

Etiology in psychiatry: embracing the reality of poly-gene-environmental causation of mental illness

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Intriguing findings on genetic and environmental causation suggest a need to reframe the etiology of mental disorders. Molecular genetics shows that thousands of common and rare genetic variants contribute to mental illness. Epidemiological studies have identified dozens of environmental exposures that are associated with psychopathology. The effect of environment is likely conditional on genetic factors, resulting in gene-environment interactions. The impact of environmental factors also depends on previous exposures, resulting in environment-environment interactions. Most known genetic and environmental factors are shared across multiple mental disorders. Schizophrenia, bipolar disorder and major depressive disorder, in particular, are closely causally linked. Synthesis of findings from twin studies, molecular genetics and epidemiological research suggests that joint consideration of multiple genetic and environmental factors has much greater explanatory power than separate studies of genetic or environmental causation. Multi-factorial gene-environment interactions are likely to be a generic mechanism involved in the majority of cases of mental illness, which is only partially tapped by existing gene-environment studies. Future research may cut across psychiatric disorders and address poly-causation by considering multiple genetic and environmental measures across the life course with a specific focus on the first two decades of life. Integrative analyses of poly-causation including gene-environment and environment-environment interactions can realize the potential for discovering causal types and mechanisms that are likely to generate new preventive and therapeutic tools.

Key words: Psychiatric genetics, environmental risk factors, gene-environment interactions, classification of mental disorders, life course research, schizophrenia, depression, bipolar disorder, autism

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Major depressive disorder, schizophrenia, bipolar disorder and autism are among the most disabling and costly diseases¹. They affect individuals from young age, and are associated with physical morbidity and early death². The causal mechanisms underlying mental illness may hide keys to effective prevention and treatment, but remain poorly understood.

The last two decades have seen an expansion of knowledge punctuated by surprises that challenge previously held assumptions about mental illness. In this paper we provide a synthesis of current knowledge and direct further research to maximize the potential for meaningful discovery. While the focus is on generic principles underlying the causation of any mental illness, the majority of information comes from studies of schizophrenia, bipolar disorder, major depressive disorder and autism, on which most data have been accumulated.

We first review the genetic and environmental factors implicated in the etiology of mental illness, before adopting an integrative perspective that jointly considers genetic and environmental elements of causation. We conclude by outlining a framework for productive causal research.

GENETIC FACTORS IN THE CAUSATION OF MENTAL ILLNESS

All types of mental illness have a tendency to run in families, and the risk of developing an illness is associated with the degree of biological relatedness to the affected individual^{3,4}. This pattern of transmission strongly suggests genetic causation. Twin studies

consistently show that monozygotic twins who share 100% of their nuclear DNA are more likely to be concordant on each disorder than dizygotic twins who share 50% of their genetic material⁵. This difference suggests that the causation of mental illness is to a large degree attributable to genetic factors.

There is a gradient of genetic contribution, with higher estimates of heritability for the more severe and less common disorders (autism, schizophrenia, bipolar disorder) and a lesser degree of heritability for more common and less severe disorders (anxiety, major depressive disorder)⁵.

The large heritability estimates promised an easy identification of the molecular genetic variants responsible for the causation of mental illness. Influential authorities estimated that severe mental illness, such as schizophrenia, was likely to be caused by several (2 to 9) genetic loci⁶, while others argued for a single gene causing most cases of schizophrenia⁷.

Three assumptions have shaped the field of genetic discovery: a) severe mental illness is caused by a small number of genes; b) there is a specific relationship between genotype and the type of mental illness and c) the genetic variants lead to mental illness through biological pathways independent of environment. Consequently, most genetic research has studied one mental disorder at a time by comparing cases with a specific diagnosis to controls, without accounting for environmental influences.

Over the last decade, the molecular genetic technology has offered the tools to study the genetic variants responsible for the transmission of liability for mental illness from parents to offspring. This decade of research has brought surprising findings that challenge the assumptions on which psychiatric genetics has been based. Genome-wide association studies have

Table 1 Genetic variants associated with mental illness

	Autism	Schizophrenia	Bipolar disorder	Depression
Number of individuals in largest genetic sample to date	13,088 cases with autism spectrum disorders and 16,664 controls	36,989 cases with schizophrenia and 113,075 controls	7,481 cases with bipolar disorder and 9,250 controls	121,380 cases with depression and 338,101 controls
Number of genetic variants associated at genome-wide level of statistical significance	4	128	18	17
Odds ratio of the most strongly associated genetic variant	1.17	1.21	1.15	1.05
Proportion of variance explained by common genetic variants across the genome	14%	25%	25%	5%

identified more than a hundred variants associated with severe mental illness (Table 1)⁸⁻¹¹. Each of the variants has small effect and the number of associated variants keeps increasing with growing sample sizes⁸.

Polygenic risk scores analyses consistently show that the prediction of mental illness improves by including more weakly associated genetic variants, suggesting that many thousands of genetic variants are involved in shaping the risk for most mental disorders^{12,13}. These involve both common single nucleotide polymorphisms and rare structural variants, such as deletions and insertions of stretches of DNA¹⁴.

Another consistent finding is that most common and rare genetic variants are non-specifically associated with a range of mental disorders^{15,16}. Overall, approximately two thirds of genetic associations are common to schizophrenia, bipolar disorder and major depressive disorder¹⁵. There are also overlaps with genetic variants contributing to autism, attention-deficit/hyperactivity disorder, and intellectual disabilities.

It has also become clear that the heritability estimates derived from twin studies do not translate into direct effects of molecular genetics variants¹⁵. The estimates based on case-control studies with molecular genomic data suggest that genetic variants contribute only a fraction of the effect that was suggested by heritability estimates from twin studies (Figure 1). The most likely explanation for this “heritability gap” is that a large fraction of genetic effects are contingent on factors that are common to individuals growing up in the same family but not to unrelated individuals who participate in case-control studies^{17,18}. A picture is emerging of a complex etiological mechanism, where genetic influence is thinly distributed across thousands of genetic variants of small effects that are contingent on environment and not specific to any single form of psychopathology.

ENVIRONMENTAL FACTORS IN THE CAUSATION OF MENTAL ILLNESS

The same twin studies which confirmed that mental illness is heritable have also demonstrated that environment matters. Concordance of genetically identical twins is far from perfect

even for the most heritable types of mental illness, such as autism or schizophrenia⁵. While it is not possible to completely separate the effects of environment from errors in diagnosis, a realistic assessment suggests that environmental and genetic factors contribute equally to the causation of mental illness.

Since the 1960s, researchers have been identifying strong relationships between adverse social environment and mental illness. The bulk of the research on social causation has been based on the assumption that a single environmental factor may explain the causation of a specific diagnosis, irrespective of enduring characteristics of the exposed individual. Thus, social researchers tended to examine one aspect of environment and one mental disorder diagnosis at a time. The highlights of this research included identification of strong associations between severe adverse life events and depression¹⁹.

A number of studies of environmental factors have included longitudinal follow-ups and documented both the long-term effects of adversity in childhood and the close temporal rela-

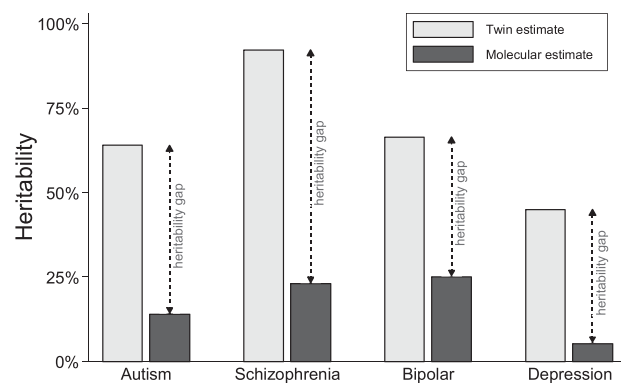


Figure 1 The heritability gap. Heritability (the proportion of causation attributable to genetic factors) has been estimated from differences of concordance between identical and fraternal twins (twin estimates) and from hundreds of thousands of single nucleotide polymorphisms across the human genome (molecular estimates). The large difference between the twin and molecular estimates is referred to as the “heritability gap”. Twin estimates are based on same-sex twin pairs from a recent comprehensive meta-analysis⁵. Molecular estimates are from large case-control genome-wide association studies⁸⁻¹¹.

Table 2 Environmental factors associated with mental illness

	Autism	Schizophrenia	Bipolar disorder	Depression
Pregnancy risk factors				
Infections	+	+++	++	+
Malnutrition		+++	++	++
Heavy metals	+++	++		
Perinatal risk factors				
Preterm birth	++	++	++	++
Season of birth	++	+++	++	+
Birth complications	+++	+++	0	
Childhood environment				
Urbanicity	+++	+++	+	+
Poverty	++	+++	+	+++
Maltreatment	N/A	++	++	+++
Bullying	N/A	++	+	+++
Drug use in adolescence				
Cannabis	N/A	+++	++	+
Stimulants	N/A	+++	++	0

The number of + marks the strength of evidence (+ means some evidence of association/single report; ++ means moderate replicated evidence of association/multiple reports; +++ means strong evidence of association/multiple replications or good meta-analysis). Evidence of no association is noted as 0. Empty cells reflect absence of evidence for or against association. No factor has been negatively associated with any of the disorders. Because of the early age at onset of autism, environmental factors occurring after age 3 cannot be reliably studied and are marked as not applicable (N/A).

tionship between severe life events and psychopathology onset in adulthood^{20,21}. With larger and more representative studies, additional and diverse environmental risk factors have been identified, including exposure to viral infections during gestation, vitamin D deficiency, growing up in urban environment, ethnic minority status, childhood maltreatment and bullying victimization (Table 2)²²⁻²⁵.

Several general principles emerged. First, the same type of environmental exposure increases the risk of many different mental disorders. For example, urban environment was first identified as a risk factor for schizophrenia, but a systematic analysis showed that it is associated with increased risk of all types of mental disorders²⁵. Second, many different types of environmental exposures contribute to the same disorder. For example, the risk of schizophrenia increases with maternal malnutrition, vitamin D deficiency and viral infections during pregnancy, low socio-economic status, urban upbringing, minority status and childhood maltreatment, as well as exposure to stimulants, cannabis and tobacco²⁶. Third, no constellation of adverse environmental exposures will result in psychopathology among all exposed individuals. Many individuals appear to be resilient and do not develop any mental disorder even if they are exposed to multiple adverse environmental factors^{27,28}.

Resilience appears to be related to a number of enduring personal characteristics that are partly heritable and partly shaped by previous environmental exposures^{28,29}. Experiences early in life may make a person more vulnerable or resilient to exposures later in development, resulting in a sequential environment-environment interaction. For example, exposure to maltreatment in childhood may cause sensitization to the effects of specific types of stressful life events in adulthood³⁰. The observation that unshared environment has greater influence on intellectual ability among twins growing up in families with low socio-economic status also suggests a complex interplay between multiple environmental factors³¹.

A synthesis of current knowledge on environmental causation of mental illness suggests a complex picture with a multitude of social, physical and chemical exposures occurring at different stages of life, affecting the risk for a range of mental disorders. It is becoming increasingly unlikely that any given environmental factor could be a necessary and sufficient cause of any mental disorder. Instead of searching for single disorder-specific environmental causes, researchers who want to explain or predict mental illness may need to jointly study a multitude of environmental influences across the life course, that may be summed up in cumulative poly-environmental scores (E-scores)³² or grouped in unique environment-environment constellations³¹.

While the array of environmental factors that are known to be involved in the causation of mental illness is impressive, it may still only be the tip of an iceberg. Research designs to date have only been powered to detect environmental factors that are harmful for the vast majority of individuals. The types of environments that may good for some and bad for others are still waiting to be discovered.

GENE-ENVIRONMENT CAUSATION OF MENTAL ILLNESS

No genetic variant and no environmental exposure on its own is a sufficient cause of mental illness. While it is possible that some cases of mental illness are caused by a combination of many genetic variants or a combination of multiple environmental exposures, the most likely scenario by far is that both genetic and environmental factors jointly contribute to the causation of mental illness. A causal mechanism where one or more genetic factors and one or more environmental factors are required to produce an outcome is gene-environment interaction (GxE).

A ubiquitous role of GxE in the causation of mental illness is suggested by a contradiction between the results of epidemiological studies and twin studies that we call the shared environment paradox. Epidemiological research shows that a substantial proportion of cases of mental illness are attributable to environmental factors which are typically shared by whole families, such as socio-economic class, poverty, urban environment, minority status, neighbourhood characteristics and childhood maltreatment^{22,25,33}. Yet, twin studies allocate only a very small role to shared environmental factors⁵ (Figure

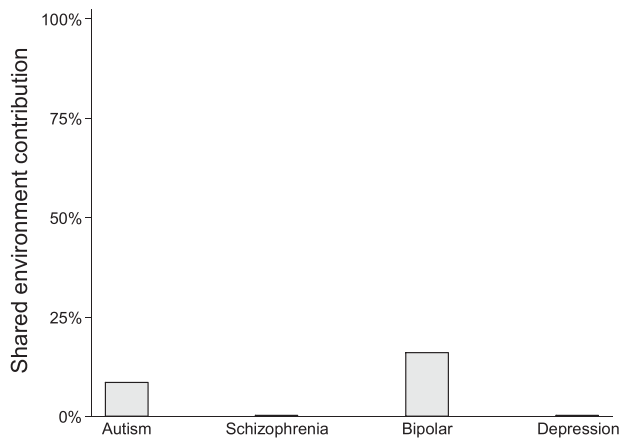


Figure 2 Shared environment paradox. Twin studies have consistently allocated little or no role in the causation of mental illness to environmental factors that are shared by members of the same family. The estimates plotted here are from a recent comprehensive meta-analysis of twin studies⁵, based on same-sex twin pairs. Estimates for schizophrenia and depression were actually negative, but since a negative contribution to variance is not possible, we plotted them at 0%.

2). One explanation of the shared environment paradox is that the impact of the family-wide environment depends on factors that are shared more between monozygotic than between dizygotic twins, i.e. genetic polymorphisms. If the effects of shared environment are conditional on genetic variants, the statistical models used in twin studies will fully attribute the joint effect to the genetic component, thus inflating heritability and reducing the estimate of shared environment³⁴. In this way, GxE provide the most parsimonious explanation for both the shared environment paradox and the heritability gap.

In the last 15 years, researchers have started to identify specific genetic variants that may sensitize individuals to environmental factors. Like most molecular genetic research, the search for GxE started with tests of candidate polymorphisms in candidate genes. The success of such studies depends not just on picking the correct combination of a genetic variant and an environmental factor based on prior knowledge, but also on sampling and design that allows an approximation of a biological interaction with a statistical test.

Remarkably, some of these studies appear to have been successful in finding causal mechanisms. Some candidate gene GxE have been consistently replicated. For example, the interaction between low activity variants of the X-chromosome-linked monoamine oxidase A (MAO-A) gene and childhood maltreatment leading to antisocial behavior in males has been replicated multiple times and confirmed in meta-analyses^{35,36}. The interaction between brain derived neurotrophic factor (BDNF) gene variants and severe life events leading to depression has also been replicated and confirmed in a meta-analysis³⁷.

Other GxEs have proven less robust or more specific than originally reported. For example, the interaction between short variants of the serotonin transporter gene length polymorphism

and adversity leading to depression has seen similar number of replications and non-replications and it may be specific to childhood maltreatment leading to persistent depressive disorder³⁸⁻⁴⁰. Yet other reported GxE have proven unreplicable. For example, the interaction between catechol-O-methyltransferase (COMT) gene and cannabis use leading to psychotic symptoms has been reported, but not replicated in subsequent studies⁴¹.

More recent studies have screened a larger number of genes and polymorphisms to search for GxE. Such systematic search has led to the identification, among 152 polymorphisms in 42 genes related to cannabinoid signalling, of an interaction between a single nucleotide polymorphism in the serine/threonine kinase encoding gene AKT1 and cannabis use leading to psychosis⁴². This GxE has been replicated in independent samples^{43,44}, suggesting that this polymorphism sensitizes individuals to the psychosis inducing effects of tetrahydrocannabinol.

Finally, several genome-wide environment interaction studies (GWEIS) have been completed to search for GxE without any pre-existing hypothesis about the genetic variants involved. The first GWEIS concerned interactions of common genetic variants with prenatal exposure to cytomegalovirus and with stressful life events in the causation of schizophrenia⁴⁵ and depression⁴⁶, respectively. The existing GWEIS have limited statistical power, because most large genotyped samples are missing adequate measures of environment. At present, it is unclear whether the results of GWEIS will be more replicable than those of candidate GxE studies. An interim synthesis suggests that multiple GxE contribute to most types of mental illness, but no specific GxE explains a substantial proportion of cases.

Several studies suggest that multiple genetic variants shape the susceptibility to harmful and protective environmental factors. One study has shown that a score derived from over 2,800 schizophrenia-associated variants in coding or regulatory genomic regions interacted with winter birth to increase the risk of schizophrenia⁴⁷. In another study, a polygenic risk score of tens of thousands of common variants tapping the overall sensitivity to environment predicted the effects of negative parenting on emotional psychopathology as well as the effectiveness of intensive psychological treatment for anxiety⁴⁸. As in studies of direct polygene-disorder associations, the GxE increased in strength with more genetic variants being included in the polygenic risk score. The emerging pattern of findings suggests that sensitivity to environment is a highly polygenic trait with contributions from thousands of common genetic variants.

The examination of gene-environment interplay is still in its infancy, and research available to date leaves many unanswered questions. The specificity of polygenic GxE to the type and timing of environmental exposures, the specificity or pleiotropy of GxE across types of mental disorders, and the role of rare structural variants in sensitivity to environment remain largely unexplored.

BOUNDARIES AND OVERLAP BETWEEN DISORDERS

The review of genetic and environmental factors above has concluded that most factors are associated with most types of mental illness. The apparent overlaps in causation has been generally ascribed either to pleiotropy, i.e. the same factors having the potential to cause multiple types of illness, or to the lack of validity of the diagnostic criteria for specific disorders.

Pleiotropy at the level of a single causal factor has been well documented: for example, the same variant (A-allele of rs1006737) of the calcium channel gene *CACNA1C* has been associated with increased risk of bipolar disorder, schizophrenia, depression, anxiety and autism⁴⁹⁻⁵¹. While inadequate validity of boundaries between diagnostic categories has also been amply demonstrated⁵², evidence supporting validity also exists, e.g. in the specificity of therapeutic response to lithium in bipolar disorder but not schizophrenia.

While both pleiotropy and inadequate validity of categorization are likely to be at play, the multifactorial causation also leaves the possibility of unique combinations of causal factors. For example: even if most risk factors are shared between bipolar disorder and schizophrenia, the loading and combination of factors that give rise to each of the two disorders may still be unique.

Since hundreds or thousands of environmental and genetic factors are likely involved in the causation of each disorder, the number of possible combinations is extremely large. The examination of these possible combinations has only just begun. One example involves both a mental disorder and a physical disorder: individuals with schizophrenia have less than half the risk of developing rheumatoid arthritis compared to the general population, even though schizophrenia and rheumatoid arthritis share environmental risk factors, including winter birth and tobacco smoking. Recently it has been shown that a polygenic risk associated with the immune system is associated with both increased risk of rheumatoid arthritis and reduced risk of schizophrenia. In addition, a polygenic risk score for schizophrenia interacts with winter season of birth to increase the likelihood of schizophrenia⁴⁷. In this case, some environmental factors are shared, but genetic disposition distributed across thousands of variants may determine the relative risk of two competing outcomes.

Even if we are able to examine combinations of genetic and environmental factors, the question remains about the level of outcomes that is most likely to lead to success in etiological research. Most of the debate to date has focused on the distinction between categorical diagnoses and dimensional measures. This may have been a false focus. At present, it is unclear whether one of the approaches is more advantageous than the other. The experience with dimensional constructs introduced as part of the Research Domain Criteria framework over the past five years does not inspire hopes for major advances in etiological research. While dimensional measures may be more powerful for examining variation in common traits across the general population, the categorical diagnostic

constructs remain more relevant to the severe types of mental illness that are most pertinent to psychiatry. When it comes to psychopathology, it is unlikely that the difference between complete absence of pathological symptoms and population average matters as much as the difference between average and severe psychopathology. Yet, the number of categories in the current classifications are too large and the boundaries between them lack validity⁵².

Because psychiatric research to date has been based on the now refuted assumption of diagnostic specificity, most studies are uninformative about the validity of specific diagnostic categories or dimensions⁵². The potential for discovery will likely be enhanced if researchers refocus on examining broad and heterogeneous samples of mental illness without exclusions based on diagnostic criteria and without constraining their measurement to consensus based constructs, categorical or dimensional. Shedding the constraints of diagnosis-specific research does not require adopting another set of constraints and it does not necessitate transition from a categorical to a dimensional framework of inquiry. Examination of overlaps in etiological factors between disorders suggest that higher level broad categorical constructs may be more appropriate targets of etiological research than specific diagnostic categories. For example, the major overlap in both genetic and environmental contributors between major depressive disorder, bipolar disorder, schizophrenia and other types of psychotic illness suggests that a broad category of severe mental illness that encompasses major mood and psychotic disorders may be an appropriate unit of investigation.

DEVELOPMENTAL CONTEXT AND CLINICAL COURSE

Two major discoveries in psychiatry remain underrated and are not reflected in most etiological research. The first one is the continuity of pathology over the life course. From cohorts with complete and intensive long-term follow up, it has become clear that most cases of mental illness start in childhood and adolescence. The early manifestations of psychopathology typically differ in kind from the eventual diagnoses in adulthood, yet are very strongly predictive of mental illness diagnosed across the life course.

Heterotypic continuity is the rule. For example, anxiety in childhood is a strong predictor of both major depressive disorder and bipolar disorder in adulthood. Oppositional defiant disorder in childhood predicts a broad range of psychopathology in adults, including depression, bipolar disorder, anxiety, substance use disorders and antisocial personality disorder. Yet, there is also a degree of specificity, with a systematic correspondence between the profile of childhood symptoms and the type of adult disorders⁵³.

The fact that most individuals with mental illness will go through a number of diagnostic categories over their life course adds to the problems associated with diagnosis-specific research⁵². It highlights the need to examine psychopathology

broadly and in a developmental context. Since most mental illness starts in childhood and retrospective report is inaccurate, etiological research needs longitudinal designs that start in childhood, at birth or even earlier⁵⁴.

The second discovery is that the course of mental illness varies between individuals and is only loosely related to the diagnostic category. Traditionally, some disorders have been conceptualized as episodic and other disorders as persistent, but longitudinal follow-ups suggest that this conceptual distinction has limited validity. Mood disorders have been codified as episodic, yet on follow-up they are marked by chronicity, with most individuals spending most of their time with depressive symptoms^{55,56}. Personality disorders have been conceptualized as persistent, but on follow-up their symptoms show similar rates of remission and relapses as mood disorders do⁵⁷.

Yet, within the same disorder, episodic and persistent cases may have distinct etiologies. For example, episodic cases of major depressive disorder are more strongly heritable⁵⁸ and persistent cases are more strongly linked to childhood maltreatment⁵⁹. The interaction between serotonin transporter gene length polymorphism and childhood maltreatment also appears to be specific to persistent depressive disorder^{39,40}. On the other hand, there is evidence that cycloid psychosis, a type of mental illness marked by a characteristic highly episodic course in spite of varied symptom content, may have distinct genetic underpinning^{60,61}. These examples suggest that time course of illness may be at least as important in etiological studies as the symptom profile.

The findings of longitudinal research outlined above highlight a massive caveat in prior etiological studies that grouped individuals into cases and controls based on symptom content in adulthood without reference to developmental context or time course of symptoms. Future etiological research will be improved by the systematic incorporation of a temporal dimension that has been conspicuously missing from both categorical and dimensional classifications used by most etiological studies to date.

LIMITS OF CURRENT APPROACHES

The last decade has seen a large amount of criticism of psychiatric research. It may be important to own up to both successes and failures and take a stock of what might have hindered the field from knowing more. Based on the review of etiological research in psychiatry outlined above, we conclude that four factors are limiting further progress.

One of the major limiting factors is assumed knowledge. Over the past five decades, psychiatry researchers have built their studies around the following assumptions: causes are diagnosis-specific, disorders are caused by a small number of factors, and genetic factors have primacy over environmental influences. It is remarkable that some of the greatest discoveries

in psychiatry occurred before these assumptions were established. For example, the discovery of lithium efficacy for bipolar disorder occurred thanks to investigation in an unselected group of patients⁶².

Another limiting factor lies in omissions. The diagnosis-focused approach of the 20th century and the ensuing categories-vs.-dimensions discussion might have led to the neglect of the developmental context and the temporal dimension of psychopathology.

The final limitations we will discuss are related: statistical power and quality of measurement. Since many genetic and environmental factors contribute to most cases of mental illness, large representative samples with accurate measurements of genetic variation, environmental exposures and psychopathology over the life course are needed for etiological research. We have many studies with good measurement of environment, but they do not overlap much with studies with high standard of genetic measurement. We have some longitudinal studies with high quality measurements and we have some studies with a large number of individuals. Unfortunately, there has been little overlap between the two. The largest studies in psychiatry are either pulled together from many variably assessed samples or they suffer from large dropout rate and less accurate measurement. We may not get the answers about causation of mental illness unless experts in developmental psychopathology, environment and genetics join forces to work together on large longitudinal studies. Early examples of such collaborations are emerging and hopefully will be completed.

FRAMEWORK FOR DISCOVERY

To substantially advance our understanding of mental illness, the next generation of studies will need to embrace the complexity of poly-gene-environmental causation. The technology and methodological knowledge available today enables studies of multiple environmental and genetic factors without assumptions of independence. It is essential that the research studies are designed in a way that maximizes the potential for meaningful discovery by avoiding the pitfalls of assumptions, omissions, inadequate measurement and statistical power (Figure 3).

Large longitudinal studies of samples that are not selected for a particular diagnosis are needed to enable new discovery. These studies should start in pregnancy, childhood or adolescence to capture the development of psychopathology and allow separation of cases from consequences. Repeated assessments of multiple aspects of environment during the individual's development should cover known environmental risk factors as well as key factors of environment that may be good for some and bad for others. Regular assessments of psychopathology across the life course are needed to establish true age at onset, track the course and record sequential comorbidity.

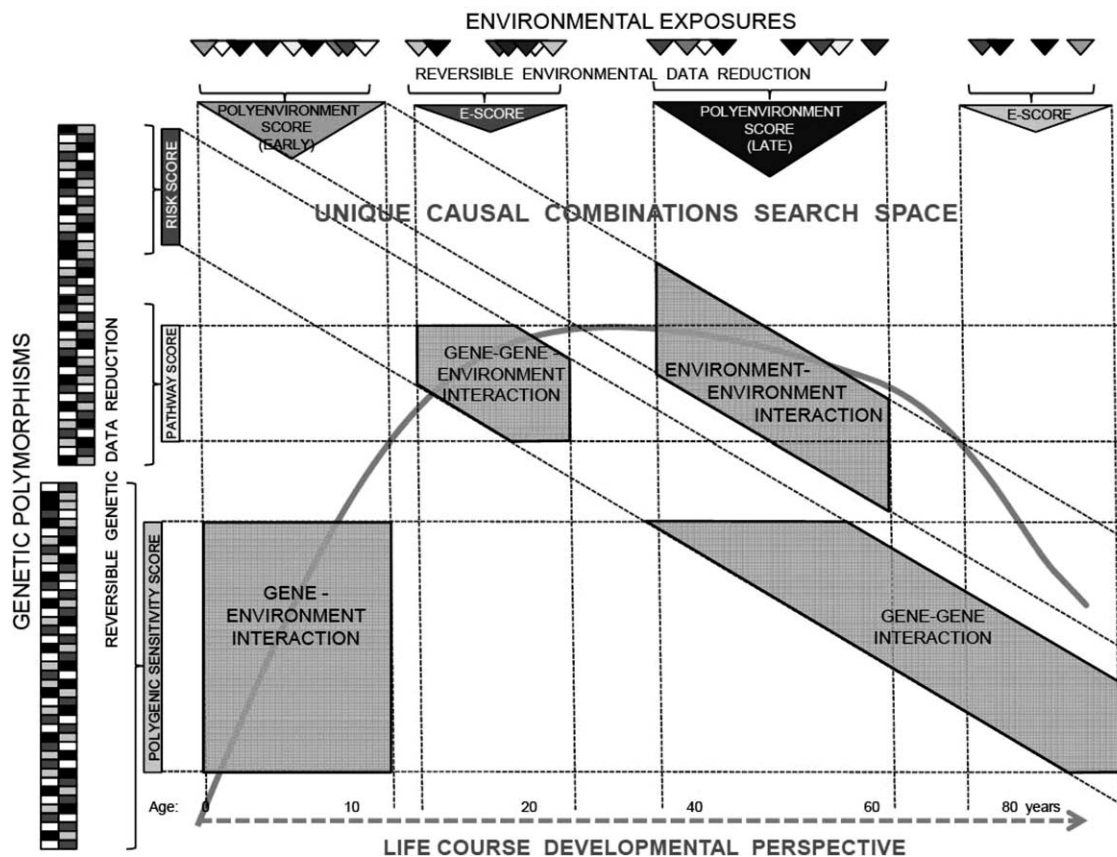


Figure 3 Framework for discovery. Life-course developmental perspective and an open search space for unique combinations of genetic and environmental factors (including gene-gene, gene-environment, and environment-environment interactions) are core elements that will enhance the potential for discovery in etiological research. Genetic and environmental data reduction – polygenic sensitivity scores, polygenic risk scores, genetic pathway scores, poly-environmental scores (E-scores) – may be a necessary intermediate step towards the discovery of broad poly-gene-environmental causal mechanisms, but the reduction process should be reversible to enable fine mapping of specific molecular and behavioral mechanisms.

Measurement of environment and psychopathology should use multiple independent sources of information to maximize objectivity and avoid common source bias (e.g., predictably high but uninformative correlations between questionnaires completed by the same individual at the same time). Instead of case-control studies, genetic measurement should concentrate on samples with high-quality longitudinal data on environment and psychopathology.

With broadly based assumption-free designs, the onus will be on data analysis to make use of the resulting data in a way that can identify complete etiological mechanisms leading to mental illness. The key challenge for data analysts will be to embrace the complexity of causation while retaining the capacity to trace specific causal mechanisms. The data analysis may need to move from theory-driven hypothesis testing focus to a theory-free explanatory framework that aims to explain the causation of a large proportion of cases. It will be important to identify unique combinations of genetic and environmental variables that lead to mental illness, irrespective of whether the biological mechanism corresponds to the constrained concept of statistical interaction. The framework

should be open to identify combinations of early and late environmental factors as well as of environmental and genetic factors.

Tools for such analyses are becoming widely available. For example, statistical learning offers a set of tools that are designed to maximize the use of rich datasets in the prediction and explanation of outcomes and at the same time provide understanding of how individual factors contribute to the prediction⁶³. Methods are also being developed that make it possible to distinguish between causal heterogeneity and poly-factorial causation⁶⁴. While the available methods potentially offer many ways of analyzing rich datasets, the model complexity will have to be kept proportional to available sample sizes. Given the vast number of potential factors to be considered, data analysis process will require a degree of data reduction in the initial stages. This may take the form of polygenic risk scores of disorder liability or environmental sensitivity⁴⁸, genetic pathway scores⁴⁷ and poly-environmental risk scores³².

The degree of data reduction should not be excessive and the process may need to preserve developmental specificity: e.g., with separate procedures for childhood, adolescent and

adulthood exposures. Data reduction also needs to be transparent, so that it is possible to follow a positive result back to the molecules and specific factors that drive the causal mechanisms. Specific constellations of molecular genetic and environmental factors will be needed to inform prevention and treatment⁶⁵.

Eventually, the role of each genetic and environmental variable has to be understood in a way that enables independent replication and examination of the underlying biological mechanism. Embracing complexity in a transparent and assumption-free framework will enable researchers to map complete causal mechanisms that explain why large groups of individuals develop mental illness. While this may be a bigger task than what previous generations of psychiatrists had envisioned, knowledge of complete causal mechanisms is necessary to meaningfully transform classification, prevention and treatment.

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