trauma and number of posttraumatic stress disorder (PTSD) symptoms is moderated by genotype. Figure 1 illustrates a hypothetical model of this gene–environment interaction in which the nonparallel lines represent three different genotypes, and their different slopes indicate interaction, such that the effect of trauma severity varies according to genotype. This example also demonstrates why attention to environmental variables and testing for interactions may ultimately be critical for a true understanding of the etiology of psychiatric disorders: Specifically, if participants experienced only mild trauma, then a main-effect analysis would suggest that the "AA" genotype is the risk genotype, whereas if only participants with severe trauma exposure were included in a study, "GG" would appear to be the risk genotype. In this example, sampling participants across the full range of trauma exposure and testing for G×E would be mandatory for identifying the true relationships among genetic, environmental, and phenotypic variables.

Although testing for interactions is critical, some of the methods that have been used to do so have been a source of controversy within the larger psychiatric genetics community. As a result, there has been a growing divide between the molecular genetic studies known and cited by traditional psychological scientists and the studies most frequently referenced by geneticists. Studies that geneticists believe to be most credible typically employ highly stringent thresholds for evidence and strict correction for multiple testing. To understand the reasons for this divide, a brief overview of psychiatric genetics methods and findings is needed.

A Brief History of Psychiatric Genetics

The history of psychiatric genetics can be roughly divided into three major eras. Advances in technology that made it increasingly possible to acquire more comprehensive genetic data drove methodological changes between these eras. First, classic heritability studies were (and are) conducted without molecular genetic data. Next, low-throughput genotyping methods permitted genotyping of a few variants at a time, making linkage and candidate gene studies possible. Finally, high-throughput methods such as array-based and next-generation sequencing have made genome-wide association studies (GWAS) and sequencing studies a reality. To fully appreciate the G×E methods that are the focus of this article, the history of these genetic methods is outlined in greater detail below.

Classic heritability studies are conducted by applying biometrical models to informative family constellations (most commonly, monozygotic twins compared with dizygotic twins) in order to estimate the relative contributions of genetic and environmental factors to phenotypes. These approaches have reliably indicated that both genetic and environmental factors contribute to psychiatric disorders (Plomin, 1990; Sullivan, Daly, & O'Donovan, 2012). According to this approach, the estimated heritability (population variance in liability to the disorder that is due to genetic variation) for schizophrenia, bipolar disorder, and autism is likely in excess of 70%, whereas heritability for depression and anxiety disorders is estimated to be 30%–40% (see Sullivan et al., 2012 for heritability estimates of these, and other, psychiatric disorders).

With knowledge about the ubiquity of genetic influences on psychiatric phenotypes established via classic heritability studies, investigators began using molecular genetic data to identify specific genetic risk factors either within families or across unrelated individuals. Until the early 2000s, technology afforded only low-throughput genetic studies in which one to a few hundred genetic loci were genotyped at one time. Given that there are many millions of polymorphic loci in the human genome, investigators had to be strategic about which loci they geno-

[1] Interaction between genetic variables, what we might think of as G×G, is called *epistasis*.

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typed. The targeted approaches required by these technological limitations included linkage analysis (examining regions of the chromosome shared by family members who also share an illness) and candidate gene studies. We focus here on candidate gene methods, as they are the main-effect equivalent of the candidate G×E (cG×E) methods that will be discussed in great detail.

Candidate gene studies rely on available neurobiological information to hypothesize *candidate genes* for analysis. For psychiatric phenotypes, candidate genes were primarily derived from the hypothesized importance of neurotransmitters, because they had been implicated by prior neurobiologic research or because they were putative targets of pharmacotherapies (e.g., antidepressants). The results of these studies made for a coherent framework linking neurobiological research with genetic results. A problem with candidate gene studies emerged, however, when different research groups tried to replicate the same associations. Failures of replication proved to be the norm and not the exception. This problem extended beyond psychiatric genetics to research on cancer, diabetes, and other complex genetic diseases (Colhoun, McKeigue, & Smith, 2003; Ioannidis, Tarone, & McLaughlin, 2011; Kraft & Hunter, 2010; Wacholder, Chanock, Garcia-Closas, Ghormli, & Rothman, 2004). As early as 2003, it was estimated that approximately 95% of positive findings from candidate gene studies were actually false positives (Colhoun et al., 2003). There was controversy about the reasons for these failures of replication but also widespread acknowledgement that they constituted a problem too serious to be ignored.

Fortunately for the field, high-throughput genetic technology improved, and it became possible to test for associations between a phenotype and hundreds of thousands to millions of common variants across the entire genome. Such an analysis is called a GWAS (genome-wide association study), and it has revolutionized the study of human genetics by addressing two major problems that led to failures of replication during the candidate gene era. First, GWAS is an unbiased approach that doesn't rely on a priori candidate hypotheses; this feature addresses concerns regarding the low probability of any one variant being associated with a phenotype of interest (out of the millions possible). Second, more stringent standards of evidence were established, such that a value of $p < 5 \times 10^{-8}$ ($p < .00000005$) became the community standard for genome-wide statistical significance.[2] This significance threshold, which accounts for the approximately 1 million possible independent tests of association between common genetic variants and a single phenotype, reduces the risk of false positives. Among psychiatric disorders, genome-wide significant, replicated risk loci for schizophrenia, bipolar disorder, autism, and substance use disorders have now been identified by whole genome approaches (Sullivan et al., 2012), and two GWAS of PTSD have been reported, with no evidence of replication across studies to date (Logue et al., 2012; Xie et al., 2013). Conversely, despite the fact that past candidate gene studies have reported associations for depression, anxiety disorders, and eating disorders, no replicated genetic risk factors have yet been established for these phenotypes via GWAS.

GWAS results provide additional clues about why past candidate gene findings were difficult to replicate. First, the effects of even the variants with the strongest association from GWAS are much smaller than those typically hypothesized in candidate gene studies. None of the common risk variants identified by GWAS for psychiatric disorders (excluding Alzheimer's disease) have odds ratios (OR) > 1.25, and power calculations suggest that variants with modest effect sizes of OR ≥ 1.5 will not be found, considering that prior studies had $> 99\%$ power to detect effects of this size (Sullivan et al., 2012). Thus, most candidate gene studies, which typically have sample sizes in the hundreds, have been underpowered to detect true associations of such small effect, and reported associations are likely to be false positives. Second, reliable risk variants found via GWAS have been located in unexpected places on the genome. Specifically, GWAS have implicated genes that were *not previously hypothesized as candidates.* These findings have begun to transform our understanding of the biology of behavioral and psychiatric disorders by implicating novel pathways. Even more important, most variants (approximately 90%) *are not even in the protein coding portions of genes.* This finding was shocking to many at first, since protein-coding portions of genes (exons) are unequivocally the most often hypothesized regions for genetic candidates. In contrast, GWAS have conclusively demonstrated that most risk variants are not even

[2] $p < 5 \times 10^{-8}$ is the appropriate threshold for GWAS of individuals of European ancestry. Stricter standards are necessary for adequate correction for multiple testing among individuals of African ancestry.

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within exons, but rather in less well-understood (intergenic and intronic) regions of the genome (Hindorff et al., 2009). This fact suggests that we currently have insufficient biological knowledge to pick good "candidates" for candidate gene studies. With this information, many in the psychiatric genetics community have become increasingly skeptical of the candidate gene approach.

From Candidate Gene Studies to G×E

The approaches described above were designed to detect genetic main effects, but interactions are also of interest. Early G×E studies typically employed candidate methods, and we refer to them as candidate G×E, or cG×E, studies. Using the cG×E approach, investigators examine whether the association between an environmental risk (or protective) factor and an outcome is moderated by the presence of a particular genetic variant, which is hypothesized a priori.

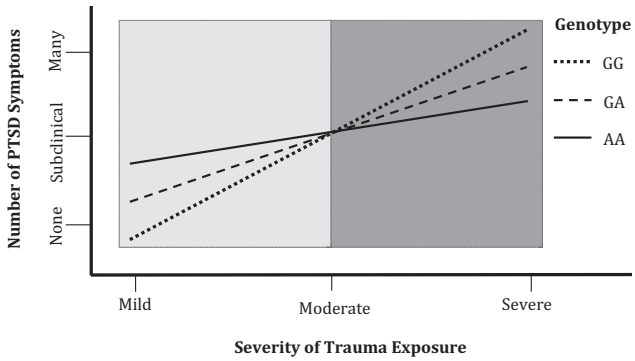
Here we provide an overview of the first decade of cG×E research in psychiatry. We included in our review all observational, nonexperimental cG×E studies published during the first decade of cG×E research: 2000–2009 inclusive. All studies reported at least one two-way interaction involving a psychiatric diagnosis or other closely related phenotype (e.g., a continuous measure of depression or neuroticism). See the Appendix for additional details about study inclusion/exclusion criteria and a list of the 103 studies (in 98 publications) identified using these criteria. In the remainder of this article we provide (a) a summary of results for the specific cG×Es that were studied most often during that period of time; (b) a review of the scope of psychiatric cG×E research in terms of phenotypic, genetic, and environmental variables studied; (c) an evaluation of the demographic characteristics of participants in these studies with respect to the ideal of equitable representation in research; and (e) a summary of the state of cG×E research and recommendations for the most productive path forward.

The First Decade of Psychiatric cG×E Research

One of the earliest cG×E studies, published by Bau, Almeida, and Hutz (2000), provided a good model for those that followed. Bau et al. (2000) reported an interaction between a dopamine-related gene, stress, and severity of physiologic dependence on alcohol. For the time, Bau et al.'s sample size (N = 229) was relatively large, and the hypothesis put forth by Bau and colleagues was based on neurobiological findings that were specific enough to afford a directional hypothesis. Furthermore, Bau and colleagues reported the effect sizes and other necessary information for replication attempts and meta-analysis.

The cG×E approach drew more attention, however, after the publication of two cG×E studies in *Science* by Caspi and colleagues (Caspi et al., 2002, 2003). The first reported that the effects of childhood maltreatment—on the development of antisocial behaviors—varied according to *MAOA* genotype (Caspi et al., 2002). The second reported that the degree to which stressful life events influenced risk for depression varied according genotype at a serotonin-related locus known as *5-HTTLPR* (Caspi et al., 2003). The Caspi et al. articles were viewed by many as an acknowledgement (perhaps much overdue) of the importance of environmental, and not just genetic, factors in the etiology of psychopathology. These articles seemed to offer an elegant and sensible explanation for previous failures of replication in candidate gene studies by virtue of previous "failures" to account for environmental moderators of

Figure 1
Hypothetical Example in Which the Number of PTSD Symptoms Is Influenced by an Interaction Between Genotype and Severity of Trauma Exposure



Note. Genotype is represented by a genetic variant with two alleles, A and G, yielding three genotypes: GG, GA, and AA. Note that this simplified example refers to a *single genotype* that interacts with an environmental variable. In reality there are likely many interactions—each with small effects. PTSD = posttraumatic stress disorder.

genetic effects. The impact of these two publications was tremendous, as demonstrated by their collective number of citations (currently 7,000+ according to Google Scholar in December 2012). The influence of these publications on the cG×E field is also shown in Figure 2, which is a histogram of studies published per year prior to 2010. The white and gray portions of the bars denote replication attempts (loosely defined) of these two studies and constitute approximately half of cG×E research studies conducted between 2002 and 2010, demonstrating just how influential Caspi and colleagues' studies have been. In the next section we review the replication status of these two studies and of all other cG×Es that were examined three or more times in the first decade of cG×E research.

What Specific Interactions Have Been Supported in cG×E Research?

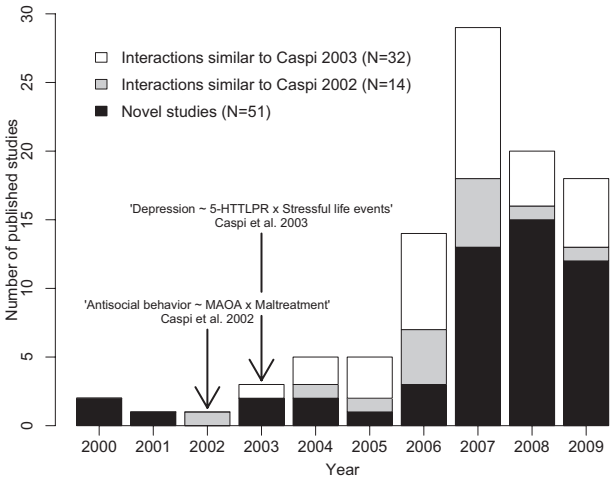
Across the 103 cG×E studies that met our inclusion criteria, six interactions had two or more replication attempts after an initial (novel, or index) study. These six interactions are summarized in Table 1, and the interactions are ordered vertically according to the number of times they were studied (from most to least often). Our review of these studies and available meta-analyses suggest that none of these cG×Es received unequivocal support, and one received no support at all. For descriptive purposes, the interactions in Table 1 fall into two groups: those that, despite reasonable efforts, do not demonstrate evidence of reliable effects, and those for which further replication attempts are warranted.

In the first group, shaded gray in Table 1, are the three interactions for which there is convincing evidence *against* association of an effect large enough to be reliably detected with standard cG×E sample sizes. The first is one of the interactions previously mentioned; an interaction between a repeat polymorphism in the serotonin transporter promoter (*5-HTTLPR*) and stressful life events in predicting depression (Caspi et al., 2003). This interaction was not supported in the two meta-analyses that used stringent inclusion criteria, an approach that provides the best test of the validity of the originally reported interaction (Munafò, Durrant, Lewis, & Flint, 2009; Risch et al., 2009). Furthermore, these two meta-analyses did not include (due to publication date) a null replication that was uncommonly similar to the original report: Both studies were population-based birth cohorts from New Zealand with high-quality, longitudinal phenotypic and environmental data (Fergusson, Horwood, Miller, & Kennedy, 2011). Given the remarkable similarity and comparable sample size, findings from this particular replication attempt should have at least exhibited trends consistent with the original report, but there was no evidence for these despite testing 104 regression models in order to exhaustively explore the possibility of replication.

Frequently mentioned in support of this particular G×E is one positive meta-analysis of this interaction (Karg, Burmeister, Shedden, & Sen, 2011). However, as reported in detail by Duncan and Keller (2011), there are two points that mitigate the results of this meta-analysis. First, a meta-analysis with stringent inclusion criteria should be *more* likely to support an original interaction than should one with liberal inclusion criteria, given that studies included in the former are more similar to the original report. The opposite is true regarding this interaction, with positive findings only from the meta-analysis with uncommonly liberal inclusion criteria. Second, in the case of a truly positive original finding, larger studies should be more likely to yield positive replications of the original finding, because of greater power. That was also not the case for these studies, in which there was a statistically significant *negative* relationship between replication-attempt sample size and outcome. *Larger* replication attempts *were less likely* to be statistically significant. Post hoc appeals have been made regarding purportedly higher quality measures in smaller studies. However, these are not credible until they are substantiated by descriptive and statistical evidence indicating that such a relationship exists. Many large-scale epidemiological studies have high-quality measurement. Guided by these two points, Duncan and Keller (2011) concluded (a) that there was extreme publication bias among the studies included in Karg et al.'s positive meta-analysis, and (b) that the findings were likely consistent with the other two meta-analyses in which the results indicate no evidence of an interaction between *5-HTTLPR* and stressful life events in predicting depression.

As depicted in Table 1, there are two additional interactions that are not supported by the literature we reviewed. One of these is an interaction between social

Figure 2
Histogram of cG×E Studies Published by Year for the First Decade of cG×E Research in Psychiatry



Note. Gray and white portions of the bars depict replication attempts of Caspi et al., 2002, and Caspi et al., 2003, respectively, the two most commonly studied candidate gene–environment interactions (cG×Es). 5-HTTLPR = serotonin transporter linked polymorphic region; MAOA = monoamine oxidase A.

Table 1
Interactions Studied Most Often in the First Decade of cG×E Research

Index study for interaction (year)	Interaction variables			Replication attempts and meta-analyses	
	Phenotype	Gene	Environment[a]	No. of studies[b] / no. of meta-analyses	Status of replication attempts and meta-analyses
Caspi et al. (2003)	Depression	*5-HTTLPR*	Adverse life events	24 / 3	Two meta-analyses failed to find support for this interaction, and one meta-analysis was positive. Evidence consistent with publication bias in the positive meta-analysis could account for the positive results. Evidence does not support interaction.
Caspi et al. (2002)	Antisocial behavior	*MAOA*	Adverse life events	11 / 1	One meta-analysis found support for the originally reported interaction. Confirmation of the meta-analysis by an independent research group is needed. Additional empirical studies would be useful.
Kaufman et al. (2007)	Alcohol use/ abuse	*5-HTTLPR*	Adverse life events	3 / 0	Results from these studies are maximally inconsistent. Evidence does not support interaction.
Kendler et al. (2005)	Anxiety	*5-HTTLPR*	Adverse life events	3 / 0	One of three studies found support for this interaction; however, different measures of phenotypic and environmental variables were used in each study, and therefore the inconsistent results are difficult to interpret. Additional empirical studies would be useful.
Kaufman et al. (2004)	Depression	*5-HTTLPR*	Social support	3 / 0	No support for this interaction in any of the studies. Evidence does not support interaction.
Bradley et al. (2008)	Depression	*CRHR1*	Adverse life events	2(4) / 0	Four *samples* have been examined in two studies. Some, but not all, of the results were consistent in 3 of 4 *samples*. Additional empirical studies would be useful.

Note. cG×E = candidate gene–environment interaction; *5-HTTLPR* = serotonin transporter linked polymorphic region; *MAOA* = monoamine oxidase A; *CRHR1* = corticotropin releasing hormone receptor 1.
[a] "Adverse life events" is used here to denote a range of detrimental environmental variables, given variability across studies. [b] Number of studies includes the index study.

support and the same repeat polymorphism mentioned above (*5-HTTLPR*) in predicting depression, which has been reported as null in three of three studies (Kaufman et al., 2004; Kilpatrick et al., 2007; Zhang et al., 2009).[3] In all three cases, this interaction was tested secondary to another significant interaction, and we are not aware of any findings in support of this interaction. The other is a putative interaction between the same genetic variant (*5-HTTLPR*) and adverse life events in predicting alcohol use disorders. Among the three studies investigating this third interaction, each of the possible genotypes (s/s, s/l, l/l) was associated with the worst phenotypic outcome in combination with high exposure to adverse life events, representing maximally inconsistent findings (Covault et al., 2007; Kaufman et al., 2007; Laucht, Treutlein, Schmid, et al., 2009). In sum, this review provides evidence against the reliability of the three cG×Es shaded gray in Table 1. Additional attempts to find evidence for these interactions using standard cG×E methods and small sample sizes are unlikely to be successful. Given this evidence, and the likely low prior probability and power to detect specific cG×Es, a parsimonious explanation for observed results is that the initial positive findings for these interactions were spurious.

[3] Though we are reviewing two-way interactions, one of these studies found a nominally significant interaction between childhood maltreatment, *5-HTTLPR*, and social support. We would argue, however, that this study was considerably underpowered to find this effect.

In contrast to the interactions described above, we have identified three interactions for which there is preliminary support. These cG×Es appear in the unshaded rows in Table 1. Arguably the most promising interaction from the first decade of cG×E research is the previously mentioned interaction between a functional polymorphism in the gene encoding monoamine oxidase A (*MAOA*) and childhood maltreatment in predicting antisocial behavior (Caspi et al., 2002). One meta-analysis, which was conducted by the research group that originally reported the interaction, supported this finding (Kim-Cohen et al., 2006). However, larger replication attempts have tended to be negative, while smaller replication attempts have tended to be positive, a pattern that can be indicative of false positives and publication bias. An independent meta-analysis that includes appropriate replication attempts, and that carefully evaluates potential sources of publication bias, is necessary before these findings can be considered robust.

As depicted in Table 1, the two other interactions from the first decade of psychiatric cG×E research that have preliminary support include an interaction between the frequently examined repeat polymorphism in the serotonin transporter promoter (*5-HTTLPR*) and stressful life events in predicting anxiety (Cicchetti, Rogosch, & Sturge-Apple, 2007; Kendler, Kuhn, Vittum, Prescott, & Riley, 2005; Laucht, Treutlein, Blomeyer, et al., 2009) and an interaction between a variant in the corticotropin-releasing hormone receptor gene (*CRHR1*) and child abuse in predicting depression (Bradley et al., 2008; Polanczyk et al., 2009). Although these two interactions have not yet been subjected to meta-analysis, initial findings suggest the possibility of replicable results. Finally, although not included in Table 1 because it didn't meet our criterion of having at least two replication attempts, the previously mentioned interaction between a variant in a dopamine receptor gene (*DRD2*) and stress in predicting alcohol use/abuse (Bau et al., 2000) is worth noting here. The two published studies on this interaction suggested consistent effects (Bau et al., 2000; Madrid, MacMurray, Lee, Anderson, & Comings, 2001), and results were also consistent with a prior study that measured intermediate phenotypes of alcohol use/abuse (Berman & Noble, 1997). In sum, of the 103 cG×E studies that met the inclusion criteria for this review, few have been subjected to multiple replication attempts and meta-analysis. Thus, from the first decade of cG×E, only four interactions emerge as having relatively consistent, preliminary evidence of effects detectable with standard cG×E methods.

Analysis of Patterns Across the cG×E Literature

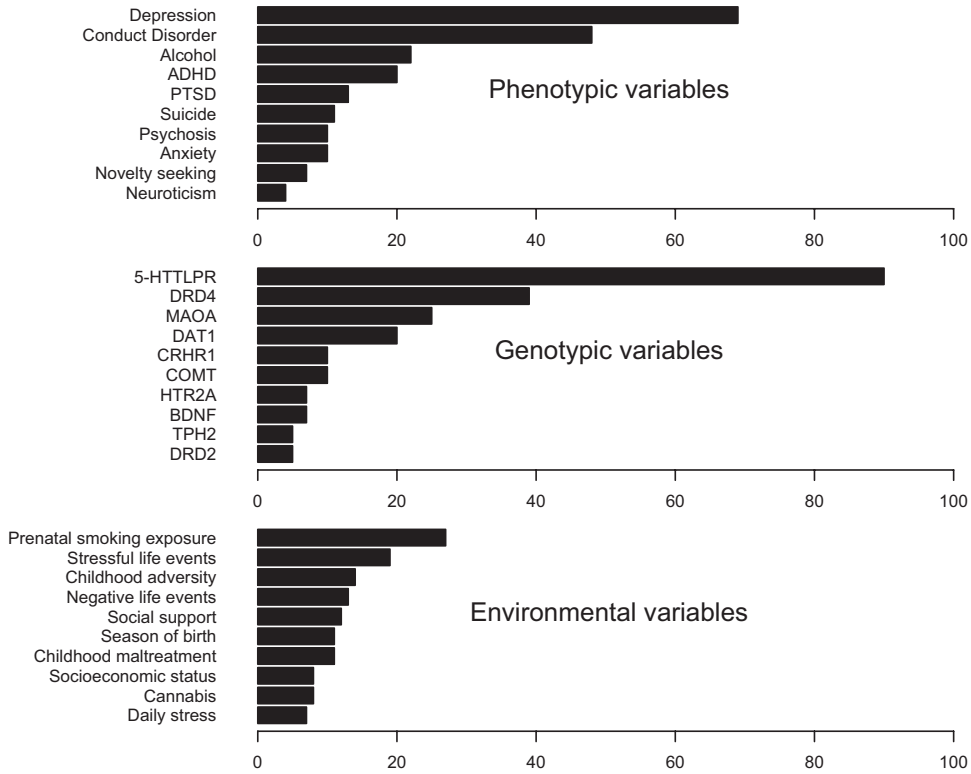
Though there are not yet meta-analyses of specific cG×E interactions other than the ones mentioned above, one study undertook analysis of patterns apparent across different cG×E studies (Duncan & Keller, 2011). Although results cannot be interpreted for any study in particular, Duncan and Keller's study provides information about the cG×E field as a whole. First, they found that in the first decade of cG×E research in psychiatry, there was evidence of substantial publication bias among novel studies (96% of which were positive) when compared with replication attempts of those studies (only 27% of which were positive). The gap between these two numbers (69%) is an estimate of the *lower bound* of publication bias, suggesting that less than one third of initially positive findings have positive replications. In addition, this study presented further evidence for publication bias, suggesting that far fewer than 27% of replication attempts are positive. The broad conclusion is that publication bias makes both novel reports and replication attempts of cG×Es appear more credible than they actually are, across the cG×E field as a whole (Duncan & Keller, 2011). In addition to providing evidence of significant publication bias, Duncan and Keller conducted power analyses for the actual sample sizes used in the first decade of cG×E studies, concluding that even if we assume G×E effects *larger than any known genetic main effect in psychiatry*, most cG×E studies were underpowered to detect true effects. Finally, estimates of the false discovery rate, meaning the proportion of positive findings that are actually *false positives,* suggested that > 97% of positive cG×E findings in the first decade of psychiatric cG×E research were likely to be false positives. In sum, while more empirical research is needed to determine the promise of cG×E research, there is sound reason to be cautious about past cG×E findings (Duncan & Keller, 2011).

Phenotypic, Genetic, and Environmental Variables Studied in cG×E Research

Although cG×E research to date has not provided us with any robust, clinic-ready findings and there is evidence of a high false discovery rate in the cG×E literature, the question of whether or not cG×E research methodology is viable has not been answered empirically, because only a tiny fraction of possible interactions have been studied to date. Since the number of possible two-way G×E interactions is the *product* of all possible genetic, phenotypic, and environmental variables, the number of possible interactions is remarkably large. Conservatively assuming 1 million genetic variants, 10 psychiatric outcomes of interest, and three relevant environmental variables per outcome, the *number of possible two-way interactions is 30 million*.

Figure 3 illustrates the frequency with which phenotypes, genes, and environmental exposures were studied in the first decade of cG×E research. First, in reviewing phenotypes, we see that all major classes of adult psychiatric disorders were studied at least once. Underscoring the impact of the aforementioned articles published by Caspi and colleagues (Caspi et al., 2002, 2003), depression and antisocial behavior/conduct disorder were the two most frequently studied phenotypes. A more thorough examination reveals opportunities for improvement of phenotypic measurement. Childhood-onset psychiatric disorders have typically been evaluated in adult participants, raising the possibility of retrospective bias. Additionally, phenotype has been analyzed almost exclusively as the binary presence or absence of a *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) diagnosis, while alternative phe-

Figure 3
Phenotypic, Genotypic, and Environmental Variables Studied Most Often in cG×E Studies



Note. cG×E = candidate gene–environment interaction; ADHD = attention-deficit/hyperactivity disorder; PTSD = posttraumatic stress disorder. From "Gene–Environment Interactions in Behavioral Genetics" by L. E. Duncan, 2014, in S. H. Rhee & A. Ronald (Eds.), *Behavior Genetics of Psychopathology* (p. 267), New York, NY: Springer. Copyright 2014 by Springer Science+Business Media New York. Adapted with permission.

notypes, including dimensional measures, have been relatively unexplored.

Second, like phenotypes, the genetic variables under study have also been limited. Hypotheses about the role of neurotransmitters informed the selection of most candidate genes during the first decade of cG×E research, with 89.2% of candidate variants located in genes directly related to neurotransmitter function. For example, often-studied variants were in genes critical for neurotransmitter synthesis (e.g., *TPH*) and degradation (e.g., *COMT, MAOA, MAOB*) and for neurotransmitter receptors and transporters (e.g., *DRD2, DRD4, DAT1, SLC6A4, NET*). Support for these candidates has largely come from the assumption that most psychotropic medications target neurotransmitter systems. It is important to keep in mind, however, that the mechanisms involved in the development and maintenance of psychiatric disorders may be distinct from those involved in their treatment. This may be one reason why, to date, robust findings from GWAS of psychiatric disorders have rarely included these candidates. With approximately 20,000 human genes, and many more functional genetic elements still to be explored, it is plausible if not likely that we have yet to investigate the most promising genetic variants for psychiatric G×Es.

Third, we see in Figure 3 that adverse life events comprised the most common class of environmental variables examined in cG×E studies. Variables in this class were referred to by many names across studies, with varying levels of generality/specificity. General variables in this class included "stressful" or "negative" life events, childhood adversity, socioeconomic status, and daily stress. More specific variables included childhood physical abuse and specific prenatal substance exposures (e.g., alcohol or tobacco). Variability was the rule across environmental variables, which differed within and across studies in terms of reporter (e.g., self-report vs. clinician rating), study design (retrospective vs. longitudinal), and measures used. This variability is problematic because it increases the difficulty of assessing whether or not a given study should be considered a replication attempt. Similarly, it complicates the interpretation of findings from replication attempts. Nevertheless, this is a challenge familiar to many, and researchers with expertise in the measurement of environmental variables are ideally suited to assist in resolving these issues.

Taken together, it is clear that the number of interactions that have been examined empirically represents only a small fraction of those possible and that there is

room for improvement in the measurement of phenotypes and environmental exposures. Thus, given current evidence, very little is known about specific interactions between environmental variables and single genetic variants.

Participants in cG×E Research

In consideration of the Belmont Report (U.S. Department of Health, Education, and Welfare, 1979), which guides the ethical practices of institutional research, and which states that risks and benefits of research should be distributed equally across all members of society, it is worth examining which participants have been included in the first decade of cG×E research in psychiatry. The combined sample size from studies published in this decade that we reviewed was 58,904 (mostly adult) participants. Of note, accounting for known re-use of samples across multiple research studies, the number of independent research participants is probably around 50,000. For the studies that provided appropriately detailed information, we provide the following summary information about participant demographics in cG×E studies.

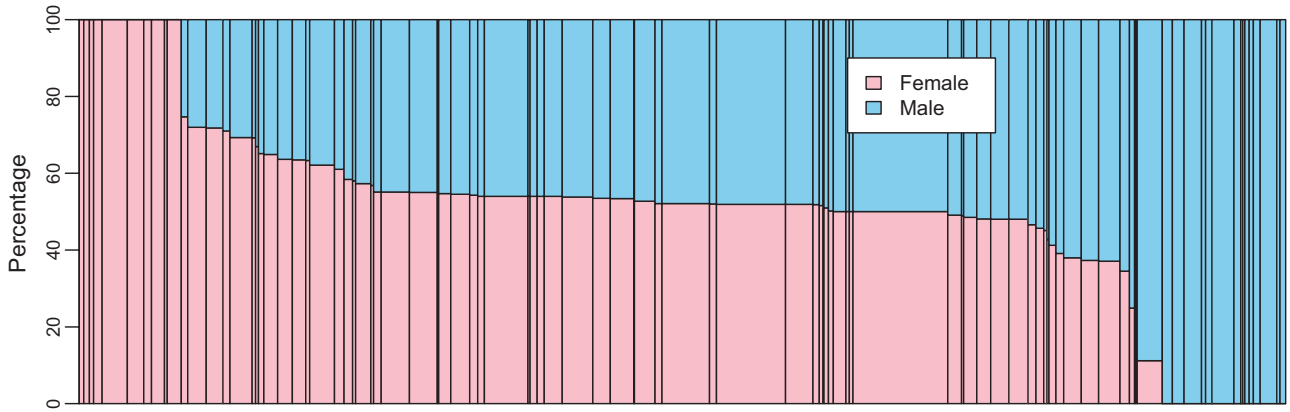
Figures 4 and 5 depict the composition of cG×E studies in terms of sex (Figure 4) and race/ethnicity (Figure 5) of participants. In both figures, each vertical bar represents one study and bar width is proportional to study size. As can be seen in Figure 4, the representation of males and females across the first decade of cG×E studies in psychiatry was remarkably even; females outnumbered males 51% to 49% in the combined samples, and the largest studies (widest bars) had male:female ratios of approximately 50:50. Single-sex studies (denoted by bars of only one color) are sometimes necessary for practical or scientific reasons, and it is encouraging to see that there are single-sex studies for both sexes. In sum, a more equitable distribution of males and females in psychiatric cG×E research could hardly be achieved, and this should be viewed as a success.

Figure 5 demonstrates the racial and ethnic composition of psychiatric cG×E studies. The predominance of solid white bars reflects the fact that most studies were composed of White, ethnically homogeneous samples. Additionally, the two largest studies (widest bars) also used White, ethnically homogeneous samples. The non-White homogeneous samples are shown on the left in the figure, starting with the six homogeneous Asian samples and followed by one homogeneous sample each of Hispanic, Native American, and Black participants.

Vertical bars of more than one color or pattern represent heterogeneous samples. Analyzing racially/ethnically heterogeneous samples presents a specific challenge in genetic research because of population stratification, a term that refers to the fact that genetic ancestry affects allele frequencies and haplotype structure in the population. Population stratification can lead to spurious results if samples are racially/ethnically heterogeneous, so homogeneous samples are often used in genetic studies. Thus, the goal of equal representation of different races and ethnicities in cG×E research can reasonably be evaluated across, rather than within, individual studies. Figure 5 demonstrates that continued efforts are needed to bring about appropriate representation of racially and ethnically diverse populations in cG×E studies. Ongoing efforts to test cG×Es in diverse racial and ethnic groups are critical if cG×E results are to be equally applicable to all people, and this goal should be a research priority.

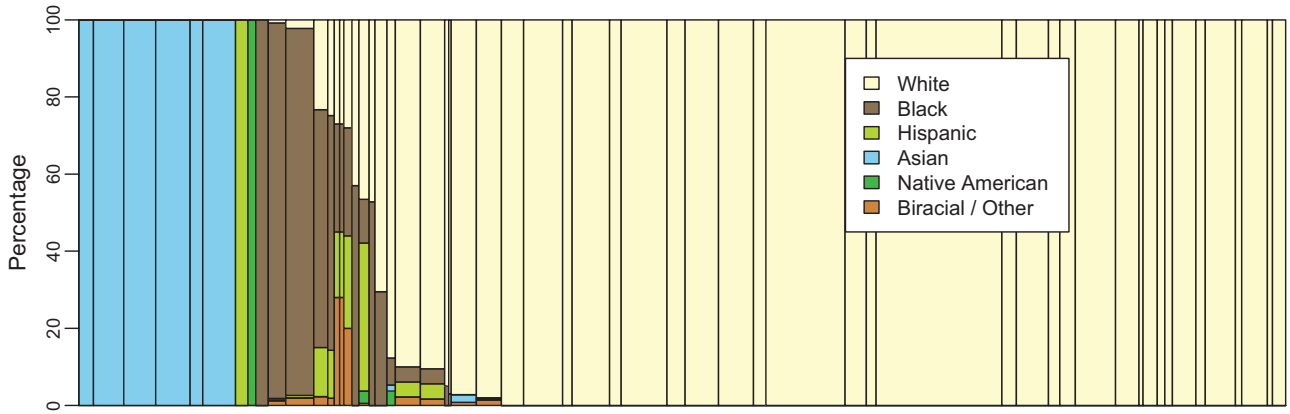
Figure 4

Graphical Depiction of Sample Sizes and Percentages of Each Sample That Are Male and Female for All 103 Samples From the First Decade of cG×E Research in Psychiatry



Note. Each column represents one study, and column width is proportional to study *N*. Samples (columns) are ordered according to decreasing female:male sex ratio for ease of interpretation. cG×E = candidate gene–environment interaction.

Figure 5
Graphical Depiction of Sample Sizes and Racial/Ethnic Composition (for All Studies That Reported It) in the First Decade of cG×E Research in Psychiatry



Note. Each column represents one study, and column width is proportional to study *N*. Samples (columns) are ordered according to majority ethnicity for ease of interpretation. cG×E = candidate gene–environment interaction.

Recommendations for Immediate Next Steps in G×E

Recommendations for G×E research can be divided into two categories: those for cG×E studies, and those for genome-wide G×E studies. The latter studies are akin to the genome-wide methods that revolutionized the search for genetic main effects and are discussed below. Regarding future cG×E studies, perhaps the most important point to keep in mind is that, as argued earlier, the first decade of cG×E research has produced few, if any, reliable results. That conclusion, which has been increasingly recognized in the psychiatric genetics community, explains the growing divide between the genetic studies most frequently referenced by psychological scientists and those most frequently referenced by psychiatric geneticists. One decade ago, geneticists studying outcomes ranging from psychiatry to diabetes, heart disease, and cancer acknowledged the fact that candidate gene studies generally did not produce reliable results (e.g., Colhoun et al., 2003). Many shifted their methodological approaches and standards of evidence in light of this fact. Though it remains to be seen whether cG×E research will follow the same path as its main-effects counterpart, psychological scientists aware of these trends will be at the leading edge of scientific knowledge about genetic effects on psychiatric disorders.

Recommendations for Traditional cG×E Approaches

First, in order to make the cG×E literature more informative, replication attempts of previously studied interactions, particularly those indicated in Table 1 as having preliminary support, will help the field determine whether cG×E research can yield reliable results. A review of the literature since 2010 is also needed to identify other high-priority cG×Es in addition to those in Table 1. Publication of replication attempts of these cG×Es should be a high priority, since they will require fewer replication attempts than novel interactions before meta-analyses can be conducted.

Second, those conducting cG×E research should consider an alternative approach to generating cG×E hypotheses: It is now possible to examine cG×E using known genetic risk variants identified via GWAS for disorders such as schizophrenia and bipolar disorder (Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011; Ripke et al., 2013; Schizophrenia Psychiatric GWAS Consortium, 2011), and many have argued that cG×Es should be investigated only after the identification of genetic main effects (Risch et al., 2009).

Third, regardless of how candidates are chosen for cG×E studies, methodological changes are needed to make interpretation more certain. For novel cG×E reports, it is critical for investigators to report *all* statistical tests conducted, including those involving alternative coding of genetic variables, alternative phenotypic or environmental variables tested, and any other analytic choices that increase the number of opportunities that, by chance alone, one could achieve a p value $< .05$. Appropriate corrections for all statistical tests will allow consumers of the literature to accurately interpret the likelihood of reported findings. The field could also consider adopting more stringent thresholds for statistical significance and require replication, as most or all genetics journals do (Hewitt, 2012). Additionally, to facilitate meta-analysis, investigators reporting replication results should specify the single statistical test that they, as experts most familiar with the particular analysis being reported, believe to be the most similar to the original report. It is currently common for

studies to report multiple results for related statistical tests, making it difficult at times to distinguish which result is most appropriate for inclusion in a meta-analysis. Finally, as a field, a willingness to publish negative findings as readily as positive findings, given equivalent methodological quality, will help to reduce positive publication bias in the literature. Often underappreciated, publication bias makes results appear more credible than they actually are, and it leads to wasted resources if positive findings are nothing more than Type I errors.

Recommendations for Genome-Wide G×E Studies

Although to date, candidate approaches have typically been used to explore individual G×E hypotheses, it is now possible to use whole-genome approaches for G×E. These are referred to as genome-wide G×E studies, or genome-wide interaction studies (GWIS). There are many available methods for genome-wide G×E studies (Aschard, Hancock, London, & Kraft, 2010; Kraft, Yen, Stram, Morrison, & Gauderman, 2007; Paré, Cook, Ridker, & Chasman, 2010), and they have begun to be applied to psychiatric disorders. For example, investigating the possibility that maternal expressed emotion moderated genetic effects on attention-deficit/hyperactivity disorder (ADHD), Sonuga-Barke and colleagues (2008) found no genome-wide significant hits in a sample of 909 family trios. However, they did report nominally significant G×Es, both in the presence, and notably also in the absence, of genetic main effects. In contrast, a very large genome-wide G×E study has recently been reported for body mass index (BMI), with one positive result (Yang et al., 2012). Yang and colleagues examined over 100,000 individuals and found that a single locus, in the *FTO* gene, showed evidence of interactive effects. Notably, *FTO* is a known genetic risk locus for BMI, consistent with the view that G×E effects will often involve polymorphisms that also have main effects.

Researchers interested in adopting genome-wide G×E approaches will need to keep in mind the need for very large sample sizes. Reliable identification of genetic risk factors for schizophrenia and bipolar disorder required sample sizes greater than 10,000 (Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011; Schizophrenia Psychiatric GWAS Consortium, 2011), which were attained through large-scale consortia of researchers across multiple sites and unprecedented collaboration. "Harmonization" of phenotypes across multiple samples was also necessary (Sullivan et al., 2012), and additional efforts toward harmonizing environmental variables will be needed for genome-wide G×E studies. The expertise of psychological scientists will be critical to such efforts.

A Note About Interaction Types

The success of G×E research ultimately depends on both the responsible practices of investigators (discussed above) and the nature of G×E effects. We currently do not know how large G×E effects may be, nor do we know which forms of interactions are most likely. Many argue that the type of hypothetical interaction shown in Figure 1, in which there is no main effect of the genetic variable, is unlikely. In this type of "crossover" interaction, a risk allele in one environment is the protective allele in another environment. Other types of interactions are generally thought to be more plausible. However, more empirical data are needed to answer this question.

Many researchers, geneticists in particular, assume that effect sizes will be very small and that the most likely form of interaction is non-crossover. If this is the case, then very large sample sizes, at least in the tens of thousands, will be necessary to detect true G×E effects. On the other hand, empirical evidence has not ruled out the possibility of crossover G×Es of large effect. If such interactions exist, then they may be detectable by both cG×E methods and modestly sized genome wide G×E studies. Large crossover interactions are often argued to be biologically implausible (e.g., it is hard to imagine that childhood maltreatment would be *beneficial* to those with a certain genotype); however, they are not impossible. For example, one could imagine that genetic variants responsible for differential learning about the environment could cause variability in response to that environment, such that some individuals are more impacted by the environment than others. Such learning-related genetic variation could plausibly underlie the so-called "differential susceptibility" or "orchid–dandelion" hypotheses, which purport that some individuals (like dandelions) are relatively impervious to the effects of the environment and can grow in a wide variety of conditions, whereas others (like orchids) can be spectacular in the right conditions but cannot tolerate much environmental hardship (Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2011). To date, however, such effects have not been demonstrated at the stringent thresholds of significance that would be required for acceptance in many genetics journals.

Cutting-Edge Topics in Genomics

To facilitate transfer of information from the genetics community to researchers with primary expertise in psychology, psychiatry, and related disciplines, in this section we provide a brief overview of cutting-edge topics in human genomics, with reference to appropriate sources for further information. We briefly cover the topics of (a) GWAS results and interpretation, (b) polygenicity, (c) cross-disorder effects/pleiotropy, (d) rare variants, (e) missing and phantom heritability, and (f) epigenetics.

Among psychiatric disorders, replicated risk loci for schizophrenia, bipolar disorder, autism, and substance use disorders have now been identified through whole genome approaches (Sullivan et al., 2012). Beyond methods that identify specific risk variants, approaches that examine collective contributions of hundreds or thousands of single-nucleotide polymorphisms (SNPs) at once, such as polygenic risk score profiling (Purcell et al., 2009) and SNP heritability estimates (Yang, Lee, Goddard, & Visscher, 2011), are now yielding additional clues about the genetic architecture of psychiatric disorders. Consistent with de-

cades of results from family studies, it has now been confirmed with molecular data that psychiatric disorders are highly polygenic (Sullivan et al., 2012). These new approaches are also yielding novel insights. For example, it has been demonstrated that the combined effects of common genetic variants are responsible for a substantial portion of liability to schizophrenia (Ripke et al., 2013), ruling out the possibility that only rare variants contribute to schizophrenia. This represents a fundamental discovery in the emerging picture of the genetic architecture of psychiatric disorders.

As mentioned earlier, due to the very small effect of any individual locus on population-level risk for a disorder, sample sizes in the tens of thousands are often necessary to detect risk loci. Underscoring this point, GWAS have been most successful for schizophrenia, with over 100 independent risk loci identified in the largest, soon-to-be-published GWAS of schizophrenia, which includes over 75,000 individuals (Stephan Ripke, personal communication, November 12, 2013). New polygenic modeling techniques have made it possible to estimate the number of common loci contributing to a given disorder, which, for schizophrenia, has been estimated at 8,300 common variants (Ripke et al., 2013; Stahl et al., 2012). Thus, it is clear that—for schizophrenia at least—there are many thousands of risk loci and that dramatic increases in sample sizes led to the detection of a large number of specific risk loci.

Third, molecular data now provide evidence for *pleiotropy*, the phenomenon in which individual genetic variants yield more than one phenotypic effect (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013a, 2013b; Purcell et al., 2009; Solovieff, Cotsapas, Lee, Purcell, & Smoller, 2013). These findings are relevant to psychiatric disorder nosology, and recent reports have largely confirmed findings from twin studies (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013a). The strongest overlap in genetic influences identified to date (using molecular methods) is between schizophrenia and bipolar disorder, but the state of genome-wide research varies widely across disorders, so a complete understanding of pleiotropy awaits studies that combine large samples of individuals across multiple psychiatric disorders.

The role of rare variants in psychiatric disorders is a source of ongoing debate and study. A *rare variant* refers to a variant whose minor allele is present in a very small proportion of the population (typically less than 1%, though definitions vary). A number of specific, rare variants have been identified that contribute to risk of various psychiatric illnesses—oftentimes in a nonspecific way. Remarkably, the first rare variant conferring risk for a psychiatric disorder was identified nearly two decades ago when deletions at the 22q11 locus were found to contribute to schizophrenia (Karayiorgou et al., 1995). Most other rare variant discoveries occurred after 2005, including a variety of rare inherited and de novo copy number variants (CNVs) that contribute to schizophrenia, autism, intellectual disability, and ADHD (International Schizophrenia Consortium, 2008; Kirov et al., 2009; Lionel et al., 2011; Sebat et al., 2007; Stefansson et al., 2008; Sullivan et al., 2012; Williams et al., 2010, 2012; Xu et al., 2008). Additionally, using exome sequence data and trio designs, a role for de novo point mutations has also been established for autism (Neale et al., 2012; O'Roak et al., 2011; Sanders et al., 2012).

The convincing success of GWAS for the discovery of risk loci associated with complex genetic phenotypes ranging from height, to diabetes, to schizophrenia has raised a new question about "missing heritability." *Missing heritability* refers to the gap between how much phenotypic variance has been explained by specific genetic variants and how much has been explained by heritability estimates from twin or other suitable studies. For schizophrenia and many other complex phenotypes, the gap is substantial. For example, in the seminal article on this topic, Manolio et al. (2009) noted that only 5% of the variance in height had been explained by the approximately 40 known loci for height, compared with a population estimate of 80% heritability for height. The gap of 75% was referred to as *missing heritability,* and extensive discussion of possible explanations for it and potential avenues for solution have been offered (e.g., Manolio et al., 2009; Parker & Palmer, 2011). Sources of missing heritability undoubtedly include undetected common and rare variants but may also include structural variants not well captured by existing arrays, nonadditive genetic effects (dominance and epistasis), and gene–environment interactions (Manolio et al., 2009). Regarding G×E effects, it's worth noting that the nature of the environmental variable involved in a G×E determines whether the effect of a particular G×E contributes to the additive genetic (h^2, narrow-sense heritability) or nonshared environmental variance component in twin models (Purcell, 2002), so it is unclear whether—on balance—G×Es may have inflated or reduced heritability estimates from twin studies. Further, the effect of G×Es on heritability estimates may vary across traits. For an argument that heritability estimates may be inflated due to interactions, thereby leading to "phantom heritability," see Zuk, Hechter, Sunyaev, and Lander (2012), and for a relevant counterpoint, which predates Zuk et al., see Hill, Goddard, and Visscher (2008). In sum, further research is needed to determine the specific sources of missing heritability across different phenotypes.

Finally, a brief mention of epigenetics is warranted. *Epigenetics* refers to heritable changes in gene expression or cellular phenotype that are caused by factors other than sequence changes in DNA.[4] Common mechanisms of epigenetic effects are methylation and histone modifications. Unfortunately, epigenetics seems particularly susceptible to gross misunderstandings vis-à-vis genetic effects on psychiatric phenotypes. One problem is that epigenetics is

[4] In the context of epigenetics, heritable refers not only to changes passed from one generation of individuals to the next (via meiosis) but also to changes that are passed to new cells via the process of cell division (mitosis). Thus, heritable epigenetic changes need not be passed from one generation to the next. Also, the definition of epigenetics varies across fields and does not always require that epigenetic effects be heritable.

in its infancy and may prove even more complex than the study of genetic sequence itself. Thus, efforts to explain psychiatric phenotypic variation via a small number of epigenetic variables (e.g., two variables out of millions possible) will likely encounter the same pitfalls evident in candidate gene and candidate G×E research. Another challenge is that epigenetic marks vary across and within tissues. Thus, peripheral (e.g., blood) measures of epigenetic variation may not reflect brain epigenetic states. For an overview of the large-scale, multinational projects that are tackling the tremendous complexity of epigenetics at a genomic scale (epigenomics), see publications from the ENCODE Consortium (ENCODE Project Consortium, 2012; National Human Genome Research Institute, 2013) and the NIH Roadmap Epigenomics Mapping Consortium (National Institutes of Health, 2010; Ziller et al., 2013).

Summary

Upon reviewing the first decade of cG×E research in psychiatry, we find both points to be commended (e.g., remarkably equal representation of males and females in studies) and areas for improvement. On balance, we report that there are reasons to be skeptical of prior cG×E findings. Yet, unequivocally, more empirical research is needed to definitively determine the promise of cG×E research. This research should be conducted with particular attention to issues of power and correction for multiple testing. As evidenced by the numerous citations to consortia versus individuals (particularly in the Cutting-Edge Topics in Genomics section of this article), it is clear that research in human genetics is becoming increasingly collaborative. These collaborations will make large-scale genome-wide G×E studies possible, and these will be increasingly common in the coming years.

If G×E effects prove similar to genetic main effects, then we can expect to find that hundreds (and likely thousands) of gene–environment interactions, each of very small effect, contribute to individual psychiatric phenotypes. This conclusion is perhaps not the most appealing, but it may be the most likely in light of current knowledge about the human genome. Consistent with the emerging picture from GWAS and sequencing studies, the hope is that G×E effects may converge on a limited number of biological pathways, yielding an understanding of specific processes underlying psychiatric disorders that is more readily interpretable. Long lists of implicated risk loci and/or G×Es are not the ultimate goal; rather, the goal is improved prevention and treatment strategies. Regardless of the ultimate outcome, we believe that this work will benefit from the collaboration and expertise of psychological scientists and psychiatric geneticists alike.

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Appendix
Studies Included in the Review

Relevant studies published in the first decade (2000–2009) of candidate gene–environment interaction (cG×E) research in psychiatry were identified through MEDLINE, PubMed, and Google Scholar, and by cross-referencing the citations in each identified article. To be included, outcomes in cG×E studies had to be *DSM–IV* (*Diagnostic and Statistical Manual of Mental Disorders,* 4th edition) diagnoses or closely related constructs (e.g., neuroticism). Only observational, as opposed to experimental, studies were included; pharmacogenetic studies were excluded. Studies were included only if there was variation across participants for phenotypic, genetic, and environmental variables (e.g., exposure-only designs were excluded). In total, 98 articles encompassing 103 studies met inclusion criteria (five of the 98 articles reported results for two independent samples). A list of included studies is provided in Table A1.

(*Appendix table follows*)

Table A1
Observational, Nonexperimental Candidate Gene–Environment (cG×E) Studies Published During the First Decade of cG×E Research: 2000–2009

First author	Article title	Year	Sample *N*
	Depression ~ 5-HTTLPR × Adverse Life Events (24 studies)		
Caspi	Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene	2003	847
Gillespie	The relationship between stressful life events, the serotonin transporter (5-HTTLPR) genotype and major depression	2004	1,091
*Kaufman	Social supports and serotonin transporter gene moderate depression in maltreated children	2004	101
*Kendler	The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression. A replication	2005	549
Surtees	Social adversity, the serotonin transporter (5-HTTLPR) polymorphism and major depressive disorder	2005	4,175
Jacobs	Stress-related negative affectivity and genetically altered serotonin transporter function: Evidence of synergism in shaping risk of depression	2006	374
Taylor	Early family environment, current adversity, the serotonin transporter promoter polymorphism, and depressive symptomatology	2006	118
Wilhelm	Life events, first depression onset and the serotonin transporter gene	2006	127
Zalsman	Association of a triallelic serotonin transporter gene promoter region (5-HTTLPR) polymorphism with stressful life events and severity of depression	2006	316
Cervilla	The risk for depression conferred by stressful life events is modified by variation at the serotonin transporter 5HTTLPR genotype: Evidence from the Spanish PREDICT-Gene cohort	2007	737
Chipman	No interaction between the serotonin transporter polymorphism (5-HTTLPR) and childhood adversity or recent stressful life events on symptoms of depression: Results from two community surveys	2007	2,095 and 584
Chorbov	Relationship of 5-HTTLPR genotypes and depression risk in the presence of trauma in a female twin sample	2007	247
*Cicchetti	Interactions of child maltreatment and serotonin transporter and monoamine oxidase A polymorphisms: Depressive symptomatology among adolescents from low socioeconomic status backgrounds	2007	339
*Covault	Interactive effects of the serotonin transporter 5-HTTLPR polymorphism and stressful life events on college student drinking and drug use	2007	302
Gunthert	Serotonin transporter gene polymorphism (5-HTTLPR) and anxiety reactivity in daily life: A daily process approach to gene–environment interaction	2007	350
Kaufman	Brain-derived neurotrophic factor-5-HTTLPR gene interactions and environmental modifiers of depression in children	2006	196
Kim	Interactions between life stressors and susceptibility genes (5-HTTLPR and BDNF) on depression in Korean elders	2007	732
Scheid	Depressive symptoms in mid-pregnancy, lifetime stressors and the 5-HTTLPR genotype	2007	568
Power	5-HTTLPR genotype, stressful life events and late-life depression: No evidence of interaction in a French population	2008	1,421
Wichers	The BDNF Val66Met × 5-HTTLPR × Child Adversity interaction and depressive symptoms: An attempt at replication	2008	621
Aguilera	Early adversity and 5-HTT/BDNF genes: New evidence of gene–environment interactions on depressive symptoms in a general population	2009	534
*Laucht	Interaction between the 5-HTTLPR serotonin transporter polymorphism and environmental adversity for mood and anxiety psychopathology: Evidence from a high-risk community sample of young adults	2009	309
*Zhang	The combined effects of the 5-HTTLPR and 5-HTR1A genes modulates the relationship between negative life events and major depressive disorder in a Chinese population	2009	792
	Antisocial Behavior ~ MAOA × Adverse Life Events (11 studies)		
Caspi	Role of genotype in the cycle of violence in maltreated children	2002	442
Foley	Childhood adversity, monoamine oxidase A genotype, and risk for conduct disorder	2004	514

(table continues)

Table A1 *(continued)*

First author	Article title	Year	Sample *N*
Haberstick	Monoamine oxidase A (MAOA) genotype and antisocial behaviors in the presence of childhood and adolescent maltreatment	2005	774
Nilsson	Role of monoamine oxidase A genotype and psychosocial factors in male adolescent criminal activity	2007	81
Huizinga	Childhood maltreatment, subsequent antisocial behavior, and the role of monoamine oxidase A genotype	2006	277
Widom	MAOA and the "cycle of violence:" Childhood abuse and neglect, MAOA genotype, and risk for violent and antisocial behavior	2006	409
Young	Interaction between MAO-A genotype and maltreatment in the risk for conduct disorder: Failure to confirm in adolescent patients	2006	247
Reif	Nature and nurture predispose to violent behavior: Serotonergic genes and adverse childhood environment	2007	184
Sjoberg	Adolescent girls and criminal activity: Role of MAOA-LPR genotype and psychosocial factors	2007	119
Ducci	Interaction between a functional MAOA locus and childhood sexual abuse predicts alcoholism and antisocial personality disorder in adult women	2008	187
Prom-Wormley	Monoamine oxidase A and childhood adversity as risk factors for conduct disorder in females	2009	721
	Alcohol use/abuse ~ 5-HTTLPR × Adverse Life Events (3 studies)		
Kaufman	Genetic and environmental predictors of early alcohol use	2007	127
Laucht	Impact of psychosocial adversity on alcohol intake in young adults: Moderation by the LL genotype of the serotonin transporter polymorphism	2009	309
*Covault	Interactive effects of the serotonin transporter 5-HTTLPR polymorphism and stressful life events on college student drinking and drug use	2007	302
	Anxiety ~ 5-HTTLPR × Adverse Life Events (3 studies)		
*Kendler	The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression: A replication	2005	549
*Cicchetti	Interactions of child maltreatment and serotonin transporter and monoamine oxidase A polymorphisms: Depressive symptomatology among adolescents from low socioeconomic status backgrounds	2007	339
*Laucht	Interaction between the 5-HTTLPR serotonin transporter polymorphism and environmental adversity for mood and anxiety psychopathology: Evidence from a high-risk community sample of young adults	2009	309
	Depression ~ 5-HTTLPR × Social Support (3 studies)		
*Kaufman	Social supports and serotonin transporter gene moderate depression in maltreated children	2004	101
Kilpatrick	The serotonin transporter genotype and social support and moderation of posttraumatic stress disorder and depression in hurricane-exposed adults	2007	589
*Zhang	The combined effects of the 5-HTTLPR and 5-HTR1A genes modulates the relationship between negative life events and major depressive disorder in a Chinese population	2009	792
	Depression ~ CRHR1 × Adverse Life Events (2 studies)		
Bradley	Influence of child abuse on adult depression moderation by the corticotropin-releasing hormone receptor gene	2009	422 and 204
Polanczyk	Protective effect of CRHR1 gene variants on the development of adult depression following childhood maltreatment	2009	1,037and 1,116
	Other G×E studies meeting criteria for this review (in alphabetical order)		
Altink	The dopamine receptor D4 7-repeat allele and prenatal smoking in ADHD-affected children and their unaffected siblings: No gene–environment interaction	2008	946
Amstadter	Variant in RGS2 moderates posttraumatic stress symptoms following potentially traumatic event exposure	2009	607

(table continues)

Table A1 *(continued)*

First author	Article title	Year	Sample *N*
Bakermans-Kranenburg	Gene–environment interaction of the dopamine D4 receptor (DRD4) and observed maternal insensitivity predicting externalizing behavior in preschoolers	2006	47
Bau	The TaqI A1 allele of the dopamine D2 receptor gene and alcoholism in Brazil: Association and interaction with stress and harm avoidance on severity prediction	2000	229
Becker	Interaction of dopamine transporter genotype with prenatal smoke exposure on ADHD symptoms	2008	305
Bet	Glucocorticoid receptor gene polymorphisms and childhood adversity are associated with depression: New evidence for a gene–environment interaction	2009	906
Binder	Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults	2008	676
Blomeyer	Interaction between CRHR1 gene and stressful life events predicts adolescent heavy alcohol use	2008	280
Brookes	Differential dopamine receptor D4 allele association with ADHD dependent of [sic] proband season of birth	2008	1,110
Brummett	Effects of environmental stress and gender on associations among symptoms of depression and the serotonin transporter gene linked polymorphic region (5-HTTLPR)	2008	288 and 142
Caspi	Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: Longitudinal evidence of a gene X environment interaction	2005	803
Chotai	Gene–environment interaction in psychiatric disorders as indicated by season of birth variations in tryptophan hydroxylase (TPH), serotonin transporter (5-HTTLPR) and dopamine receptor (DRD4) gene polymorphisms	2003	1,349
Dick	Marital status, alcohol dependence, and GABRA2: Evidence for gene–environment correlation and interaction	2006	1,916 and 915
DiLalla	Genetic and gene–environment interaction effects on preschoolers' social behaviors	2009	62
Eley	Gene–environment interaction analysis of serotonin system markers with adolescent depression	2006	377
Fox	Evidence for a gene–environment interaction in predicting behavioral inhibition in middle childhood	2008	73
Frazzetto	Early trauma and increased risk for physical aggression during adulthood: The moderating role of MAOA genotype	2007	235
Gacek	Tryptophan hydroxylase 2 gene and alcohol use among college students	2008	351
Gervai	Infant genotype may moderate sensitivity to maternal affective communications: Attachment disorganization, quality of care, and the DRD4 polymorphism	2007	96
Gibb	Serotonin transporter (5-HTTLPR) genotype, childhood abuse, and suicide attempts in adult psychiatric inpatients	2006	30
Grabe	Mental and physical distress is modulated by a polymorphism in the 5-HT transporter gene interacting with social stressors and chronic disease burden	2005	976
Grabe	Serotonin transporter gene (SLC6A4) promoter polymorphisms and the susceptibility to posttraumatic stress disorder in the general population	2009	3,045
Haeffel	Association between polymorphisms in the dopamine transporter gene and depression	2008	176
Henquet	COMT Val158Met moderation of cannabis-induced psychosis: A momentary assessment study of "switching on" hallucinations in the flow of daily life	2009	61
Jokela	Serotonin receptor 2A gene and the influence of childhood maternal nurturance on adulthood depressive symptoms	2007	1,212
Jokela	The influence of urban/rural residency on depressive symptoms is moderated by the serotonin receptor 2A gene	2007	1,224
Jokela	The serotonin receptor 2A gene moderates the influence of parental socioeconomic status on adulthood harm avoidance	2007	1,246
Jokela	Tryptophan hydroxylase 1 gene (TPH1) moderates the influence of social support on depressive symptoms in adults	2007	341
Kahn	Role of dopamine transporter genotype and maternal prenatal smoking in childhood hyperactive-impulsive, inattentive, and oppositional behaviors	2003	161
Keltikangas-Jarvinen	Nature and nurture in novelty seeking	2004	92

(table continues)

Table A1 *(continued)*

First author	Article title	Year	Sample *N*
Kim-Cohen	MAOA, maltreatment, and gene–environment interaction predicting children's mental health: New evidence and a meta-analysis	2006	975
Koenen	Modification of the association between serotonin transporter genotype and risk of posttraumatic stress disorder in adults by county-level social environment	2009	651
Lahti	Socio-demographic characteristics moderate the association between DRD4 and novelty seeking	2006	154
Langley	Testing for gene x environment interaction effects in attention deficit hyperactivity disorder and associated antisocial behavior	2008	266
Lasky-Su	A study of how socioeconomic status moderates the relationship between SNPs encompassing BDNF and ADHD symptom counts in ADHD Families	2007	345
Laucht	Interacting effects of the dopamine transporter gene and psychosocial adversity on attention-deficit/hyperactivity disorder symptoms among 15-year-olds from a high-risk community sample	2007	305
Lazary	New evidence for the association of the serotonin transporter gene (SLC6A4) haplotypes, threatening life events, and depressive phenotype	2008	567
Madrid	Stress as a mediating factor in the association between the DRD2 TaqI polymorphism and alcoholism	2001	304
Neuman	Prenatal smoking exposure and dopaminergic genotypes interact to cause a severe ADHD subtype	2007	770
Nobile	Socioeconomic status mediates the genetic contribution of the dopamine receptor D4 and serotonin transporter linked promoter region repeat polymorphisms to externalization in preadolescence	2007	607
Nobile	The influence of family structure, the TPH2 G703T and the 5HTTLPR serotonergic genes upon affective problems in children aged 10-14 years	2009	607
Ozkaragoz	Extraversion: Interaction between D2 dopamine receptor polymorphisms and parental alcoholism	2000	98
Perroud	Interaction between BDNF Val66Met and childhood trauma on adult's violent suicide attempt	2008	813
Propper	Parenting quality, DRD4, and the prediction of externalizing and internalizing behaviors in early childhood	2007	169
Racine	The possible influence of impulsivity and dietary restraint on associations between serotonin genes and binge eating	2009	344
Retz	A functional serotonin transporter promoter gene polymorphism increases ADHD symptoms in delinquents: Interaction with adverse childhood environment	2008	184
Roy	Interaction between childhood trauma and serotonin transporter gene variation in suicide	2007	306
Seeger	Gene–environment interaction in hyperkinetic conduct disorder (HD + CD) as indicated by season of birth variations in dopamine receptor (DRD4) gene polymorphism	2004	227
Sjoberg	Development of depression: Sex and the interaction between environment and a promoter polymorphism of the serotonin transporter gene	2006	180
Sonuga-Barke	Dopamine and serotonin transporter genotypes moderate sensitivity to maternal expressed emotion: The case of conduct and emotional problems in attention deficit/hyperactivity disorder	2009	728
Stein	Gene-by-environment (serotonin transporter and childhood maltreatment) interaction for anxiety sensitivity, an intermediate phenotype for anxiety disorders	2008	150
Stevens	Dopamine transporter gene polymorphism moderates the effects of severe deprivation on ADHD symptoms: Developmental continuities in gene–environment interplay	2009	217
Sun	The combined effect of norepinephrine transporter gene and negative life events in major depression of Chinese Han population	2008	776
Todd	Gene–environment interactions in the development of combined type ADHD: Evidence for a synapse-based model	2007	770
van Winkel	Evidence that the COMTVal158Met polymorphism moderates sensitivity to stress in psychosis	2008	56
Vanyukov	The MAOA promoter polymorphism, disruptive behavior disorders, and early onset substance use disorder: Gene–environment interaction	2007	148

(table continues)

Table A1 *(continued)*

First author	Article title	Year	Sample *N*
Waldman	Gene–environment interactions reexamined: Does mother's marital stability interact with the dopamine receptor D2 gene in the etiology of childhood attention-deficit/hyperactivity disorder?	2007	211
Xu	The norepinephrine transporter gene modulates the relationship between urban/rural residency and major depressive disorder in a Chinese population	2009	835
Yen	A multilevel analysis of the influence of Apolipoprotein E genotypes on depressive symptoms in late-life moderated by the environment	2008	301

Note. Index studies are shaded gray.
* Indicates a study that is repeated in this table because it contains more than one interaction that falls into the six replication categories. Such studies are repeated multiple times in the table to make clear the full list of studies that were counted as direct replication attempts of index interactions.