Gene–environment interactions in humans across multiple units of analyses: A focus on psychopathology and imaging

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Abstract:

The present chapter examines four overarching topics: theoretical models undergirding G×E research, a brief history of G×E and its controversies, the current state of G×E research and emerging approaches, and future directions. We give particular attention to how G×E research examines an array of outcomes in order to inform not only associations of genetic differences with diagnoses, but also their mechanisms. Within the field of psychopathology, G×E research examines proximal outcomes (physiological variables) and distal outcomes (affect, symptoms, and diagnoses) in an effort to inform a nomological network across multiple units of analysis. Among the most compelling of these intermediate outcomes have been physiological variables that cannot readily be biased by research participants— neuroendocrine responses to lab- induced stress and patterns of brain activity in functional magnetic resonance imaging.

Within this framework, we focus on the candidate- gene perspective (testing a priori hypotheses about specific genetic differences) as opposed to the genome- wide association perspective (examining genetic differences throughout the genome in case- control comparisons without specific hypotheses). Similarly, we focus on G×E interactions in most cases, except when research on the main effects of genetic variables is particularly informative.

Keywords: gene-environment interactions | psychopathology

Article:

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Chapter 3

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3.1 Introduction

Imagine two hypothetical children—Casey and Sam—who both experience early emotional abuse. But as they develop, Casey shows resilience and goes on to thrive, while Sam struggles under this burden, and experiences depression in a downward spiral that may even plague her life course.

Understanding this variability in responding to circumstances across the lifespan has captured the attention of psychopathology researchers, the press, and the public alike. In an era of advancing molecular genetic sophistication, this attention has led to a singular question: Can we identify common genetic differences that aid in predicting how people will respond to their circumstances?

Such is the question at the heart of gene–environment interaction (G×E) research in psychopathology. G×Es characterize how genetic differences influence how people respond to environmental conditions, or vice versa. Measured G×E research capitalizes on behavioral genetic research showing that genetic factors contribute at least moderately to psychopathology, and lends specificity by identifying the individual common genetic variations involved.

The present chapter examines four overarching topics: theoretical models undergirding G×E research, a brief history of G×E and its controversies, the current state of G×E research and emerging approaches, and future directions. We give particular attention to how G×E research examines an array of outcomes in order to inform not only associations of genetic differences with diagnoses, but also their mechanisms. Within the field of psychopathology, G×E research examines proximal outcomes (physiological variables) and distal outcomes (affect, symptoms, and diagnoses) in an effort to inform a nomological network across multiple units of analysis. Among the most compelling of these intermediate outcomes have been physiological variables that cannot readily be biased by research participants—neuroendocrine responses to lab-induced stress and patterns of brain activity in functional magnetic resonance imaging.

Within this framework, we focus on the candidate-gene perspective (testing a priori hypotheses about specific genetic differences) as opposed to the genome-wide association perspective (examining genetic differences throughout the genome in case-control comparisons without specific hypotheses). Similarly, we focus on G×E interactions in most cases, except when research on the main effects of genetic variables is particularly informative.

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Ultimately, the hope of G×E research in psychopathology is to use identified genetic risk factors to ameliorate suffering in a number of ways. We may one day be able to screen individuals and identify circumstances placing them at elevated risk, shunting individuals such as "Sam" in our opening example toward preventive interventions before pathology takes hold. Similarly, we may also improve our understanding of how genetic factors enable individuals to benefit more robustly than their peers from *positive* environments. But perhaps the greatest hope is that learning about the genetic risk factors and what environments trigger their actions will shed light on the full etiology of both disorders and positive developmental outcomes and lead to markedly enhanced interventions.

3.2 Gene–environment interaction: Theoretical models

Complex behavioral and health phenomena rarely boil down to the direct influence of individual genes (1), hindering the discovery of genes "responsible" for pathology. In light of this, two primary theoretical models are key for contemplating the role of genes in mental health and beyond.

Vulnerability-stress or *diathesis-stress models* suggest a latent biological vulnerability to psychopathology that is activated by a particular trigger or "stressor" (for a review, see 2). In this view, biological vulnerability is necessary but not sufficient to develop psychopathology. For example, although depression is often precipitated by a stressful life event (e.g. 3), if biological vulnerability to depression (e.g. genetic risk) is not present, depression is unlikely to develop despite that stress. Similarly, one may possess biological vulnerability but experience minimal stress, making it unlikely that one would develop depression.

An offshoot of the vulnerability-stress model is the *differential susceptibility model*, which proposes that one's genetic makeup may heighten sensitivity to both good and bad aspects of environmental influences, leading to both heightened positive and heightened negative outcomes (4). Accordingly, if an individual possesses genetic "risk" for psychopathology in the face of adverse life circumstances, in an enriching, positive environment, the same individual may flourish more than their counterparts. Although both diathesis-stress and differential susceptibility models predict interactive G×E effects (i.e. moderation), they differ in the precise form the interaction takes, as well as their implications for measurement of the environment and phenotypes (Figure 3.1).

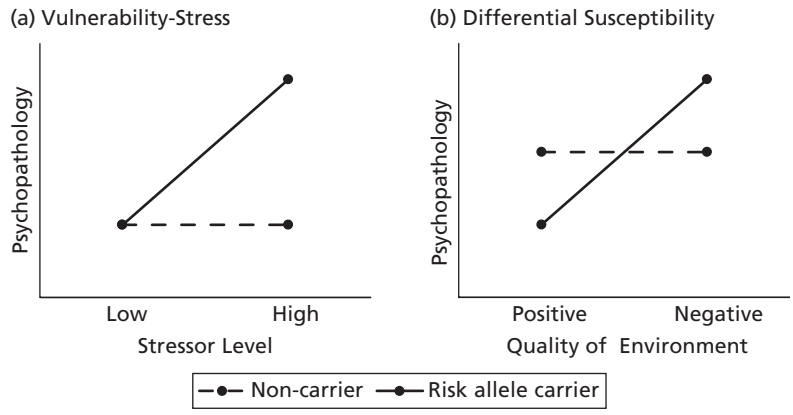

Figure 3.1 (a) Shows vulnerability-stress models in which a risk allele moderates the effect of stressful life events on risk for psychopathology. (b) Shows differential susceptibility models in which genotype differentially affects the outcome dependent on type of environment.

3.3 Brief history of gene–environment interaction and controversies

A handful of essential studies launched the field of measured G×E research. Caspi and colleagues (5) found that a polymorphism in gene encoding the monoamine oxidase A enzyme (MAOA)—relevant in metabolizing monoamines such as norepinephrine, serotonin, and dopamine—moderated the relationship between early childhood maltreatment and antisocial behavior in males. Also, in a report exploring the association between cannabis use and later development of schizophrenia, Caspi and colleagues (6) found that valine (Val) allele carriers of a polymorphism located in the catechol-*O*-methyltransferase (COMT) gene—critical in catabolizing catecholamines—were more susceptible to symptoms of psychosis as a function of their cannabis use than those homozygous for the methionine (Met) allele.

But perhaps the most influential, if controversial, of these early studies, was a report that carriers of the less transcriptionally efficient short ("S") allele for a functional polymorphism, 5-HTTLPR, in the serotonin transporter gene promoter were more susceptible to depression symptoms, diagnoses, and suicidal ideation after stressful life experiences than were long allele ("L") homozygotes (67). An earlier study on the 5-HTTLPR polymorphism also revealed that S-carriers also exhibited greater amygdala reactivity to fearful stimuli versus fixation in an fMRI paradigm, as compared to their L/L counterparts, providing an intermediate pathway by which the S-allele may heighten risk for psychopathology (7). Research into the 5-HTTLPR polymorphism, while captivating researchers and lay-people alike, has been deeply controversial. Conflicting meta-analyses add to the controversy (Table 3.1). Taken together, meta-analyses with fewer papers have generally drawn negative conclusions, while more inclusive meta-analyses have drawn positive conclusions. Regarding the status of G×E research broadly, we provide a comprehensive table of the findings of meta-analyses of G×E investigations in mental and physical health outcomes (Table 3.1).

Table 3.1. Extant G×E meta-analyses in mental and physical health

Citation	Genetic Target	# Studies Examined	Environmental Target and Key Moderators	Summary of Conclusions
Risch et al., 2009 (58)	Serotonin Transporter Gene (5HTTLPR)	14	Ordinal scale of stressful life events	No main effect or G×E effect of 5HTTLPR on depression
Munafò et al., 2009 (59)	Serotonin Transporter Gene (5HTTLPR)	5	Stressful life events dichotomized into absence or presence	No evidence that 5HTTLPR is associated with depression independent of or in interaction with life stress
Karg et al., 2011 (60)	Serotonin Transporter Gene (5HTTLPR)	54	Stressors by type and assessment method by type	Support for a 5HTTLPR G×E effect on depression. More robust associations for interview & objective stress assessments
Sharpley et al., 2014 (61)	Serotonin Transporter Gene (5HTTLPR)	81	Stressors by type and assessment method	Support for a 5HTTLPR G×E effect on depression. More robust associations for interview and objective stress assessments

Table 3.1. Continued

Citation	Genetic Target	# Studies Examined	Environmental Target and Key Moderators	Summary of Conclusions
van Ijzendoorn et al., 2012 (62)	Serotonin Transporter Gene (5HTTLPR)	30	Negative vs positive environments	Partial support for differential susceptibilityhypothesis. S-carriers showed more negative outcomes in adverse environments, and in primarily Caucasian samples, S-carriers also showed *better* outcomes in positive environments.
Kim-Cohen et al., 2006 (63)	Monoamine Oxidase-A (MAOA)	5	Physical abuse	In males, low activity MAOA associated with antisocial behaviors when preceded by early adversity.
Byrd & Manuck, 2014 (64)	Monamine Oxidase-A (MAOA)	27	Maltreatment or other childhood adversities	In males, low activity genotype associated with antisocial behaviors following early adversity. In females, no overall relationship but opposite effect with high activity genotype linked with antisocial behavior following early adversity
Marcus et al., 2000 (65)	*N*-acetyltransferase 2 (NAT2)	16	Tobacco Use	Slow acetylators show a stronger relationship between cigarette smoking and bladder cancer risk than fast acetylators
Zeiger et al., 2005 (66)	*Taq1,* Transforming Growth Factor α	5	Maternal cigarette smoking	Association of maternal smoking with cleft palate stronger in C2-carriers. No effect for cleft lip.

Note: Meta-analyses focused on main effects of genetic variants rather than interactions, such as main effects of variants found in catechol-*O*-methyl transferase and FKPB5, are not included here.

3.4 Current approaches in psychopathology G×E research

In the roughly 15 years since the first publication of a measured G×E effect in humans, there have been significant advancements in G×E research. Among these advancements are giving greater theoretical consideration to the selection of environment, to development, to bidirectional relationships between stress and depression (i.e. stress generation), and to additive genetic risk.

3.4.1 Interaction with what environment?

In a scathing review of 5-HTTLPR G×E depression research, life stress experts Monroe and Reid (8) decried the relative lack of care devoted to measuring life stress in studies of the

5-HTTLPR G×E interaction. In particular, they note the well-known poor validity of commonly used life event checklists, as well as the confounding of the predicted outcome with the participant's perception of life stress. As in other papers focused on methodological recommendations for the measurement of recent life stress (e.g. 9), they recommend using objective life stress interviews. They advocate the view that it is important to conceptualize stress as in the definition derived from physics—of pressure pushing down on an organism—rather than stress as defined in the Selye tradition, where stress represents the organism's response to that pressure. Defining stress as the organism's response to adversity confounds stress with its outcome, risk for psychopathology.

Beyond improving the quality of measurement, we take the perspective that G×E research can benefit from devoting as much care to selecting the "candidate environment" as most give to selecting candidate genes. For example, Vrshek-Schallhorn and colleagues (10) showed in two samples of emerging adults studied with repeated diagnostic and life stress interviews for five years, that interpersonal chronic and major episodic stress consistently uniquely predicted depressive episode onsets over and above non-interpersonal chronic and episodic stress. Moreover, the particular stressor mattered in a related G×E investigation: interpersonal major stressful life events and one form of chronic interpersonal stress (in family relationships) interacted with 5-HTTLPR genotype to predict major depressive episode onsets as hypothesized, while other forms of stress did not (11). We would never expect the same environment that elicits depression necessarily also to elicit schizophrenia, diabetes, or cancer, but we must apply the same scrutiny to our assumptions within disorders to boost effect sizes and power for G×E effects, as well as to clarify explanatory models.

3.4.2 Importance of developmental considerations.

Recent work also highlights the need for developmentally sensitive research designs in G×E endeavors. Evidence supports changes across development in all aspects of G×E effects: the amount and nature of genetic contributions to risk, the salience of particular stressors, and the manifestation of the outcome of interest.

First, a meta-analysis focused on behavioral genetic studies of adolescence and young adulthood demonstrated that levels of heritability (i.e. studied as main effects without considering G×E interactions) significantly increase between approximately age 10 and age 25 for externalizing behaviors (acting out) and internalizing (anxious, depressive) behaviors, but stay roughly static for attention-deficit hyperactive disorder (12). Furthermore, not only does level of heritability vary, but the genetic variants that contribute to these aggregate estimations also change. Using a developmental twin design and latent variable modeling, Kendler, Gardner, and Lichtenstein (13) provided evidence for a common genetic factor that contributes to symptoms of anxiety and depression, in an attenuating fashion from pre-adolescence through early adulthood. Further, during early adolescence, late adolescence, and early adulthood, new sets of risk genes began contributing at each stage—although *which* genes come online or attenuate in their contribution to risk is as yet untested. Few studies consider how specific molecular genetic risk factors vary in their contributions to psychological functioning across development, an area to which we ought to devote increased attention as we cultivate larger samples spanning developmentally sensitive periods.

Second, there is also evidence that the salience of potential stressors changes over development. For example, in a G×E investigation, romantic involvement at age 15 predicted concurrent depression symptoms, but the same was not true at age 20, when romantic involvement is more developmentally normative (14). In this investigation, romantic involvement at age 15 interacted with 5-HTTLPR genotype to predict age-20 depression symptoms. Future efforts ought to probe

the developmental salience of stressors further in order to tailor the "candidate environment" in a better way.

Third, appropriate outcomes to measure vary over the course of development. For example, one G×E study predicted diagnoses of depression in older adolescents but focused on prediction of the severity of peak *symptom* onsets in early adolescent girls when full onsets are too rare to detect with sufficient power (15). Thus as predicted, Hankin and colleagues (16) showed that *late* adolescents demonstrated a significantly stronger G×E effect 5-HTTLPR with peer stress (lack of a supportive social circle) on depression diagnoses (broadly defined to include minor depressive episodes) than did *early* adolescents.

Finally, evidence of G×E effects across the developmental spectrum strengthens arguments for the influence of particular genes on a given outcome. In an example outside of psychopathology, additive risk from a collection of genetic variants identified through genome-wide association studies for obesity predicted greater weight gain in infancy, faster and higher adiposity rebound in childhood, and chronic obesity during adulthood (17). Similarly, an additive genetic risk variable developed from meta-analyses of nicotine dependence did not predict trying nicotine, but did predict converting to smoking daily in the teen years, more rapid progression to and longer duration of heavy smoking, and greater failure rates when attempting to quit, among other outcomes (18). Ultimately, if G×E research is to realize its full potential, it must be mindful of developmental considerations.

3.4.3 Polygenic approaches to genetic and G×E research

An exciting new direction for G×E research in psychopathology grew from the evidence supporting behavioral genetic assumptions: many common genetic variants each contribute small amounts of risk for pathology, and act together in an additive rather than multiplicative fashion to increase risk (19, 20).[1] Interest in additive genetic risk has led to the development of polygenic, additive risk variables. These are known by several names including polygenic risk scores and multilocus genetic risk profile scores (including biologically informed multilocus profile scores). All comprise either weighted or unweighted total numbers or proportions of "risk" alleles across multiple polymorphisms.

Genetic main effects research has examined these with respect to a wide array of outcomes spanning physical and mental health including obesity (17), nicotine dependence (18), as discussed at section 3.4.2, ventral-striatal neural reactivity to reward (21), high cholesterol levels (22), childhood intelligence (23), and intellectual and economic outcomes across development (24), among others. Many such reports draw on empirically indicated candidates from genome-wide association studies for their additive genetic risk variables, but others draw on theoretically or biologically indicated candidate genetic variants. For example, Nikolova and colleagues (21) developed their biologically informed dopaminergic multilocus risk profile score using five putatively functional polymorphisms from the DA system, which collectively account for almost 11% of variance in between-person ventral striatal fMRI reward-related activity.

[1] It merits noting that beyond additive effects of common variants, there is evidence for minor multiplicative effects (52, 53) leading to investigations in gene-gene interactions (54, 55). Further, for some mental health conditions with especially large genetic contributions, such as schizophrenia and autism spectrum disorder, there is also evidence for supporting contributions from rare genetic variants idiosyncratic to particular families (56), as well as contributions from de novo mutations (57).

Polygenic approaches are also being applied in G×E investigations. In the first application of polygenic risk in a G×E, Pagliaccio and colleagues (25) showed that additive risk from ten SNPs located in four stress-relevant genes (*CRHR1, NR3C2, NR3C1*, and *FKBP5*) predicted greater cortisol levels under lab stress, and interacted with early-life adversity to predict left hippocampal and amygdala volumes. In the first to apply this approach to diagnoses of psychopathology in a G×E test, Salvatore and colleagues (50) used a genome-wide polygenic score for externalizing disorders derived from an adult sample. This polygenic score significantly interacted with two risk factors for adolescent externalizing disorders (high peer substance use and low parental monitoring) to predict externalizing disorders in a separate sample of adolescents. Further, a novel serotonergic multilocus profile score from four functional SNPs and one meta-analytically indicated SNP, interacted with recent major interpersonal stressful events to predict major depressive episode onsets in emerging adults, and in a replication sample, interacted with recent interpersonal stress severity to predict peak past-year onsets of depressive symptoms in adolescent girls (15). Of note, in this report, higher numbers of so-called risk alleles both significantly increased risk for elevated depression symptoms under more stressful conditions, but protected *against* symptoms under less stressful conditions, consistent with differential susceptibility theoretical models (4).

3.4.4 Stress generation in G×E research

While diathesis-stress models in which stress precedes negative outcomes have received much attention, *stress generation* is also key to understanding and testing G×E effects. The stress generation model posits that individuals with depression (or in some studies, risk for depression) actively generate stress for themselves through their cognitive styles, attachment styles, traits, and behaviors (26, 27). According to this conceptualization, these individuals experience a greater number of dependent (i.e. self-induced) life stressors than their counterparts (26). Importantly, diathesis-stress and stress generation models are not mutually exclusive, and can be conceptualized in a bidirectional or transactional model (see Figure 3.2) whereby stress influences the development of depression, and depressive symptoms or characteristics generate greater number of stressors, perpetuating the cycle of depression.

The genetic underpinnings of stress generation have been explored in two studies of the 5-HTTLPR polymorphism, finding that S-carriers had a stronger relationship between depression at age 15 and dependent and interpersonal stressful life events at age 20 (28). Additionally, S-carriers experiencing low relational security at age 15 experienced more stressful life events at age 20. However, S-carriers experiencing high relational security at age 15 experienced *fewer* stressful life events at age 20 than their L/L counterparts (29), consistent with a differential susceptibility model.

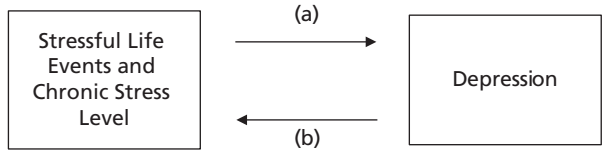

Figure 3.2

Note: Bidirectional/transactional model of stress and depression where path (a) shows stress increasing risk for depression, and path (b) shows stress generation whereby depression or depressogenic characteristics increases number of stressful life events or level of chronic stress.

3.5 Historical and current fMRI genetics

An emerging subfield examines G×E effects on neurobiological processes implicated in psychiatric disorders. Although this subfield encompasses diverse methodological paradigms, all seek to further our understanding of the transdiagnostic mechanisms that contribute to maladaptive behavior, from gene to cell to brain to behavior. Two particularly exciting paradigms within this subfield are imaging genetics (30), and imaging G×E (iGxE; 31), which use neuroimaging techniques to examine the influence of genetic main effects and G×E interactions respectively on neural features. Here we briefly review imaging genetics and iG×E studies involving 5-HTTLPR, as well as some methodological concerns specific to iG×E research. This section is not a comprehensive review of imaging genetics or iG×E studies broadly (for such a review, see 32), or even neuroimaging studies involving 5-HTTLPR specifically. Rather, it seeks succinctly to provide examples of how these methodological paradigms have been used to explore biological mechanisms linking genetic variants to maladaptive behaviors.

3.5.1 5-HTTLPR and imaging genetics

Given the plethora of research investigating behavioral effects of the 5-HTTLPR polymorphism, it is not surprising that this polymorphism has also been the focus of numerous imaging genetics and iG×E studies. Much research on 5-HTTLPR has focused on its effect on the amygdala (33), which exhibits markedly increased activity in response to threatening stimuli (34). For example, as noted in section 3.3, one of the earliest imaging genetics study found that S-carriers exhibited increased amygdala reactivity to angry and fearful faces relative to L/L individuals, and proposed that this mechanism may mediate the association between the 5-HTTLPR polymorphism and symptoms of psychopathology (7). Since the publication of this study, several other groups have replicated this finding (e.g. 35), and a meta-analysis indicated that 5-HTTLPR genotype accounts for up to 10% of the variance in amygdala reactivity to threatening stimuli (36). The 5-HTTLPR S-allele has also been associated with decreased grey matter volume in the amygdala and the perigenual anterior cingulate cortex (pACC), as well as decreased functional connectivity of these two regions, which was significantly associated with self-reported anxiety (37). Thus, it appears that an amygdala–pACC circuit may play an important role in internalizing symptoms, and may be affected by differences in serotonergic function conferred by 5-HTTLPR genotype (33).

3.5.2 5-HTTLPR in iG×E

Several iG×E studies have examined whether the 5-HTTLPR polymorphism interacts with life stress to differentially predict neural reactivity. For example, the first study to utilize the iG×E paradigm found that S-carriers exhibited increased resting amygdala and hippocampal activity in response to increasing levels of life stress, while L/L individuals exhibited decreased resting amygdala activity in response to increasing life stress (38). These researchers similarly found that S-carriers exhibited a significant positive association between rumination and life-stress, while L/L individuals exhibited the opposite pattern. These findings suggest that amygdala and hippocampal function may play an important role in linking 5-HTTLPR genotype and life stress to rumination, a critical risk factor for internalizing disorders (39). Additional studies have found that the short (S) allele is associated with greater increases in amygdala reactivity to fearful faces and amygdala–hypothalamus functional connectivity (40), as well as decreased hippocampal volume (41), in the context of greater life stress. Given evidence that stimulation of the amygdala elicits increased HPA activity, one interpretation of these findings is that the 5-HTTLPR S-allele might be associated with increased cortisol reactivity to threat (42) via its effects, in interaction with life stress, on the amygdala and amygdala–hypothalamus functional connectivity (40).

3.5.3 Methodological challenges for iG×E

Although iG×E paradigms have many unique benefits, they also present unique methodological challenges (for a review, see 31). First, although effect sizes in imaging genetics and imaging G×E studies are generally larger than those observed in G×E studies using diagnostic outcomes, they are still likely to be quite small (32, 43). Thus, the sample sizes required to obtain adequate statistical power can be very large: researchers have previously estimated that the analyses necessary to test mechanistic hypotheses in iG×E research require at least 500–1000 participants (31). Second, neuroimaging is expensive, compounding challenges caused by large sample size requirements. Third, participant recruitment for iG×E studies can be difficult. Participants must pass safety screenings for neuroimaging (e.g. many medical devices are barred), consent to both DNA analyses and neuroimaging, commit hours and often multiple visits to the lab, and disclose personal details to research staff during stress assessments. Fourth, as discussed in section 3.4.1), accumulating research suggests that interview measures more accurately assess life stress than checklist measures (8); however, these interviews are time and personnel intensive.

Because of these factors, iG×E research requires an enormous investment of resources on the part of research teams. However, these challenges are not insurmountable; several independent research teams have implemented iG×E paradigms in the past decade. Furthermore, an emerging zeitgeist of inter-institution collaboration and data pooling has resulted from acknowledgement of these challenges (32), and researchers who conduct iG×E research should strongly consider participating in such collaborations to obtain larger sample sizes and increase replicability. Last, recent theoretical advances such as the use of biologically informed multilocus profile scores in imaging genetics (e.g. 21) have resulted in increased statistical power (44), which may ameliorate these challenges.

3.6 Future directions

In addition to the emerging directions noted, we highlight four additional directions for future focus: transdiagnostic considerations, accounting for the role of culture, characterizing main effects of risky environments for less studied forms of psychopathology, and bolstering quality research practices.

3.6.1 Transdiagnostic G×E

Recently, funding agency priorities have fostered increased support for examining transdiagnostic dimensions (e.g. negative valence systems) across multiple units of analysis, ranging from genetics to neural activation to behavior (45). Such an approach acknowledges the need to "carve nature at its joints," and echoes many genetic researchers' longstanding interest in intermediate outcomes or "endophenotypes" (e.g. 46) that appear more proximal to biological (and thus genetic) functioning than more distal diagnoses of psychopathology. Future G×E research ought to increasingly apply such an approach to examining the impact of genetic variation not only on complex phenotypes such as neural activation, but also more mundane ones, such as affect in naturalistic settings, measured through experience sampling and daily diary methodologies. Evidence across a full spectrum of outcomes bolsters the nomological network for G×E effects.

3.6.2 Culturally-informed G×E

To date, G×E research has largely been conducted in high-income countries (68), with focus on individual variation at the expense of population-level characteristics including culture. We advocate a broader approach, accounting for the role of culture and its influence on psychopathological

processes. The relativist viewpoint suggests that cultural context shapes both biological and psychological development, and that this culturally driven variation in development influences experience of psychopathology; in accord, evidence suggests that large variation exists in risk and protective factors for psychopathology across cultures (47). For example, in an analysis of cross-national samples in 29 countries from 124 prior publications, 5-HTTLPR S-allele frequency was higher in countries with a collectivist rather than individualistic culture. S-carrier frequency predicted lower mood and anxiety disorder prevalence, and this association was mediated by collectivist tendencies (48). This discrepancy in risk for psychopathology, explained by cultural differences, highlights the importance of cross-cultural consideration when interpreting G×E research. Thus, we suggest G×E interaction research moves forward with particular attention to replication across various ethnic and cultural groups, while attending to population stratification concerns, with the goal of identifying cultural variation in risk and protective factors.

3.6.3 Future directions for environmental conceptualization

An important precursor to G×E research for many forms of psychopathology will be initially defining the environmental precipitant. Many forms of psychopathology lack research on specific types of environmental hazards contribute to disorder onsets. We know most about environmental contributors to depression (e.g. major stressful life events, chronic stress; 10), schizophrenia (e.g. perinatal complications, 49), and externalizing disorders (e.g. peer models and insufficient supervision, 50), but have only hints about provocateurs of the anxiety disorders, despite widely held diathesis-stress models for these conditions. Defining environmental risk factors is an essential step.

3.6.4 Future directions for research practices

G×E research must also heed criticism of tenuous research practices, including underpowered sample sizes (51) and analytic flexibility. As other research areas move toward more transparent research practices, G×E research ought to lead the way. Finally, we urge greater collaboration that may make large sample sizes possible while preserving use of rigorous environmental and outcome measures.

3.7 Conclusion

Taken together, although gene–environment interaction research in psychopathology is in its relative infancy as a scientific discipline (just over 15 years from the first reported molecular genetic G×E effects in humans) and faces numerous hurdles, it is also making exciting and rapid progress. Strengths of this area include cross-cutting findings which show the influence of various genetic factors across multiple levels of analysis, demonstrating a continuum of effects beginning with intermediate phenotypes or endophenotypes and ranging to full-blown psychopathology, characterizing a nomological network that builds confidence in findings. The challenges ahead for G×E psychopathology research will be to shift toward polygenic models, and to adopt cutting-edge measures and conceptualizations of the environment.

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