Published in final edited form as:
J Child Psychol Psychiatry. 2014 October ; 55(10): 1092–1101. doi:10.1111/jcpp.12261.

Limitations of Gene × Environment Interaction Models in Psychiatry

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Abstract

Background—Psychiatric disorders run in families, and early twin, family and adoption studies confirmed that this was due in part to shared genetic inheritance. While candidate gene studies largely failed to reliably identify genetic variants associated with psychiatric disorders, genomewide association studies are beginning to do so. However, the proportion of phenotypic variance explained remains well below what would be expected from previous heritability estimates.

Scope—We review possible reasons for this "missing heritability", and in particular whether incorporating gene by environment interactions into our models will substantially improve our understanding of the aetiology of psychiatric disorders, and inform clinical perceptions and practice.

Findings—We discuss potential limitations of the gene by environment interaction approach. In particular, we discuss whether these are likely to be a major contributor to psychiatric disorders at the level of the specific interaction (as opposed to at an aggregate level).

Conclusions—Gene by environment interaction studies offered initial promise that a far greater proportion of phenotypic variance could be explained by incorporating measures of environmental exposures into genetic studies. However, in our opinion there are few (if any) clear examples of gene by environment interactions in psychiatry, and their scope for informing either our understanding of disease pathology or clinical practice remains limited at present.

Keywords

Genetics; GWAS; Heritability; Gene × Environment Interaction; Psychiatric Disorder

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Understanding the pathological mechanisms underlying psychiatric disorders is a critical step in developing novel treatments, and also offers the potential that we may be able to identify high-risk groups in advance, and intervene at an early stage in the development of the disorder. Here we review the extent to which genetically-informed studies have advanced this understanding. In particular, we focus on the difficulties inherent in attempting to identify and interpret gene by environment interactions. We conclude with a discussion of whether focusing on gene by environment interactions is likely to improve our understanding of these pathological mechanisms, and aid the identification of high-risk groups, and what other opportunities molecular genetic techniques provide.

Genetics of Psychiatric Disorders

It has been established for some time that psychiatric disorders run in families, and early twin, family and adoption studies confirmed that this was due in part to shared genetic inheritance. It is now widely recognised that all psychiatric disorders have a considerable genetic component. This is typically expressed using the heritability statistic (h^2), which quantifies the proportion of phenotypic variance attributable to additive genetic variance, and the h^2 for most psychiatric disorders is typically in the 30-80% range (Kendler, 2013). Twin and family studies have also provided evidence for shared genetic influences on psychiatric disorders such as major depressive disorder and generalised anxiety disorder (Kendler et al., 1992).

However, while heritability studies can tell us whether the risk of a particular psychiatric disorder is under a degree of genetic influence, and to some extent allow us to quantify the degree of this influence (at least in a specific population at a specific time – see Text Box 1), they cannot tell us anything about which genes influence risk, or how. For this we need molecular studies which directly measure genotype and relate this to our outcome of interest. Until recently, the favoured method was to use a candidate gene approach, whereby variants within a gene of known or presumed relevance to the outcome of interest are directly genotyped. Early studies of disorders such as major depression (Collier et al., 1996) and alcoholism (Blum et al., 1990), and related personality traits such as neuroticism (Lesch et al., 1996) and extraversion (Ebstein et al., 1996), gave rise to the hope that the molecular genetic risk factors for psychiatric disorders would be uncovered.

Unfortunately this early promise was not ultimately realized – very rapidly it became clear that these initial findings could not be reliably replicated (Munafo and Flint, 2004), with meta-analyses indicating that if any of these effects were real they were of considerably smaller magnitude than originally supposed (Clarke et al., 2010, Munafo et al., 2003, Munafo et al., 2009b, Munafo et al., 2007, Munafo et al., 2008b). Rather than progressing to a deeper understanding of the biology of psychiatric disorder, moving from genetic variant, to gene, to the neurons and neuronal circuitry associated with the disorder, debate continues as to whether these genes are involved at all. The one clear lesson that has been learned from this literature is that single common genetic variants associated with complex behavioural phenotypes, including psychiatric disorders, contribute only a tiny proportion of phenotypic variance (typically < 0.1%).

More recently, genome-wide association studies (GWAS) have allowed us to interrogate common genetic variation across the entire genome, testing at least 500,000 loci (and now, more commonly, in excess of 2 million loci). Given the growing consensus that the effects of common genetic variants on psychiatric disorders were likely to be small (and much smaller than originally anticipated), it has become clear that very large sample sizes will be necessary to reliably detect real genetic effects. For a common quantitative phenotype such as height, each locus robustly identified and replicated typically explains less than 0.1% of the phenotypic variance (Sullivan et al., 2012). The Wellcome Trust Case Control Consortium (WTCCC), using 2,000 cases and 3,000 controls, identified loci for only five of seven investigated traits (Wellcome-Trust-Case-Control-Consortium et al., 2010); for example, no loci that contributed to variation in blood pressure were found, which required the analysis of over 30,000 subjects, followed up by genotyping an additional 80,000 subjects (Newton-Cheh et al., 2009). Critically, of the ten loci reported each accounted for 0.05-0.1% of the variance, in total explaining about 1% of the variance.

The advent of GWAS therefore necessitated sample sizes beyond what any single study could achieve, leading to the formation of a number of consortia, such as the WTCCC and the Psychiatric Genomics Consortium (Psychiatric-GWAS-Consortium-Coordinating-Committee et al., 2009). These have now reported on a number of psychiatric disorders, such as major depression (Major-Depressive-Disorder-Working-Group-of-the-Psychiatric-GWAS-Consortium et al., 2013), schizophrenia (Schizophrenia-Psychiatric-Genome-Wide-Association-Study-Consortium, 2011), and bipolar disorder (Cross-Disorder-Group-of-the-Psychiatric-Genomics-Consortium et al., 2013b). From these, it is now apparent that the genetic architecture of complex traits, from height through to psychiatric disorders, consists of a very large number of common variants of very small effect, perhaps together with additional contributions of rarer variants of larger effect (Munafo and Flint, 2009, Sullivan et al., 2012).

The “Missing Heritability” Problem

The recent success of GWAS has given rise to a new difficulty, which is the discrepancy between the proportion of phenotypic variance explained by known loci, and the proportion estimated by heritability studies; this has become known as the “missing heritability” problem (Manolio et al., 2009). The discrepancy is typically very large: GWAS using a few thousand individuals typically identify a handful of genome-wide significant loci, the sum of whose effects might account for less than 10% of the genetic variance (much less than the heritability estimated from twin studies). Four explanations for this discrepancy have been considered.

First, the heritability estimates from twin studies might be overestimates. Most twin studies use at most a few hundred twins, typically much fewer, and their estimates have very wide confidence intervals. For example, one review found that every twin study of depression included a heritability estimate of zero within its 95% confidence interval (Sullivan et al., 2000). Second, twin studies might also fail to distinguish interaction effects from additive genetic effects. When we add up the individual effect sizes from a GWAS to estimate heritability we assume nature does the same to create heritability, but this need not be so.

Some combinations of loci may act multiplicatively, rather than additively, and there may be environmental interactions that have not been taken into account. Thus, heritability estimates may hide in interaction effects. Third, missing heritability might be due to the contribution of rare variation to complex traits. The methods for detecting loci in a standard GWAS only interrogate a fraction of sequence variants, those that are most common (typically the allele frequencies are greater than 5%). We now know that variation at the vast majority of loci in the genome is rare, occurring at frequencies much less than 5% (Abecasis et al., 2012). In addition, GWAS relies upon methods that assay only one type of sequence variation (single nucleotide polymorphisms; SNPs), while a substantial component of sequence variation occurs as small insertions or deletions in the genome and larger forms of structural variation. Again, these may be contributing to the missing heritability. Fourth, and finally, it is possible that GWAS to date have simply been underpowered. Perhaps there are a very large number of loci of very small effect, and even larger samples will be required to detect them.

Gene × Environment Interactions

Two high profile studies, published in 2002 and 2003, offered hope that the limited success of candidate gene studies could be overcome by resolving the apparently inconsistent findings across studies of main effects of individual candidate genes. The first suggested that a polymorphism in the monoamine oxidase A gene modified the association between early childhood maltreatment and antisocial behaviour in later life (Caspi et al., 2002), while the second suggested that possession of the ‘short’ allele of a length polymorphism of the serotonin transporter gene (5-HTTLPR) increased the risk of developing depression, but only in the presence of adverse life events (Caspi et al., 2003).

These early examples of gene by environment interactions (G×E) offered the exciting possibility that many more such effects could be detected in studies that measured both environmental and genetic predisposition. While quantitative genetic studies indicated strongly that G×E exist in aggregate (Kendler et al., 1995), these were the first studies to suggest that it could be detected at a single locus. The hope was that studies of G×E, using carefully phenotyped individuals, might yield robust results that could be replicated. Since then, countless G×E studies have emerged, encompassing a range of genetic variants, environmental exposures, and psychiatric outcomes.

Unfortunately, the field has not developed in a way that has matched this early promise. For example, in the last few years three meta-analyses of the 5-HTTLPR, stressful life events and depression literature have been published, and they reach opposite conclusions: two found no evidence for an interaction (Munafo et al., 2009a, Risch et al., 2009), while one concluded that there was an effect (Karg et al., 2011). Despite this mixed evidence, the G×E literature has continued to grow exponentially. However, it is worth considering why it has proved so difficult to identify robust G×E effects, and what such studies might actually tell us of clinical relevance.

Difficulties in Identifying Gene × Environment Interactions

Most of the difficulties associated with identifying robust G×E effects are equally applicable to all candidate gene studies. However, in most cases, these difficulties are made worse when

interaction terms are included alongside main effects. For example, the use of retrospective self-report outcome measures, in particular in very large cohort studies, has been suggested as one contributing factor to the unreliability of findings across studies (Uher and McGuffin, 2010). However, when this has been investigated empirically, little evidence of a systematic difference in effect sizes indicated by self-report and clinical interview measures has been observed (Clarke et al., 2010).

Here we focus in particular on four factors which may contribute to the difficulty in identifying G×E effects that reliably replicate: 1) the ease with which multiple statistical testing can give rise to spurious findings, 2) the impact of low statistical power (i.e., small sample size) on the reliability of findings and the risk that these findings represent Type I error, 3) the extent to which converging evidence from other domains (e.g., animal studies and human neuroimaging studies) should increase our confidence in epidemiological findings, and 4) the evidence from whole genome approaches regarding the likely genetic architecture of complex traits.

Multiple Statistical Testing

It has been shown via simulation (Sullivan, 2007) how easy it is to obtain potentially publishable ‘findings’ from random data; by simulating a candidate gene association dataset Sullivan showed that a potentially publishable (i.e., nominally significant) association could be found in over 90% of cases. This is a result of the large number of statistical tests which it is possible to conduct on such a dataset, given multiple possible groupings of genotypes, polymorphisms that can be tested, and so on. This simulation study focused on gene–disease associations (i.e., main effects), but the degree of analytical flexibility in G×E studies is likely to be greater still. For example, one G×E study of the moderating effect of *COMT* genotype on the association between cannabis use and psychosis (Caspi et al., 2005) used a different definition of cannabis use compared to another analysis of the same data which only investigated the association between cannabis use and psychosis (Arseneault et al., 2002). The impact of undisclosed flexibility in data analysis (i.e., running numerous statistical analyses and then selecting the one for reporting that presents the most compelling story) on false positive rates has also been demonstrated elsewhere (Simmons et al., 2011).

All of this emphasises the need for clear evidence of direct replication before G×E findings can be considered robust. Unfortunately, as we have already seen, the diverse range of environmental measures and outcomes in most datasets available for secondary analysis precludes this, and it then becomes an open question whether an apparent replication is sufficiently similar to the original report to be considered helpful. Unfortunately, many G×E studies focus on the presence of a statistical interaction, and do not necessarily consider whether the nature of the interaction observed properly reflects a replication of the original finding (Munafo and Flint, 2009). A recent article illustrates the difficulties that have been encountered when attempting to replicate initial G×E reports: positive results are more common among initial reports than replication attempts (indicating publication bias against null results for initial reports), and larger replication studies are less likely to show successful replication than small studies (Duncan and Keller, 2011). The authors argue that

most G×E studies lack statistical power, and that well-powered direct replications deserve more attention than novel G×E findings and indirect replications

Statistical Power

The issue of statistical power is therefore an important one. Initially it was hoped, at least implicitly, that by incorporating environmental measures into candidate gene studies larger effects would be revealed through their interaction. However, this appears to be misplaced – whether G×E studies will improve statistical power depends very much on the nature of any interaction effect operating, and this is typically not known. It may very well be the case, for example, that a study with sufficient power to detect an interaction effect would also have sufficient power to detect a main effect, in which case the apparent presence of an interaction effect but not a main effect should be a reason for caution (Munafo et al., 2009a).

In general, larger sample sizes are required to detect interaction effects than are required to detect main effects. Despite this, the vast majority of G×E studies use relatively small samples (typically in the 100s or occasionally in the low 1,000s) which would not be adequate even if only searching for main effects of common genetic variants. While it is theoretically possible that G×E studies might afford increased statistical power, by allowing us to focus on specific subgroups where any genetic effects might be expected to be largest, this is difficult in practice because it is rare that we will have strong *a priori* reasons for expecting any effect to be restricted to any specific subgroup (Clayton and McKeigue, 2001).

The impact of low statistical power on the reliability and reproducibility of findings in the neuroscience literature has recently been highlighted (Button et al., 2013). Critically, the combination of a low prior probability for a specific interaction and low statistical power substantially increases the likelihood that any findings will be false positives.

Converging Evidence

Other evidence in support of putative G×E effects typically comes from either animal studies or human laboratory studies (e.g., using drug challenge or neuroimaging methods). Here we briefly review what these studies might tell us regarding the plausibility of G×E effects.

Neuroimaging phenotypes have been suggested to have two key advantages over more traditional phenotypes. First, it has been argued that genetic effects on brain structural and functional variation are necessarily larger, based on the assumption that some phenotypes (often called endophenotypes) are biologically closer to the site of genetic variation, and therefore the impact of genetic variation must be larger. Thus one study of just twenty-eight subjects reported an association between 5-HTTLPR genotype and variation in amygdala activation (Hariri et al., 2002), explaining about 28% of phenotypic variance. Another reported an association between *COMT* genotype and prefrontal cortex activation (Mier et al., 2010), explaining about 12% of phenotypic variance. These effect sizes are much higher than anything reported from genetic analyses of disease phenotypes, but is it likely to be true? Results of neuroimaging GWAS are beginning to emerge, and suggest that the genetic architecture of these phenotypes is not dramatically different to that of disease phenotypes (Stein et al., 2012), which has been argued previously (Flint and Munafo, 2007). Therefore,

while neuroimaging and other human laboratory methods can provide information regarding mechanism, the small sample sizes these methods impose (primarily due to cost) mean that they are not well suited to discovering novel genetic associations. Moreover, as evidence accumulates, these literatures appear to follow the now-familiar pattern of initial promise followed by inconsistency and failures to replicate, so that the evidence in support of specific associations frequently diminishes over time (Murphy et al., 2013, Munafo et al., 2008a).

Non-human primate studies are also often cited in support the human G×E evidence. For example, rhesus monkeys have an orthologue of the human 5-HTTLPR, and this has been reported to modulate the influence of early life stress (Barr et al., 2004c, Barr et al., 2004b, Champoux et al., 2002, Barr et al., 2004a). However, animal studies of this kind can be difficult to directly relate to the human literature. For example, none of these reports document linkage disequilibrium between markers at the serotonin transporter and the rest of the genome, so we have no way of establishing whether the findings could be due to linked polymorphisms. In addition, n these studies animals are maintained in colonies where social groups each consist of 8 to 14 females giving rise to varying degrees of genetic relatedness between animals, none of which is accounted for in the genetic analysis. Such population structure is well known to give rise to false positives and methods have been developed to take it into account (Newman et al., 2001, Helgason et al., 2005, Kang et al., 2010).

Converging evidence (such as from human laboratory studies and animal studies) may increase the prior probability of a putative G×E interaction, but these literatures are themselves often inconsistent. More importantly, they cannot ultimately resolve whether G×E effects are robust – this question can only be resolved by human epidemiological data.

Whole Genome Methods

A critical question is the extent to which interaction effects are important contributors to the genetic architecture of complex traits. On one hand there are convincing data from quantitative genetics that overall G×E does make a contribution, with genetic risk impacting on the depressogenic effects of environmental adversities (Kendler et al., 1995, Kendler et al., 2004, Silberg et al., 2001); on the other, the relatively unconvincing findings from analysis of single loci (describe(Yang et al., 2011)d above) give us reason to be cautious. The likely resolution lies in considering molecular data across the whole genome that gives us a global picture of how genetic variants act to increase susceptibility.

One of the most important recent observations from GWAS is that it is possible use the SNP data to answer questions about genetic architecture (i.e., to determine the number of loci that are contributing, and the way in which they act). The classical way to analyse GWAS data is to look for loci that exceed a predetermined significance threshold (usually $P < 1\times10^{-8}$). However, just because a locus does not exceed the significance threshold does not mean it does not contribute; it might simply be of too small an effect to be detected, even in the very large samples common in GWAS. Peter Visscher, adopting methods from agricultural genetics, has proposed using all variants, regardless of their significance, to estimate heritability. Visscher and colleagues have developed software to estimate heritability from

SNP data (Genomewide Complex Trait Analysis; GCTA) . Recall that GWAS data interrogates common variation – if heritability is attributable to a set of common variants, then all those with the same disease will share those variants. The sharing will not be perfect; we simply expect that for a SNP with two alleles, the affected individuals will share one allele more often than not (in other words one allele will occur in the disease cases more often than expected by chance ($P < 0.5$, in other words nothing like as stringent as $P < 1\times10^{-8}$) (Lee et al., 2011, Yang et al., 2011).

SNP-based estimates of heritability are typically less than estimates from twin and family based assessments (unsurprisingly, since GWAS variants do not interrogate all common variants, capturing at best about 80%). The striking finding is that the SNP-based estimates are consistent with the view that the majority of the heritability arises from many variants of small effects; in fact the estimates support the hypothesis that *all* of the heritability of depression is from this source (Lubke et al., 2012, Ripke et al., 2013). Interaction effects, therefore, are most likely to be attributable to the interaction between these common small effect variants. That will make their detection difficult, and will certainly require the collection of much large samples than has hitherto been achieved.

Clinical Relevance of Gene × Environment Interactions

Two arguments are often put forward as to why such studies of G×E may be helpful: 1) They may increase our understanding about underlying pathological mechanisms of disease, and 2) They may aid identification of high-risk groups that might benefit from targeted interventions. We now consider these two arguments.

Improving Understanding of Pathological Mechanisms

For multifactorial complex disorders, risk factors are neither necessary nor sufficient to cause disease, so for any given individual multiple risk factors (both genetic and non-genetic) almost certainly contribute to disease onset. In this sense, it is a certainty that genes and environment “interact” (i.e., both play a contributory role in some cases of disease). However, we cannot usually study what factors contribute to disease onset in specific individuals, although we can examine how incidence of disease in the population varies in relation to co-exposure to two or more factors by comparing data to predictions from statistical models. Statistical interaction (i.e., G×E) occurs when the measure of disease if exposed to both the gene (G) and the environmental exposure (E) is different from that predicted by the statistical model being used.

If both genetic and environmental factors are risk factors for a disease, then assuming a study is adequately powered, one can *always* find evidence of statistical interaction by testing different statistical models (e.g., testing both additive and multiplicative models by looking at both risk differences and risk ratios within the same data). This is because one set of data cannot fit two different models at the same time. Finding evidence that an environmental exposure has a ‘greater effect on disease’ in the presence of a risk allele compared to absence of that allele has limited potential to inform about underlying pathological mechanisms, because under a different statistical model one could theoretically find evidence for the opposite conclusion from the same data. The hypothetical data in Table

1 shows that, under an additive model, the effect of E on risk of disease is greater when G is also present compared to G being absent. However, under a multiplicative model, the same data shows that the effect of E on risk of disease is *smaller* when G is also present. Both models show evidence of G×E, but with opposite conclusions.

There is no limit on the range of models that can be tested, and therefore in most cases providing statistical evidence of G×E has no intrinsic value with regards to understanding underlying biological mechanisms (Thompson, 1991). The exception to this is where qualitative interactions occur, whereby the effect of one exposure (for example E) has *opposite* effects on disease risk according to whether another exposure (G) is present or not (i.e., E can be a risk factor *or* a protective factor for disease, depending upon a person's genotype) (Zammit et al., 2010b). Where qualitative interactions occur the conclusions will be the same irrespective of the statistical model used, and therefore such interactions can be informative about pathological mechanisms (Thompson, 1991). The differential susceptibility hypothesis (Belsky et al., 2007, Belsky et al., 2009, Belsky and Pluess, 2013) also describes qualitative patterns of interaction, although it requires studies that include both negative and positive (rather than just *lack* of negative) measures of the exposure or outcome for differential susceptibility effects to be revealed, and most studies to date have not examined a wide-enough spectrum of measurements to provide an adequate test. As with all qualitative interactions, few robust examples supporting the differential susceptibility hypothesis have been described, although two meta-analyses provide some support (Bakermans-Kranenburg and van Ijzendoorn, 2011, van Ijzendoorn et al., 2012).

Evidence of G×E is also model-independent where the effect of one exposure occurs only in the presence of another, but is absent otherwise. Such patterns of interaction are sometimes seen in single gene disorders (e.g., phenylketonuria, where genetic variants resulting in a non-functional phenylalanine hydroxylase enzyme are *necessary and sufficient* components for disease given that phenylalanine is present in the normal human diet) but seem much less likely for multifactorial complex disorders (although it may be more feasible for studies of adverse effects of pharmacotherapy).

Identification of High-Risk Groups

It is theoretically possible that G×E might inform clinical practice via the identification of high-risk groups. A basic principle in multifactorial complex disorders is that the greatest absolute reduction in risk of disease by an intervention will be in those with more risk factors. Therefore, if resources are limited, providing interventions to those most at risk would be a sensible strategy. However, this does not arise from G×E *per se*, and the lack of robust G×E findings means that we are some distance from such information being useful in practice. Moreover, some specific technical issues highlight the difficulties inherent in relying on evidence of G×E to inform this practice.

Where the relationship between two risk factors is greater than additive, the largest reduction in absolute risk of disease will always be obtained from interventions targeted at those exposed to both factors. However, where two risk factors (e.g., G and E) both play a causal role in some cases of disease within the population (i.e., for some individuals the disease would not have occurred if either G or E were absent), co-exposure to G and E will show

departure from additivity (Greenland et al., 2008). For multifactorial complex disorders we would rarely expect to observe additivity between risk factors as it is very unlikely that two risk factors never co-participate in any causal models of disease (Greenland et al., 2008). Empirical evidence shows that where combined effects of established risk factors on disease have been examined, the data support greater than additive patterns of joint risk (Zammit et al., 2010a). This is reflected by findings in other fields of medicine (Godsland et al., 2000, Wraith and Mengersen, 2007) and psychiatry (Clarke et al., 2009, van Os et al., 2008). Indeed, the programme of interventions aimed at reducing cardiovascular disease by specific targeting of high-risk groups is based upon the assumption of multiplicative (i.e., greater than additive) models of combined effects on risk (Joint-British-Societies, 2005). That the greatest reduction in absolute risk of disease will be obtained by targeting individuals who are co-exposed to two or more risk factors for disease seems a reasonably safe assumption to make. Evidence of G×E showing a greater than additive relationship between two risk factors will support this approach, but will probably only have important implications for targeted interventions where very strong (e.g., qualitative) patterns of interaction occur.

Most research supports a framework whereby joint exposure to risk factors in medicine is greater than additive. In other words, the greatest absolute reduction in risk of disease by an intervention will be in those with more risk factors. Therefore, the indication of individual risk factors (i.e., main effects) should be the most efficient strategy.

Future Directions

Whole genome approaches have begun to elucidate the genetic architecture of complex traits and psychiatric disorders, and demonstrate that we will not find common genetic variants of large effect (Sullivan et al., 2012). Therefore, very large samples will be required to reliably identify common genetic variants associated with these phenotypes. Incorporating environmental measures, via G×E studies, will not solve this problem. By extension, the clinical implications of G×E are likely to remain limited for the foreseeable future. These concerns are not new – many of the specific issues we have been identified have been discussed in detail elsewhere (Clayton and McKeigue, 2001, Duncan and Keller, 2011, Munafo et al., 2009a, Zammit et al., 2010b).

Despite this, genetic information is already being used in other contexts to inform our understanding of the aetiology of psychiatric illness. One such example is Mendelian randomisation, whereby genetic variants known to be robustly associated with environmental exposures (e.g., tobacco smoking) can be used as unconfounded instrumental variables in observational studies, enabling causal inferences to be drawn if certain assumptions are met (Gage et al., 2013). One of the key assumptions of this approach is that the instrumental variable (i.e., genetic variant) is not associated with the outcome except via the exposure of interest (e.g., tobacco smoking). This assumption can be tested, by stratifying the analysis by smoking status, so that the association is tested separately in smokers and non-smokers – if the assumption is valid there will be an association in the former, but not in the latter. This, of course, is a special case of G×E, but one quite different to those described above; the association of the genetic variant with the exposure is known

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(and treated as a main effect), and the interaction merely reflects the lack of any pathway through which this association can operate if the exposure is not present.

Another important development is the use of polygenic risk scores to capture disease risk, in the absence of knowledge of the precise nature of individual risk alleles, and approach initially to schizophrenia and bipolar disorder (Purcell et al., 2009). As we have discussed, studying individual G×E effects is complicated by the highly polygenic nature of psychiatric disease. In principle, the large sample sizes available through various GWAS consortia will enable the more systematic study of G×E, but this is offset by the lack of comparable measures of environmental risk factors across these cohorts (McGrath et al., 2013). One possible solution is to stratify samples by polygenic risk score, to define sub-groups with higher or lower scores. By extension, those with a high polygenic risk score will have a lower environmental risk, and vice versa. This could provide important clues as to the underlying risk architecture of psychiatric diseases (McGrath et al., 2013).

While G×E research has not, in our opinion, substantially advanced our understanding of the pathological mechanisms of psychiatric disease, other approaches are beginning to yield important findings. GWAS have only emerged in the last seven years, but already have reliably identified more than 8,500 associations with more than 350 complex traits in humans (Solovieff et al., 2013). Although progress with respect to psychiatric disorders has been relatively slow, this is changing. In particular, as evidence emerges for distinct and overlapping genetic architectures across psychiatric disorders (Lichtenstein et al., 2009), this will inform efforts to develop a psychiatric nosology based on aetiology rather than symptom clusters (Solovieff et al., 2013). Studies that have examined shared genetic effects across different disorders, as well as disorder-specific effects, are already starting to make this goal of moving beyond descriptive syndromes in psychiatry, where diagnostic systems are based on clinical description, towards a nosology informed by disease cause, a more plausible one (Cross-Disorder-Group-of-the-Psychiatric-Genomics-Consortium et al., 2013a, Cross-Disorder-Group-of-the-Psychiatric-Genomics-Consortium et al., 2013b). Such findings can increase our knowledge about the aetiology of psychiatric disease, but can also help us to understand more about the common co-occurrence of different psychiatric disorders, and instability of diagnoses over time, in many individuals.

Acknowledgements

MRM is a member of the UK Centre for Tobacco and Alcohol Studies, a UKCRC Public Health Research: Centre of Excellence. Funding from British Heart Foundation, Cancer Research UK, Economic and Social Research Council, Medical Research Council, and the National Institute for Health Research, under the auspices of the UK Clinical Research Collaboration, is gratefully acknowledged.

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Text Box 1

Heritability.

We express the proportion of variation in phenotype that is due variation in genotype as the *heritability* of a trait, sometimes expressed as h^2. A heritability coefficient of 0.50 means that 50% of the variation in that trait is due to genotypic variation. When we talk about the relative influence of genotype and environment on phenotype we are talking about the relative influence of *variability* in the former on *variability* in the latter. Accurate estimates of h^2 can be arrived at using structural equation modelling, which assumes that there are three distinct influences on phenotypic variation, comprising additive genetic effects (A), common or shared environmental effects (C) and unique or non-shared environmental effects (E). Such models are often referred to as ACE models.

The calculation of the heritability coefficient rests on several assumptions, such as that genes influence phenotypes in an additive (rather than multiplicative) way, and that genotype is not correlated with, and does not interact with, environment. In fact, it is likely that these assumptions do not always hold: gene × gene interactions (also known as epistatic genetic influences), gene × environment interactions, and gene – environment correlations may in fact occur. More complex statistical and methodological techniques exist for teasing apart these effects. Evidence for such effects comes from some surprising findings: Common environmental factors that children in the same family are exposed to tend to promote differences between these children, rather than similarities; also, measures of environmental factors seem to be genetically influenced, suggesting they are somehow *selected*; finally, genetic sensitivity to environments suggests interactions between genotype and environment.

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Key Points.

What is known?

We cannot yet be confident that gene × environment effects on psychiatric outcomes reported so far are robust.

What is new?

Whole genome approaches are beginning to elucidate the genetic architecture of psychiatric disease, and indicate that individual G×E effects will be small.

What is clinically relevant?

This literature provides few (if any) implications for clinical practice (including risk prediction, patient information, and court hearings).

What future research areas may be particularly relevant?

New genetic techniques may provide insight into the aetiology of psychiatric disease, and help us understand more about the co-occurrence of psychiatric disorders.

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Table 1

Hypothetical one-year cumulative incidence of disease (per 10,000) in relation to environmental (E) and genetic (G) exposures.

	E-	E+
G-	1	10
G+	5	20

This table demonstrates why statistical evidence of G×E has no intrinsic meaning; one can come to completely opposite conclusions about the 'effect' of one exposure on disease in the presence or absence of another exposure by examining the same data under different statistical models. It should be noted that there is no 'correct' model to use, and both approaches are equally valid. In an additive model the risk difference for E is 9 where G is absent (i.e., 10-1), and 15 where G is present (i.e., 20-5); the effect of E on disease is *greater* when G is also present. However, in a multiplicative model the risk ratio for E is 10 where G is absent (i.e., 10/1), and 4 where G is present (i.e., 20/5); the effect of E on disease is *smaller* when G is also present.