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Competing interests statement

The authors declare no competing financial interests.

DATABASES

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OPINION

Gene–environment interactions in psychiatry: joining forces with neuroscience

Avshalom Caspi and Terrie E. Moffitt

Abstract | Gene–environment interaction research in psychiatry is new, and is a natural ally of neuroscience. Mental disorders have known environmental causes, but there is heterogeneity in the response to each causal factor, which gene–environment findings attribute to genetic differences at the DNA sequence level. Such findings come from epidemiology, an ideal branch of science for showing that gene–environment interactions exist in nature and affect a significant fraction of disease cases. The complementary discipline of epidemiology, experimental neuroscience, fuels gene–environment hypotheses and investigates underlying neural mechanisms. This article discusses opportunities and challenges in the collaboration between psychiatry, epidemiology and neuroscience in studying gene–environment interactions.

Gene–environment interactions occur when the effect of exposure to an environmental pathogen on a person's health is conditional on his or her genotype. The first evidence that genotype moderates the capacity of an environmental risk to bring about mental disorders was reported in 2002 (REF. 1). Although mental health research into gene–environment interactions is new, it seems to be gathering momentum. We argue that, to fulfill its potential, gene–environment interaction research must integrate with neuroscience. Moreover, the gene–environment interaction approach brings exciting opportunities for extending the range and power of neuroscience. Here, we examine opportunities for collaboration between experimental neuroscience and research on

gene–environment interactions. Successful collaboration can solve the biggest mystery of human psychopathology: how does an environmental factor, external to the person, get inside the nervous system and alter its elements to generate the symptoms of a disordered mind? Concentrating the considerable resources of neuroscience and gene–environment research on this question will bring discoveries that advance the understanding of mental disorders, and increase the potential to control and prevent them.

Psychiatric genetic approaches

The recent history of psychiatric research that has measured genetic differences at the DNA sequence level can be divided into three approaches, each with its own

logic and assumptions. The first approach assumes direct linear relations between genes and behaviour (FIG. 1a). The goal of this approach has been to correlate psychiatric disorders with individual differences in DNA sequence. This has been attempted using both linkage analysis and association analysis, with regard to many psychiatric conditions such as depression², schizophrenia³ and addiction⁴. Although a few genes have accumulated replicated evidence of association with disorder, replication failures are routine and overall progress has been slow⁵. Because of inconsistent findings, many scientists have despaired of the search for a straightforward association between genotype and diagnosis⁶, that is, for direct main effects.

The second approach has sought to make more progress by replacing the disorder outcomes with intermediate phenotypes, called 'endophenotypes' (FIG. 1b). Endophenotypes are heritable neurophysiological, biochemical, endocrinological, neuroanatomical or neuropsychological constituents of disorders⁷. Endophenotypes are assumed to have simpler genetic underpinnings than disorders themselves. Therefore, this research approach pursues the hypothesis that it will be easier to identify genes associated with endophenotypes than genes associated with their correlated disorders. Although this approach substitutes the psychiatric diagnosis with an intermediate brain measure, it still searches for direct main effects.

The third approach to psychiatric genetics, unlike the first two approaches, seeks to incorporate information about the environment (FIG. 1c). This gene–environment interaction approach differs fundamentally from the 'main-effect approaches', with regard to the assumptions about the causes of psychiatric disorders. Main-effect approaches assume that genes cause disorder, an assumption carried forward from early work that identified single-gene causes of rare Mendelian conditions. By contrast, the gene–environment interaction approach assumes that environmental pathogens cause disorder, and that genes influence susceptibility to pathogens. In contrast to main-effect studies, there is no necessary expectation of a direct gene-to-behaviour association in the absence of the environmental pathogen. The gene–environment interaction approach has grown out of two observations: first, that mental disorders have environmental causes; second, that people show heterogeneity in their response to those causes⁸.

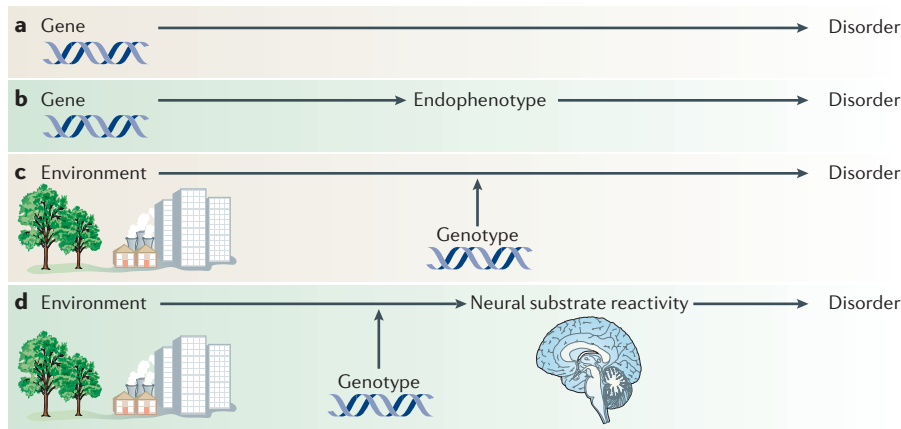


Figure 1 | **Approaches to psychiatric genetics research.** **a** | The gene-to-disorder approach assumes direct linear relations between genes and disorder. **b** | The endophenotype approach replaces the disorder outcomes with intermediate phenotypes. **c** | The gene–environment interaction approach assumes that genes moderate the effect of environmental pathogens on disorder. **d** | Neuroscience complements the latter research by specifying the proximal role of nervous system reactivity in the gene–environment interaction.

Nature and nurture

Like other non-communicable diseases that have common prevalence in the population and complex multi-factorial aetiology, most mental disorders have known non-genetic, environmental risk factors (that is, predictors whose causal status is unproven) and/or environmental pathogens (that is, proven causes)^{9,10}. Environmental pathogens have been documented for substance-use disorders¹¹, antisocial disorders¹², depression¹³, and even schizophrenia-spectrum disorders^{14,15}. The pool of environmental factors is currently more limited for disorders such as autism, Alzheimer’s-type dementia, and attention-deficit hyperactivity disorder (ADHD). Nevertheless, the concordance of monozygotic twins for even these highly heritable disorders is less than perfect, indicating the existence of non-genetic contributing causes. Environmental risk factors for mental disorders discovered to date include (but are not limited to) maternal stress during pregnancy, maternal substance abuse during pregnancy, low birth weight, birth complications, deprivation of normal parental care during infancy, childhood physical maltreatment, childhood neglect, premature parental loss, exposure to family conflict and violence, stressful life events involving loss or threat, substance abuse, toxic exposures and head injury.

These environmental causes are considered to be only contributory because exposure to them does not always generate disorder. Both human and animal studies consistently reveal variability in individuals’ behavioural responses to environmental pathogens. Heterogeneity of response characterizes all known environmental risk factors

for psychopathology, including even the most overwhelming of traumas. Such response heterogeneity is associated with pre-existing individual differences in temperament, personality, cognition and autonomic physiology, all of which are known to be under genetic influence¹⁶. The hypothesis of genetic moderation implies that differences between individuals, originating in the DNA sequence, bring about differences between individuals in their resilience or vulnerability to the environmental causes of many pathological conditions of the mind and body. This pathogenesis hypothesis is under study in relation not only to mental disorders, but also to cancer¹⁷, diabetes¹⁸, and cardiovascular¹⁹, immune/infectious^{20,21} and respiratory²² diseases.

Gene–environment interaction studies in psychiatry are new, but some of the initial findings are intriguing. Our own studies provided proof of principle of this approach. In the first report of gene–environment interaction in relation to behaviour, we tested the hypothesis that a functional polymorphism in the promoter region of the gene encoding the neurotransmitter-metabolizing enzyme monoamine oxidase A (MAOA) would moderate the effect of child maltreatment in the cycle of violence. Results showed that maltreated children, whose genotype conferred low levels of MAOA expression, more often developed conduct disorder, antisocial personality and adult violent crime than children with a high-activity *MAOA* genotype¹. In a second study, we proposed that a functional polymorphism in the promoter region of the serotonin transporter (*5-HTT*) gene would moderate the influence

of stressful life events on depression. Individuals with one or two copies of the *5-HTT* ‘short’ allele exhibited more depressive symptoms, diagnosable depression, and suicidality following stressful life events than individuals with two copies of the ‘long’ allele²³. A third study, by investigating the differential effects of cannabis on its users, demonstrated that gene–environment interactions involve environmental pathogens apart from psycho-social risks. We suggested that a functional polymorphism in the catechol-*O*-methyltransferase (*COMT*) gene would moderate the link between adolescent cannabis use and risk of developing adult psychosis. Cannabis users carrying the *COMT* valine allele were likely to exhibit psychotic symptoms and to develop schizophrenia-spectrum disorder, but cannabis use had no such adverse influence on individuals with two copies of the *COMT* methionine allele²⁴. Additional gene–environment findings are emerging. In two studies of ADHD, polymorphisms in the dopamine system interacted with antenatal risk factors (for example, low birth weight and maternal use of alcohol) to predict key symptoms associated with the disorder^{25,26}. In another report, polymorphisms in the glucocorticoid receptor-regulating gene *FKBP5* interacted with acute injury to predict psychological dissociation, a key feature of post-traumatic stress syndrome²⁷.

The study of gene–environment interactions has been the province of epidemiology, in which genotypes, environmental pathogen exposures and disorder outcomes are studied as they naturally occur in the human population²⁸. Genetic epidemiology is ideal for achieving three goals. First, epidemiological studies identify the involvement of hypothesized gene–environment interactions. Second, to increase confidence in the interaction, epidemiological studies incorporate control factors necessary for ruling out alternative explanations. Third, epidemiological studies attest whether an interaction accounts for a non-trivial proportion of the disorder in the human population. However, genetic epidemiology is limited for understanding the biological mechanisms involved in an interaction, and therefore its potential will be better realized when it is integrated with experimental neuroscience. Neuroscience can complement psychiatric genetic epidemiology by specifying the more proximal role of nervous system reactivity in the gene–environment interaction (FIG. 1d). Such information about proximal mechanisms will be essential for developing theory and treatments.

‘Bootstrapping’ with neuroscience

The original impetus for conducting each of our epidemiological gene–environment interaction studies came from findings that had been established by neuroscience research. We have subsequently observed that, once a novel gene–environment interaction is reported, a wave of new neuroscience follows. This suggests a mutually beneficial relationship of ‘bootstrapping’ between the two fields (FIG. 2).

In the initial phase of research into gene–environment interactions, neuroscience provides building blocks that are needed to construct a hypothesis (FIG. 2a). The building blocks correspond to the three elements of the triad: the disorder, the environmental pathogen and the genotype. First, evidence is needed about which neural substrate is involved in the disorder. Second, evidence is needed that an environmental cause of the disorder has effects on variables indexing the same neural substrate. Third, evidence is needed that a candidate gene has functional effects on variables indexing that same neural substrate. It is this convergence of environmental and genotypic effects within the same neural substrate that allows for the possibility of gene–environment interactions. At present, such evidence concerning environmental and genotypic effects in relation to neural substrate measures is sparse, and therefore gene–environment interaction hypotheses are likely to be circumstantial at best, and flimsy at worst. But this situation is steadily improving. When we were constructing our hypothesis regarding the genetic moderation of the depressogenic effects of stressful life events²³, we were aided by direct evidence linking the *5-HTT* candidate gene to individual differences in physiological responsiveness to stress conditions in three different experimental paradigms, including knockout mice²⁹, stress-reared rhesus macaques³⁰ and human functional brain imaging³¹. Such helpful studies are uncommon as yet, but they are emerging.

In the second (epidemiological) phase of research, the new gene–environment interaction hypothesis is tested against data (FIG. 2b). Elsewhere, we have discussed potential pitfalls of gene–environment interaction studies and have outlined strategies to guide this research^{8,32}. If the initial data are consistent with the hypothesis, the finding must be replicated to determine whether it is sufficiently reliable to warrant further neuroscience investigations³³. Most gene–environment interaction findings have emerged too recently to be evaluated according to their replication records.

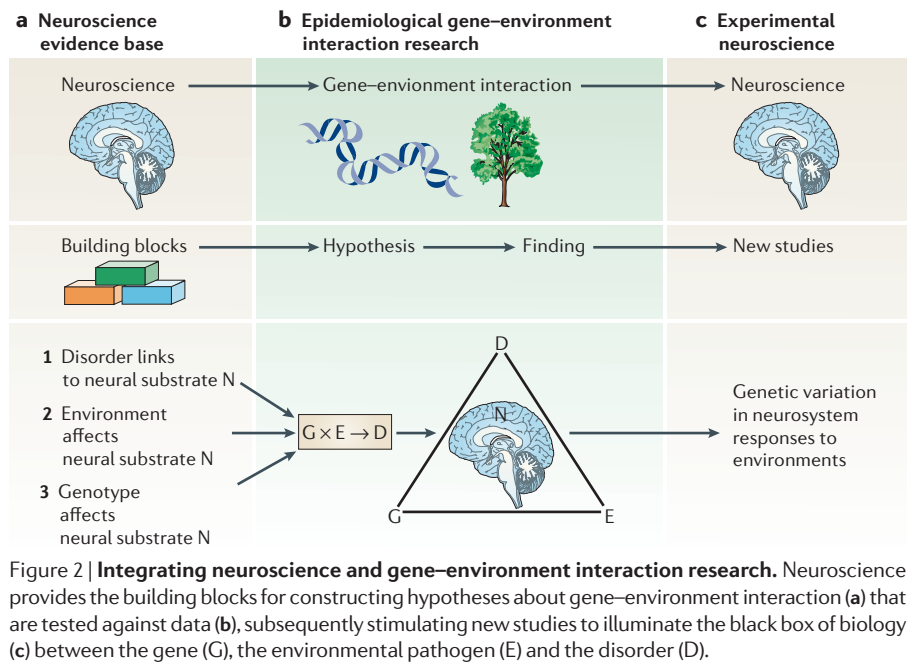


Figure 2 | **Integrating neuroscience and gene–environment interaction research.** Neuroscience provides the building blocks for constructing hypotheses about gene–environment interaction (a) that are tested against data (b), subsequently stimulating new studies to illuminate the black box of biology (c) between the gene (G), the environmental pathogen (E) and the disorder (D).

However, two of these findings are promising. First, several studies have sought to replicate the interaction between the high- and low-activity *MAOA* genotypes and maltreatment^{34–38}; a meta-analysis revealed a significant pooled effect³⁶. Second, positive replications of the interaction between *5-HTT**long/*5HTT**short genotypes and life stress have also appeared^{39–47}, along with two failures to replicate^{48,49}. It is important to note that useful information can also be gleaned from inconsistencies across study findings. For example, as more studies accumulate it will be possible to evaluate whether the moderating effect of the *5-HTT* genotype on life stress is stronger among females or males, younger adults or older adults, and first-onset or recurrent depression cases.

In the third phase of research, scientific activity comes a full circle, back to neuroscience (FIG. 2c). A new wave of studies is stimulated, each aiming to illuminate the black box of biology between the gene, the environmental pathogen, and the disorder⁵⁰ (as illustrated in the triangle in FIG. 2). For example, evidence that variation in the promoter region of the *5-HTT* gene shapes depressogenic responses to life stress has led to more focused neuroscience research on a genetic susceptibility mechanism for stress-related depression^{51–54}. Similarly, evidence that a polymorphism in the *MAOA* gene might contribute to the cycle of violence in maltreated children¹ — a hypothesis stimulated by behavioural evidence from mouse knockouts for *MAOA*⁵⁵ and functional gene knockouts in humans⁵⁶ — has, in turn, stimulated

efforts to probe circuits of emotional arousal in the brain by studying this polymorphism in imaging paradigms⁵⁷ (see also BOX 1).

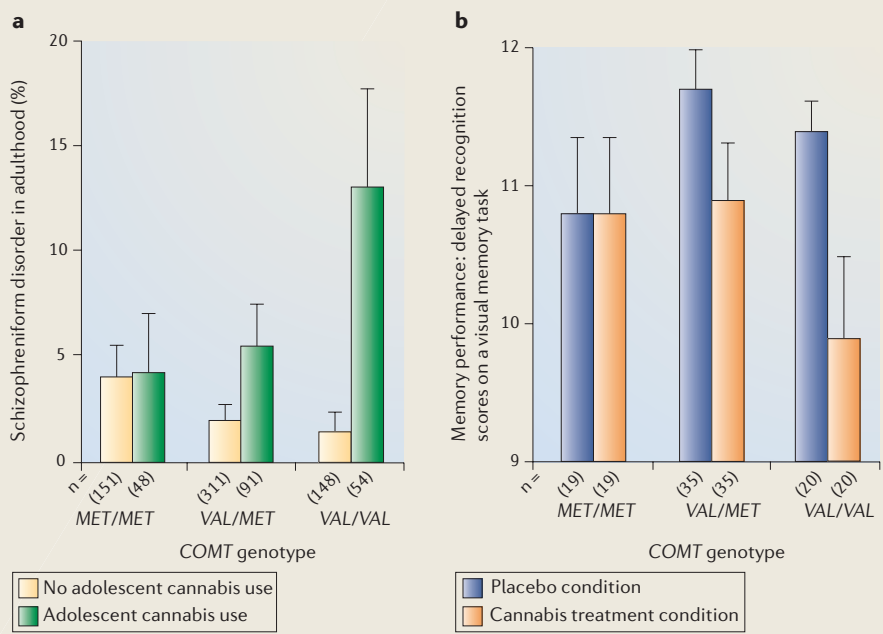
Enhancing neuroscience

A replicated finding on gene–environment interactions adds new information, producing a stimulating effect on neuroscience. The result of a reliable gene–environment interaction finding is clear evidence for a pathway of causal neural process connecting the three disparate ‘end points’ that form the triad of gene, environmental pathogen and disorder. The pathway might initially be hidden from scientific view, but knowing three endpoints (instead of two) enhances the likelihood of finding the neurobiological paths that unite them. Candidate genes can add information about where in the body, cell and molecule the environmental pathogen’s effect on disorder occurs.

A replicated finding on gene–environment interactions yields at least three insights. First, the insight that the result of exposure to an environmental pathogen depends on the person’s genotype offers clues about the root beginnings of a causal pathway. Variation in the DNA sequence antedates all other variables in the triad. Therefore, covariation between a measured genotype and a neural substrate variable is useful for making deductions about the position of the neural substrate variable in the causal chain. For example, if a study showed that amygdala activation in response to emotional stimuli was abnormal in depressed subjects, this could indicate either

Box 1 | How does genotype moderate the psychological effects of cannabis use?

Evidence from studies around the world shows that cannabis use is a statistical risk factor for the emergence of psychosis, ranging from psychotic symptoms (such as hallucinations and delusions) to clinically significant disorders (such as schizophrenia)⁹³. However, most people who use cannabis do not develop psychosis, which suggests that some individuals may be genetically vulnerable to its effects. This hypothesis received initial support from research showing that the association between cannabis use and psychosis outcome is most marked in subjects with an established vulnerability to psychosis⁹⁴. However, the genetic risk involved was not specified. Subsequent research focused on risk measured by individual differences on the catechol-O-methyltransferase (COMT) gene; in particular, a valine allele at codon 158 producing more enzymatic activity and faster breakdown of dopamine than the methionine allele. Both the COMT valine allele⁷⁷ and cannabis use⁹⁵ have been independently associated with brain endophenotypes for schizophrenia^{96,97}. An epidemiological study (see panel a) that traced a longitudinal cohort from prior to the onset of cannabis use (age 11 years), through to the peak risk period of psychosis onset (age 26 years), revealed that individuals with one or more high-activity valine alleles (VAL/MET or VAL/VAL) showed subsequent increased risk of psychotic symptoms and psychosis-spectrum disorder if they used cannabis²⁴. Cannabis use had no such adverse influence on individuals with two copies of the methionine allele (MET/MET). But is the quantification of drug exposure information using the self-reports of adolescent subjects sufficiently accurate? Is it possible that valine-allele carriers who use cannabis are unusual in some unmeasured way? And how does the valine allele influence sensitivity to cannabis? These questions have been addressed by researchers in the Netherlands, who used an experimental design to extend the epidemiological finding⁹⁸. In their studies, subjects were tested on two occasions, separated by 1 week, as part of a double-blind, placebo controlled cross-over design. In randomized order, they received either 0 µg or 300 µg -9-tetrahydrocannabinol (the principal component of cannabis) per kilogram bodyweight. Cannabis affected cognition and state psychosis, but this was conditional on COMT genotype. As illustrated in panel b, individuals carrying two copies of the valine allele exhibited more cannabis-induced memory and attention impairments than carriers of the methionine allele, and were the most sensitive to cannabis-induced psychotic experiences. Further research — including the use of both animal and imaging paradigms — is needed to provide a fuller understanding of genetically moderated responses to cannabis⁹⁹.



a causal role for the amygdala in depression, or a consequence of depression on the amygdala. However, if such amygdala activation depends on the subjects' genotype, this suggests that amygdala activation has precedence. Such precedence is not sufficient for causation, but it is necessary.

Second, awareness of gene-environment interactions can help to reveal stronger effects

in neuroscience data. Neuroscience variables are generally responsive to environmental input. If responsiveness is under the influence of hidden genetic variation within a research sample, this unmeasured heterogeneity will dilute findings. Returning to the prior example, amygdala activation to an emotional stimulus can appear positive but weak across all subjects in an experiment, as the result

of unwittingly averaging data from two genotype groups, one of strong responders and another of non-responders. If genetically vulnerable subgroups can be identified for analysis, modest associations may be revealed as stronger than previously thought.

Third, gene-environment interactions might help to solve the perennial riddle of disorder-specific pathophysiology. Most environmental pathogens constitute a nonspecific risk for many disorders. For example, smoking influences cancer, osteoporosis, lung disease, heart disease and fetal growth; child maltreatment influences both aggression and depression; birth complications influence both ADHD and schizophrenia. A potential explanation for why there are different outcomes from one environmental pathogen is that the pathogen is connected to each disorder through a different pathophysiological pathway; there is little research into this, although genes of known functionality may offer clues.

Furthering gene-environment research

Psychiatric genetics has earned an ignoble reputation for its methodological problems, but this reputation should not discourage neuroscientists from bringing genetics into their laboratories to study the genetic moderation of environmental pathogens' effects on neural substrates. Many initial reports of gene-to-disorder associations proved to be false positives⁵, prompting the publication of methodological warnings⁵⁸⁻⁶⁰. However, most of the methodological problems arise from the fact that genetic epidemiology is an observational discipline that measures genotypes, environmental risk conditions and disorder outcomes as they naturally occur. This observational method involves several compromises to validity, but the same problems do not afflict the experimental method. Therefore, experimental neuroscience paradigms will benefit gene-environment interaction research by addressing some of the methodological concerns that are now plaguing genetic epidemiology, as explained below.

First, there is concern about the need for very large samples in genetics research⁶¹. In case-control studies, large samples are needed because genetic effects are expected to be very small. In cohort studies, small effects are also a concern, and there is the added need for large samples due to the fact that the environmental exposure and/or the disorder might have a low prevalence in cohorts³³. By contrast, experimental studies have more control over the group sizes and intensity of environmental stimulus needed

to obtain a detectable effect⁶². Moreover, unlike mental disorders, neural substrate outcome measures (such as emotional arousal or adrenocorticotrophic hormone responses) tend to be quantitatively distributed such that low prevalence is not at issue.

Second, there is concern about gene–environment correlation^{63,64}. When genes influence the probability of subjects' exposure to an environmental pathogen, this results in the contamination of measures of environmental exposure with genetic variation, thereby clouding interpretation of the findings. For example, the probability of experiencing certain stressful life events is known to be under partial genetic influence, as is the tendency to expose oneself to environmental pathogens such as cannabis or tobacco. By contrast, experimental random assignment of subjects to the environmental risk condition rules out this type of self-selection. For example, epidemiologists study self-initiated cigarette smoking, while neuroscientists can study participants that are randomly assigned to nicotine exposure.

Third, there is concern about the difficulty of achieving precise and reliable measures of environmental exposure, particularly if the exposure typically occurs over extended periods of the life course^{8,65}. For example, it is very difficult to ascertain the frequency, timing and extent of the trauma that is entailed in stressful life events. Likewise, it is notoriously difficult, using survey methods, to measure the amount of active drug that is ingested during recreational cannabis use over many years. Experimental administration of the environmental pathogen or stimulus with standardized dosage and timing rules out this concern.

Fourth, there is concern about the low prior probability of a true association between a disorder and any one among many thousands of genetic polymorphisms⁶⁶. If little or nothing is known prior to a statistical test of association between a gene and behaviour, then this results in a low prior probability of the hoped-for association, and any association uncovered could easily be a chance false positive result. Neuroscience research enhances the prior probability of a candidate gene being associated with disorder by connecting that genotype with brain responsiveness to a known environmental cause of the disorder. Thus, a key contribution from experimental neuroscience is evidence and theory that supports the biological plausibility of genetic hypotheses, which helps to prevent false positives. Consider research in cognate medical fields, where caffeine consumption has been linked to the risk of myocardial

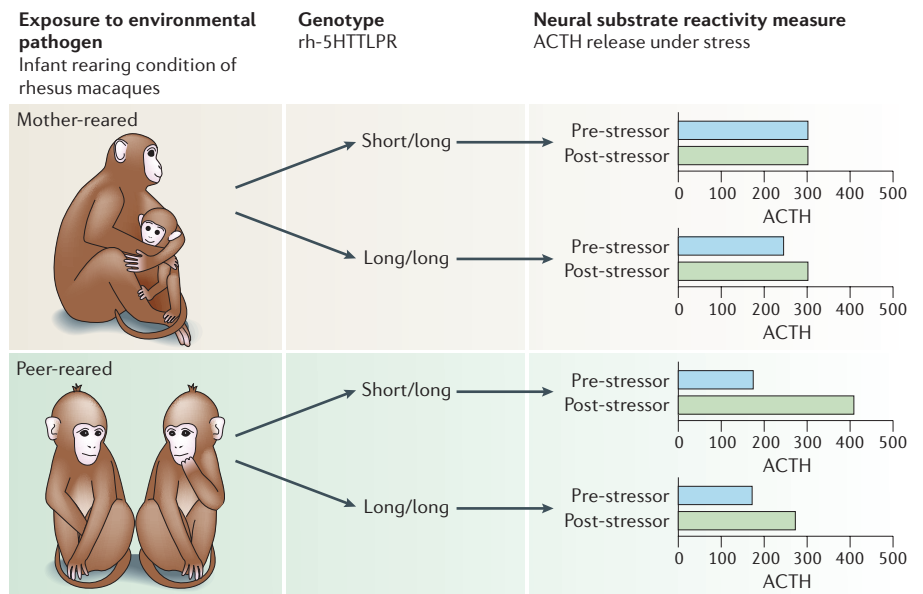


Figure 3 | Exposure to adverse rearing, genotype and adrenocorticotropin hormone (ACTH) levels. Influence of exposure to early stress (peer rearing) on subsequent exaggerated responses of the limbic-hypothalamic-pituitary-adrenal axis (LHPA) responses to stress is conditioned by serotonin transporter gene promoter variation (rh-5HTTLPR) in rhesus macaques. When exposed to stress later in life, peer-reared animals with the short/long genotype had higher ACTH levels than animals with the long/long genotype. There were no differences between genotypes among animals reared with their mothers (data from REF. 105).

infarction. Caffeine is metabolized by an enzyme (CYP1A2) in the liver, knowledge that allowed researchers to test (and confirm) the hypothesis that carriers of the slow metabolizer variant of the *CYP1A2* gene are at a heightened risk of myocardial infarction⁶⁷. As researchers learn more about genes, the brain and environmental pathogens, the prior probability of hypotheses will become stronger, and false positive gene findings fewer.

One caveat must be mentioned. Experiments that randomly assign subjects to environmental pathogens will inevitably be limited to using substitutes analogous to the environmental pathogens that cause mental disorders. Real environmental pathogens are not amenable to experimental administration for three reasons: first, ethics prohibit exposing humans to risk; second, animal-model exposures cannot be equated with human exposures; and third, harm from naturally occurring environmental pathogens often accumulates for months or years longer than a laboratory experiment. These shortcomings of experimental gene–environment interaction studies must be acknowledged. However, the shortcomings are diminished where a chain of inference can link experimental findings involving an analogue pathogen to epidemiological findings involving its counterpart natural environmental pathogen.

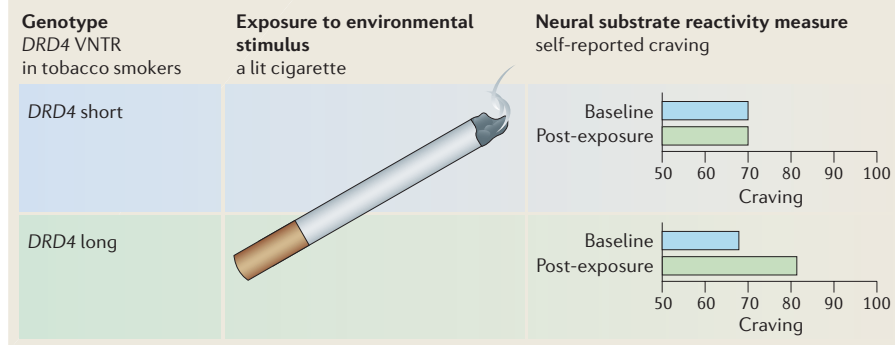
Towards a nomological network

A nomological network refers to the interlocking system of laws — the predicted pattern of theoretical relationships — which define a construct⁶⁸. A chain of inferences is required to validate the claim that specific gene–environment interactions are surrounded by a nomological network of individual supporting findings. In mental health research, such an emerging nomological network is illustrated by many approaches that are used to understand the role of *5-HTT* gene variation in emotion regulation and emotional disorders^{69,70}. We hope that the present article will encourage further collaboration between genetic epidemiology and experimental neuroscience in a joint effort to unravel the complex mechanisms that underlie gene–environment interactions. We envisage six ways forward.

First, animal models of environmental pathogen exposure are needed (FIG. 3). In non-human animals, both genotype and exposure to a pathogen can be manipulated under experimental control^{71,72}. Studying non-human subjects is an advantage because they can be assigned to detrimental conditions that are not permitted in human studies (for example, deprivation of maternal rearing). These experiments use different strains, genetically modified animals or animals that have known human-relevant

Box 2 | Bringing genetics into experimental psychopathology

The use of experimental models in behavioural genomics is exemplified by research on substance-use disorders. Rather than search for direct main-effect associations between candidate genes and addiction, this research uses experimental paradigms to identify how genotype moderates subjects' reactions to environmental stimuli (such as to priming doses or drug cues) that are associated with addictive substances. In one experiment, the researchers investigated whether a functional variable number of tandem repeats (VNTR) polymorphism in the D4 dopamine receptor gene (*DRD4*) affected craving after priming doses and drug cues. Participants were tested on two occasions, randomly assigned to receive three alcoholic drinks on the first session and three control drinks on the second session, or the reverse. Individuals carrying the *DRD4* long (L) allele reported a stronger urge to drink in the alcohol condition than in the placebo condition. By contrast, individuals with two short *DRD4* alleles (S) reported no differences in the urge to drink between the two conditions¹⁰⁰. Next, the investigators manipulated the putative pharmacological mechanism that mediates the effect of *DRD4* on craving. It was suggested that alcohol increases craving through activation at the D4 receptor and that carriers of the *DRD4**L allele are especially vulnerable to this effect. Subjects classified as *DRD4**L or *DRD4**S were administered olanzapine (a D4 antagonist that was proposed to block the ability of alcohol to trigger craving) or cyproheptadine (a control medication) prior to the alcohol-challenge study. Olanzapine was more effective for *DRD4**L subjects, helping to narrow the mediating mechanism involved in genetic control of sensitivity to the environment^{101,102}. These findings suggest that the *DRD4* polymorphism moderates craving after alcohol consumption, and indicate that *DRD4**L individuals may be more susceptible to losing control over drinking. But the *DRD4* polymorphism is not simply a genetic risk for alcohol abuse. Individuals carrying the L allele also experience more craving and arousal after exposure to tobacco smoking cues, whereas *DRD4**S individuals do not (data for the panel are from REF. 103). This suggests that *DRD4* may influence the incentive salience of appetitive stimuli more generally, and offers a clue as to why different addictive disorders tend to co-occur in the same individuals¹⁰⁴.



polymorphisms. The experiments measure responsiveness through various physiological and behavioural phenotypes. We emphasize the value of animal models of environmental pathogen reactivity, rather than animal models of mental disorders. Animal models of mental disorders have been criticized because they cannot represent core cognitive symptoms of human mental disorders⁷³. By contrast, animal models of genetic susceptibility to environmental pathogens offer a valuable window for understanding the effects of pathogen exposure on disease processes^{74–76}.

Second, studies that compare human genotype groups on their responses to experimentally administered environmental stimuli are needed. In the vanguard of such research is imaging genomics, which compares the responses of genotype groups using functional neuroimaging measures^{77–80}. There is untapped potential in other

experimental psychopathology paradigms. We look towards a new wave of investigations asking whether genotype influences humans' responsiveness to emotion-eliciting stimuli, laboratory stress paradigms or other analogue environmental pathogens. These human gene–environment experiments will use neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, emotional or neuropsychological measures as phenotypes. Likely examples might include peripheral psychophysiological measures such as the electroencephalogram, electrodermal or heart rate reactivity^{81–83} and adreno-cortical reactivity⁸⁴ (see also BOX 2).

Third, more epidemiological cohort studies should collect neuroscience measurements. Many ongoing cohort studies are now adding DNA to their data collection protocols. These longstanding cohort studies already have prospective longitudinal histories of participants' environ-

mental exposures and mental disorders that make them ideal for gene–environment interaction research, if their participants' genotypes are characterized⁸. New cohort studies of gene–environment interactions are also being planned^{85,86}. To the extent that these studies incorporate neuroscience measures of individual differences (for example, neuropsychological tests, heart rate reactivity and immune-system markers), they will create opportunities to integrate experimental and epidemiological findings. Taking neuroscience measurements in large cohorts can be costly and, for functional imaging paradigms, prohibitive. However, with more measures in common, epidemiological findings about genetically moderated environment-to-disorder associations can be integrated with experimental findings about genetically moderated environment-to-brain associations (FIG. 1d).

Fourth, the characterization of subjects' genetic vulnerability as opposed to their resilience needs to move beyond single genetic polymorphisms. New approaches will use information about biological pathways to identify gene systems and study sets of genetic polymorphisms that are active in the pathophysiology of a disorder⁸⁷. For example, in relation to depression, information about the biology of psycho-social stress^{88–90} can be used as a first step to characterize a set of genes that define a genotype that is vulnerable as opposed to resilient to stressful life events. Incorporating information about genetic pathways into gene–environment interaction studies will enhance explanatory power, but it will also present unique statistical challenges related to the use of data-mining tools and the pooling of data across different studies³³.

Fifth, although we have largely focused on testing hypotheses about gene–environment interactions using candidate genes, the gene–environment interaction approach might also aid the identification of new genes that are responsible for vulnerability to a particular disease. Genome-wide scans for new disease genes, like most designs in psychiatric genetics, aim to discover genes that have direct main effects on disease susceptibility⁹¹. However, this main-effects approach is inefficient for detecting new genes whose effects are conditional on environmental risk. As a result, genes that show no direct connection to disorders in genome-wide scans may nevertheless be connected to disorder through hidden gene–environment interactions. Genome-wide scans might be more powerful if 'gene hunters' recruit samples selected for known exposure to an environmental pathogen for

the disorder they wish to study, and then scan for genetic variants in subjects who have, versus those who have not, developed the disorder⁸. Known environmental pathogens might be profitably exploited as research tools for gene hunting.

Sixth, any serious initiative to understand aetiology and inform prevention, including genetics, must be able to explain fundamental demographic patterns of disorder. The most solid facts we have about most mental disorders are that prevalence and incidence vary according to age and sex. There are two leading contenders for explaining these differences⁹². First, the demographic groups (such as males and females) could be equally vulnerable to causal factors, but differentially exposed to them. Alternatively, the demographic groups could be equally exposed to causal factors, but differentially vulnerable to them. To date, lacking a good empirical handle on biological vulnerability, research has made little progress towards understanding age and sex differences in mental disorders. Gene–environment interaction research, with its focus on hypotheses of environmental exposure and biological vulnerability, is ideally suited to investigate age and sex differences.

Mental disorders have well-documented environmental causes. But why do some people who are exposed to an environmental pathogen develop mental disorders, while others do not? Why do some disorders excessively afflict one sex or one age group? How can two people experiencing the same environmental pathogen later develop very different disorders? How does an environmental pathogen, especially one that is psycho-social in its nature, get under the skin to alter the nervous system and generate mental disorders? All of these important questions are questions about the interaction between diathesis and stress, between host and pathogen and, in essence, between genotype and environment. Neuroscience and gene–environment interaction research are joining forces to look for answers.

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