Review

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Understanding risk for psychopathology through imaging gene–environment interactions

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Examining the interplay of genes, experience and the brain is crucial to understanding psychopathology. We review the recent gene–environment interaction (G × E) and imaging genetics literature with the goal of developing models to bridge these approaches within single imaging gene–environment interaction (IG × E) studies. We explore challenges inherent in both G × E and imaging genetics and highlight studies that address these limitations. In specifying IG × E models, we examine statistical methods for combining these approaches, and explore plausible biological mechanisms (e.g. epigenetics) through which these conditional mechanisms can be understood. Finally, we discuss the potential contribution that IG × E studies can make to understanding psychopathology and developing more personalized and effective prevention and treatment.

Genes, experience and the brain

A burgeoning synergy of disciplines and technologies are providing unique insights into how the dynamic interplay between genes, brain and experience shapes individual risk for psychopathology. This interplay is being articulated at multiple levels of analysis from molecules to cells to neural circuits, from emotional responses to cognitive functions to personality, and from populations to families to individuals [1–4]. Here, we briefly review recent endeavors that highlight the potential value of such interdisciplinary research. We then provide perspectives on how existing approaches and methods could be leveraged further to advance understanding of the etiology, pathophysiology and, ultimately, treatment and prevention of psychopathology.

Gene–environment interaction (G × E) [5] and imaging genetics [6] studies have both been very useful approaches to studying psychopathology. G × E studies have emphasized the transactional nature of experience and the genome in the development of behavior, and imaging genetics studies have provided more proximal phenotypes and plausible mechanisms through which genes affect

Glossary

5-HTTLPR: serotonin (5-HT) transporter gene linked polymorphic region. The 5-HTTLPR is a variable number of tandem repeats polymorphism in the promoter region of the serotonin transporter gene. The serotonin transporter mediates active reuptake of synaptic serotonin and is thus crucial to regulating the duration and magnitude of serotonin signaling.
Candidate gene: a gene whose protein product suggests that it could be involved in a phenotype of interest or a construct relevant to the phenotype or a gene that has been linked to a phenotype through GWAS.
Epistasis: interaction between two or more polymorphisms so that the observed phenotype differs from what would be expected by either polymorphism independently.
Gene–environment correlation (rGE): occurs when exposure to environmental conditions is dependent on one's genotype. For example, the correlation between an 'environmental' risk factor such as harsh parenting and aggression could actually reflect a genetic pathway (mothers who are harsh could pass on genes to their children that increase the likelihood that they are aggressive).
Genetic polymorphism: a variation in DNA with a frequency of at least 1% in the population. Functional genetic polymorphisms could reflect changes in a single (or multiple) base pair that can affect subsequent transcription of a gene or the structure of the resulting translated protein.
Genome-wide association study (GWAS): an examination of genetic variation across the entire genome.
Heritability: extent to which individual genetic differences contribute to phenotypic individual differences. Statistically, heritability represents the relative contribution of 'genetics' as compared to 'environment' when conceptualized as independent forces in shaping behavior and thus is a measure of the reliability estimate of the passage of traits from parent to offspring [4].
Hidden heritability: variance accounted for in twin studies of phenotypes that is unaccounted for by molecular genetic studies.
Latent variables: mathematically inferred variables that represent the underlying commonality between directly measured variables. In practice, latent variables are variables that model the shared variance of similar predictor variables and thus decrease the error inherent in any one individual measure. For example, a measure of harsh parenting that includes observations of parenting, self-reports of parenting and reports of parenting by a significant other would more precisely model the underlying harsh parenting construct.
Minor allele: less common allele at a polymorphic locus.
Penetrance: likelihood that a genotype will result in a phenotype.
Statistical mediation/Indirect effects: occurs when the link between a predictor and dependent variable is dependent on the effects of the predictor variable on an intermediate variable. This intermediate variable could serve as the mechanism linking the independent and dependent variable. Similarly, indirect effects denote the extent to which the independent variable affects the dependent variable through the independent variable's effect on the mediator (and the mediator's effect on the dependent variable). Note that consistent with others [58], we use the terms mediation and indirect effects interchangeably in this paper and thus do not imply that direct effects must be present between independent and dependent variables in order to find indirect effects.
Statistical moderation: occurs when a 'moderator' variable affects the direction and/or strength of the relationship between a predictor variable and a dependent variable. A moderator variable is thus one that qualifies a relationship between two other variables. In other words, the relationship between variable *A* and *B* differs depending on the level of variable *C*.

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behavior. However, these approaches are not yet well integrated even though they have great potential to inform each other. In designing and carrying out studies that combine these methods, it is crucially important for researchers to address and understand challenges to progress inherent in each approach and to consider approaches that address these challenges. Moreover, in order to fruitfully combine these approaches, it is also important to consider statistical methods for analyzing these studies and to have an appreciation for biological mechanisms (e.g. epigenetics) through which genes and experience affect subsequent brain function and behavior. With careful consideration of all of these points, future research that combines G × E and imaging genetics approaches has the potential to greatly inform our understanding of psychopathology and delineate more personalized and successful prevention and interventions.

Gene-Environment Interactions

G × E occurs when the relationship between an environmental experience (e.g. exposure to toxins, trauma, stress) and the emergence of altered physiological or behavioral responses (e.g. compromised immune function, psychopathology) is contingent on individual differences in genetic make-up (i.e. genetic polymorphisms) (see Glossary) [5]. With G × E, the effect of an environmental experience on outcome is conditional on genetic background (i.e. genotype) or, conversely, the effect of individual genotype on behavior or health is conditional on an environmental experience (Figure 1). For example, in key early work, Caspi and colleagues demonstrated longitudinally that well-established links between life stress and subsequent depression were contingent on serotonin transporter linked polymorphic region (5-HTTLPR) genotype [7]. Specifically, individuals with the transcriptionally less efficient short allele (fewer transporter molecules available to remove serotonin from the synapse) had a strong and positive relationship between life stress and depressive phenotypes, whereas those with the long allele had little or no relationship between life stress and depression. These findings are supported by meta-analysis [8] and animal models [3], and a wealth of other G × E studies have demonstrated similar associations across other genes, environments and phenotypes; for example monoamine oxidase A (*MAOA*) genotype moderates the relationship between maltreatment and antisocial behavior [9], and catechol O-methyltransferase (*COMT*) genotype moderates the relationship between cannabis use and psychosis [10].

Theoretical reviews have revealed several key principles for conducting G × E research and evaluating resulting patterns [2,5]: researchers should consider the broad heritability of the target behavior, and then leverage knowledge generated in physiology and neuroscience to select polymorphisms in candidate genes that are of functional significance in the biological response to the environmental experience. Moreover, there should be evidence of variability in the response to the selected environmental experience, for which accurate measurement and, ideally, quantification should be available. Finally, there should be causal evidence linking the environmental experience with psychopathology.

Because this approach does not presuppose a large main effect of single genetic variants (or experiences) on behavior but rather emphasizes an interaction with experience, carefully conducted studies of G × E are instrumental in addressing issues of 'hidden heritability' (see glossary [11]), the generally weak penetrance of polymorphisms in candidate genes [11], and the lack of consistent replication in genetic association studies of psychopathology [2,12]. G × E research often represents a more plausible model of disease in which individual experiences and genetic make-up interact across development to influence relative risk rather than more simplistic models hypothesizing independent effects of particular genes or experiences.

Challenges to progress and possible advances in the field

Although G × E research has already advanced our understanding of the etiology of psychopathology, there are outstanding issues that deserve further consideration.

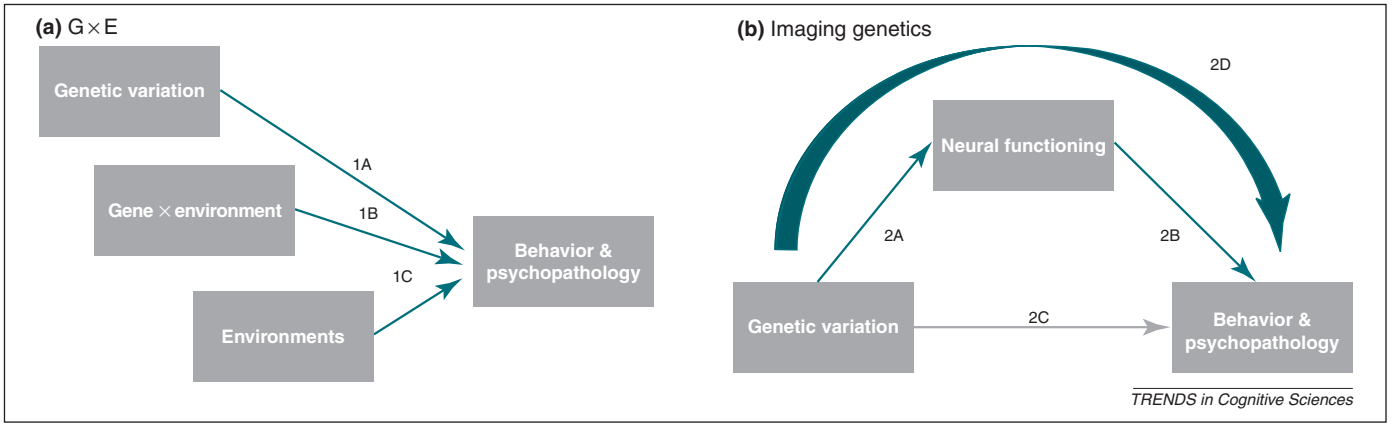

Figure 1. A conceptual and statistical diagram of G × E and imaging genetics studies. **(a)** G × E framework. Genes and environments might each have a 'main effect' on behavior (paths 1A and 1C) but the focus of these studies is on the interaction term which is modeled as a product of the two variables. **(b)** An ideal imaging genetics framework. Genetic variation in individuals leads to individual variability in neural functioning (path 2A), individual variability in neural functioning leads to differences in behavior or psychopathology (path 2B). Genetic variation might or might not have a direct impact on distal complex behavior (path 2C). Genetic variation has an indirect or mediated effect on behavior via its effect on neural functioning (arrow 2D: note that this path is not actually modeled statistically but is provided for conceptual clarity; this effect can be modeled as the product of the 2A and 2B paths).

First, it is unclear if G × E pertains only to harsh environments and undesirable outcomes [13]. Some authors have argued that 'crossover' effects (in which a specific polymorphism is disadvantageous in some environments but advantageous in others) suggest that some polymorphisms cannot be cast as simply conferring relative 'risk' but rather as shaping the range or 'plasticity' or 'differential susceptibility' to environmental triggers or contexts [14,15]. Although a 'plasticity' model is appealing, others have argued that the limited empirical data thus far suggest that the hypothesized 'plasticity' effects might not fall within a meaningful range of the data (i.e. actually observed in the real world) [16]. Fortunately, this question can be addressed through continued research, especially research that addresses enriching environments and positive outcomes.

A second outstanding issue reflects controversy in the use and definition of 'environment' in G × E research [17]. Typically, environment refers to both experiential phenomena, including childhood abuse or adult stressors such as divorce or unemployment [7], and exposure to physical forces such as toxins, natural disasters (e.g. hurricanes, tornadoes) and acts of violence (e.g. war, terrorism) [18]. However, experiential phenomena and physical forces differ crucially in the degree to which the affected individual contributes to the environmental trigger: little to none with physical forces but possibly a significant amount with experiential factors. Reflected in the latter is gene–environment correlation (rGE), which captures the influence of genetically driven variability in behavior as a precipitator or correlate of specific experiential triggers (e.g. difficult temperament resulting in harsh parenting). Thus, some G × E studies might be biased by rGE [19]. This issue of rGE has been addressed through using designs including behavior genetic approaches [20] (e.g. adoption [21], twin studies [22]), natural disaster [23] and natural experiments [24], experimental manipulation in humans [25] and non-human primates [26], and treatment designs [27].

Third, although G × E research alone has increased the depth and complexity of our understanding of factors influencing the etiology of psychopathology, it is certain that even greater complexity exists in the form of G × E × E and G × G × E [28–30]. For example, in a G × E × E study, the authors report that the 5-HTTLPR genotype × maltreatment interaction predicting depressive symptoms originally reported by Caspi and colleagues [7] was further moderated by social support wherein only short homozygotes with a history of childhood maltreatment and low social support showed increased depressive symptoms [28]. These results emphasize the complex and multifaceted nature of these systems in which some experiences exacerbate risk (maltreatment), whereas others are protective (high social support). Consistently replicating such increasingly complex interactions requires sample sizes and statistical power not present in even the largest datasets published, particularly when analyzing interactions using canonical approaches that involve identifying first the main effects of each variable (e.g. genotype 1, genotype 2, environment 1, environment 2) [31]. In this approach, the interaction is limited in power by inherent distributional properties of the interaction term in nonexperimental studies and by the need to account for main effects before examining interactions. Moreover, this limitation in power is often compounded by the frequency of the minor allele of the polymorphism, the rate at which individuals are exposed to a given trigger (and severity of the exposure [32]) and the frequency (and error of measurement) of possible dichotomous psychiatric diagnosis ([3,33] although see [34]) (see [31] for a discussion of approaches that might yield more power and note that experimental studies have much greater power to detect interactions).

Fourth, it is also important to be cautious of spurious G × E findings, which could arise due to selected sampling as well as scaling artifacts within logistic regression. Ideally, Eaves [35] suggests that these issues can be addressed by evaluating transformed data to examine if the interaction remains and using continuous variables and random sampling when possible (for more details see [33,36]).

Fifth, it is important for G × E findings to be replicated and these findings to be supported by meta-analysis. Conflicting reports on the interaction of the 5-HTTLPR and life stress predicting depression underscore this point. After initial findings (e.g. [7]), a meta-analysis suggested no reliable effect of this interaction on depression diagnosis [37]. However, this meta-analysis has been criticized for a biased selection of included studies. Specifically, authors have noted that included studies were characterized by relatively poor stress measurement [38], and an emphasis on dichotomous outcomes [33]. In line with these concerns, and in contrast to the conclusions of this meta-analysis [37], more thorough and inclusive meta-analyses support the reliability of the 5-HTTLPR × stress interaction predicting depression [8,38]. Moreover, recent reviews have documented this interaction effect across model species (e.g. rhesus macaque and transgenic mice) and methodologies [3]. Nevertheless, this ongoing debate clearly highlights the importance of good construct measurement (of both environment and outcome).

Finally, beyond issues of measurement, demographic variables such as age [39] and gender [40], as well as race/ethnicity [41–43] and possible genetic substructure [44] are all likely to influence findings and require careful control and examination as additional moderators.

G × E research has provided a more nuanced understanding of the interplay between biology and environment in shaping risk for psychopathology. However, G × E alone has not revealed the specific biological mechanisms for this risk [45]. Ultimately, for a genetic or environmental variable to affect behavior, it must 'get under the skin' [29,36,46]. G × E must be instantiated in the brain if it is to affect behavior and the etiology of psychopathology.

Imaging genetics

Linking common genetic polymorphisms to variability in brain structure, function and connectivity is the foundation of imaging genetics [6,47,48]. This foundation is important for several reasons: first, by connecting genetic variation to an intermediate biological phenotype (the brain), a plausible mechanism is provided through which genes affect behavior (Figure 1). For example, several studies have demonstrated a link between the short allele of the 5-HTTLPR and increased amygdala reactivity to threat

[6,47], as well as altered functional connectivity between the amygdala and prefrontal regions [48]. Given links between increased amygdala reactivity and anxiety and depression [49,50], these studies address how and why variation in the 5-HTTLPR might affect risk for these psychopathologies. Second, when the target polymorphism is of known functionality (e.g. altered gene transcription), the genetic variant serves as a proxy for individual differences in brain chemistry and thus offers clues into the molecular mechanisms through which differences in brain arise at the genetic and molecular (e.g. neurotransmitter) level. For example, in the case of the 5-HTTLPR, the short allele has been linked to decreased transcription of the serotonin transporter [51] which affects serotonin signaling. Third, the neural and genetic variables of interest allow for more effective synergy with animal models (e.g. transgenic mouse models, optogenetics), which in turn can advance the detailed understanding of molecular and cellular events ultimately linking genetic variation to brain to behavior [3,45,52]. In addition, imaging genetics using multimodal positron emission tomography (PET)/functional magnetic resonance imaging (fMRI) [53] and pharmacological fMRI designs [54] has the potential to further illuminate specific molecular pathways mediating genetic effects on brain [1,3]. Fourth, by focusing on dimensional and relatively objective intermediate phenotypes (e.g. regional brain activation to specific stimuli), analyses are not limited by broad nosological definitions (e.g. DMS-IV diagnoses) that are often plagued by heterogeneity in symptoms/behaviors or inherent biases in self-report (e.g. [55]). Moreover, by using a biological phenotype (i.e. behaviorally relevant brain structure and function) more proximal to the functional effects of genetic variants, imaging genetics gains power relative to research with more distal behavioral phenotypes, and is poised to uncover novel candidate genetic variants (possibly through GWAS). As these novel candidates identified through imaging genetics will necessarily provide demonstrated effects on specific neurobiological pathways, they can in turn be targeted in association studies with behavioral and/or clinical phenotypes [56]. In sum, imaging genetics offers new insight into psychopathology by mapping predictive links between genes, brain and behavior, furthering our understanding of the etiology of disorders at the genetic and molecular level.

Challenges to progress and possible advances in the field

As in G × E, imaging genetics studies have contributed to our understanding of psychopathology but some major issues are worth noting. For example, a majority of imaging genetics studies, especially early research, established links between genetic polymorphisms and brain but failed to link either directly to meaningful differences in behavior [47,48]. Recently, imaging genetics studies have begun to establish such meaningful links by modeling indirect pathways from genes to behavior via the brain [49,57]. Studies that draw indirect pathways between gene and behavior through the brain, when no direct gene–behavior link exists [49], emphasize the importance of using statistical approaches that can model indirect (mediated) pathways [58]. Moreover, similar to G × E studies, imaging genetics studies demonstrate that there are important relationships between genes and behavior even when large direct relationships are not evident.

Another crucial challenge is to model even greater complexity of genetic effects on the brain. G × E studies clearly demonstrate the importance of environmental experience in understanding the ultimate effects of genetic variation on behavior and thus the environment should be modeled in future studies (see description of imaging gene–environment interactions (IG × E) below). Beyond issues of the environment, as in G × E, the issue of epistasis and the probable small effect of any single polymorphism highlights the need for novel analytic approaches such as investigating G × G interactions [59,60], constructing cumulative genetic profiles [61], attempting hypothesis-free imaging GWAS [62] as has been done with G × E [63] (although greater application of GWAS to G × E and neuroimaging are both needed), examination of rare gene or copy number variants [45], and novel statistical approaches to integrate multiple genes into models [64,65]. Furthermore, beyond interaction effects (G × E, G × G), future studies that incorporate complementary techniques (e.g. neuroreceptor PET, pharmacologic challenge, animal models) or approach the modeling of neural reactivity in novel ways (e.g. machine learning [66], graph theory [67]) will better capture the molecular mechanisms mediating genetic effects on brain [1,68].

Imaging G × E

Both G × E and imaging genetics research examine potential relationships between genetic variation and individual differences in behavior and risk for psychopathology. In G × E, the relationship is conditional (statistical moderation) on experiences that are necessary to unmask genetic effects (or vice versa). In imaging genetics, a biological mechanism can be specified (statistical mediation/indirect effects) in which variability in brain links genes and behavior. Here, we advocate for an integration of these approaches to help understand conditional mechanisms through which genes, environments and the brain interact to predict behavior and risk for psychopathology. We term this integrative strategy: imaging gene-environment interactions (IG × E) (Figure 2). Several recent reviews [3,46,69] have demonstrated possible IG × E by combining findings from research in animal models, G × E and imaging genetics to explain the interactions of genetic variants with environmental variables to predict learning, memory and psychopathology. Although these reviews are exciting, empirical studies are only beginning to test components of IG × E directly [70,71] and thus we explore how these conditional mechanisms can be specified statistically and conceptually in a human neuroimaging study.

Conceptual models

Statistically, the concept of IG × E can be modeled by a moderated mediation framework (also called conditional indirect effects) [58] in which mediated/indirect effects are moderated by a third variable. In this framework, any or all paths within a mediation framework (gene to brain, brain to behavior, gene to behavior via brain) could differ

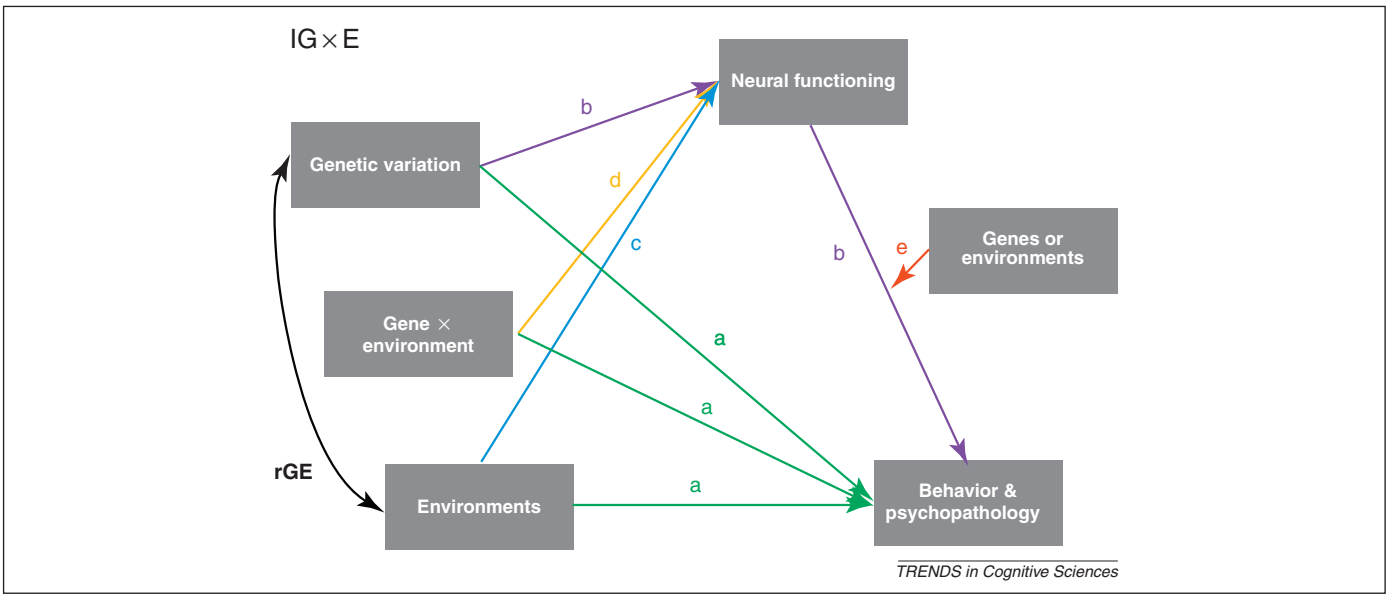

Figure 2. A conceptual model of IG × E. To understand how IG × E might be modeled conceptually and statistically, we demonstrate the relationship of the variables through highlighting traditional G × E and imaging genetics paths as well as new paths possible in IG × E studies. The a paths (green) model typical G × E relationship. The b paths (purple) model the paths from an ideal imaging genetics study. The c path (blue) models the direct effect of the environment on neural functioning demonstrated in epigenetic studies. The d path (gold) models a G × E predicting neural functioning (IG × E effect). In this interaction, a gene would be more predictive or have a greater effect on a neural phenotype in some environments but not others (or the reverse: the environment would be predictive of neural functioning for those with one genetic variant but not another). The e path (red) represents another interaction: the possibility that genetic variation or an environmental variable could interact with neural functioning to predict behavior. For example, those with a variant in a gene affecting endocannabinoid signaling show greater correlation between reward-related brain reactivity and a measure of impulsivity [93]. Additionally, those with low social support have a greater relationship between their threat-related neural reactivity and trait anxiety [94]. Interactions involving the environment could be between gene and environment predicting neural function (d path) or between gene and neural functioning predicting behavior (e path) but in typical G × E studies both of these interactions would be equivalent even though these interactions are likely to be due to very different mechanisms. Note that indirect and mediated pathways can be connected between many of the variables (e.g. G × E to behavior through neural functioning) and thus an ideal IG × E finding would be that the G × E interaction term predicts behavior through neural functioning. Finally, within an SEM model, modeling a continuous interaction, the covariance between a genetic variant and an environment can be modeled which reflects the rGE between the specific genetic variant and specific environment.

depending on the level of a moderator variable (e.g. presence or absence of childhood abuse). As seen in Figure 2, there are multiple ways in which genetic, neural, environmental and behavioral variables could interact, and each model yields answers to slightly different questions (see also [58]).

A particularly intuitive IG × E model is a G × E in which the interaction term predicts behavior through its effect on brain function (Figure 2, path D). In this case there are direct effects of both genetic and environmental variables on brain function but their interaction predicts nonadditive unique variance, which in turn predicts behavior. For example, genetic variation in serotonin signaling predicts increased amygdala reactivity [47], as do experiences of extreme early environmental deprivation [72], and individuals with both this genetic variation and environmental experience could show a synergistic increase in amygdala reactivity which could then predict increased anxiety symptoms. Alternatively, a positive environment such as parental warmth could negate any relationship between genetic variation in serotonin signaling and amygdala reactivity, and this lowered amygdala reactivity could then predict average levels of anxiety symptoms (Figure 3). This particular interaction (G × E predicting brain function) also underlies much of the potential of IG × E approaches. By combining the power of proximal intermediate phenotypes and the potential of G × E to clarify such relationships, IG × E can provide further insight into the conundrum of hidden heritability. For example, if a genetic variant has no association with a neural or behavioral phenotype in most circumstances but has a robust association in relatively rare environments (e.g. physical abuse), IG × E might be able to detect this association particularly with more proximal neural phenotypes.

Such relationships can be tested using path or Structural Equation Modeling (SEM). As in G × E studies, the way these relationships are tested (and graphed) can affect the interpretation of the results. For example, following from imaging genetics models, the environment could be seen in IG × E studies as the moderator of the paths in an imaging genetics analysis (Figure 4). However, this approach privileges genetic factors as the 'direct' predictors of neural activity even though there is evidence that experience can affect the brain in direct and causal ways (see epigenetics section below) and G × E studies often model genes as the moderator.

Beyond this conceptual distinction, the analysis method can also affect results and their interpretation. For example, moderation in SEM is often tested in a multigroup model in which the path between genetic variation and brain function could be compared across two groups of subjects (e.g. those with or without a history of abuse). This multigroup model is best for dichotomous moderators (e.g. two different alleles of a polymorphism or an environmental extreme) and could be more easily and intuitively understood by readers. However, multigroup approaches have less value when otherwise continuous variables (e.g. continuously measured parenting) are dichotomized (e.g. harsh versus warm parenting). The alternative is to specify continuous interactions between variables of interest, even

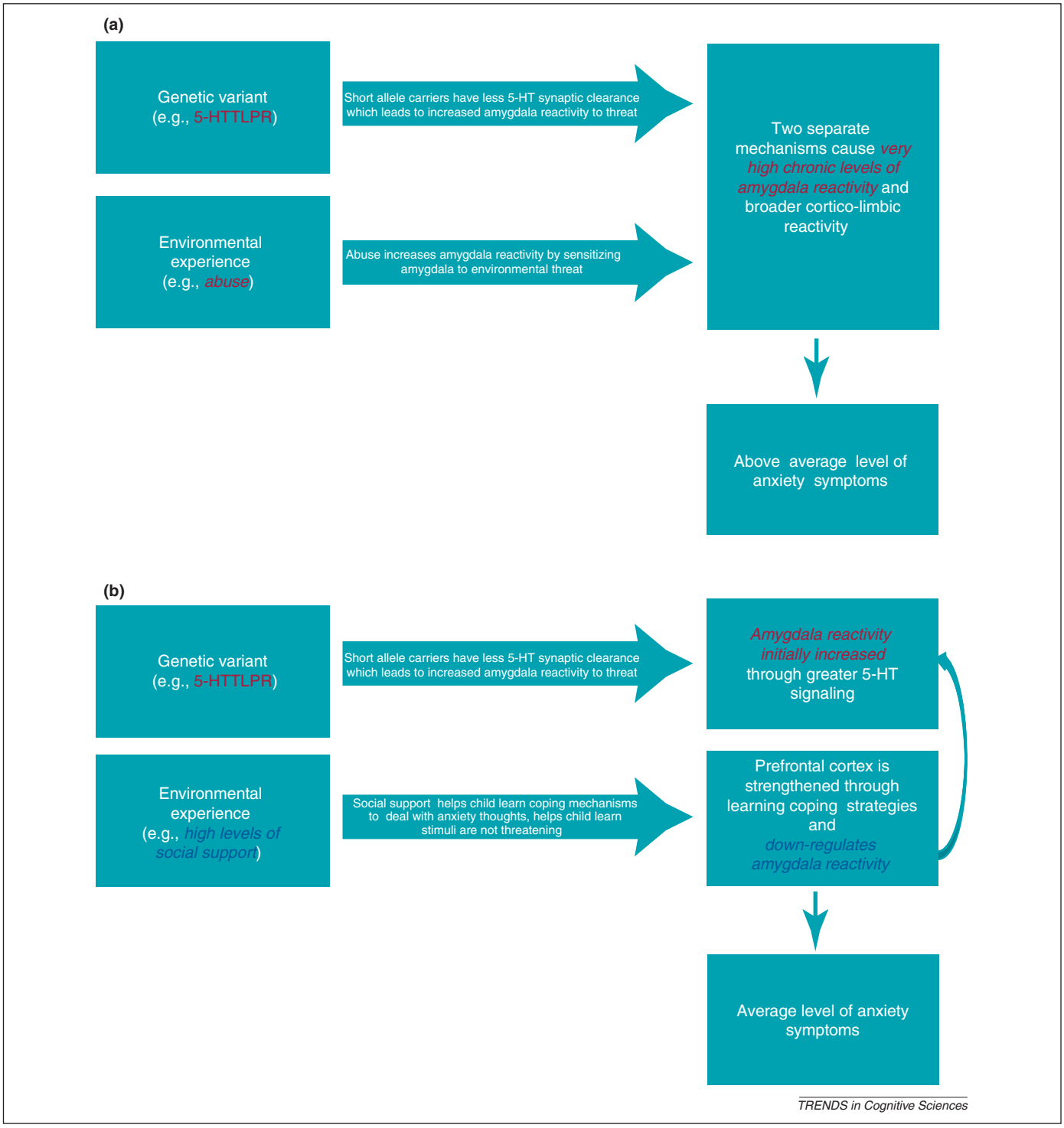

Figure 3. Possible biological models of IG × E interactions within the brain. As research suggests there are plausible causal biological mechanisms through which experience affects transcriptional effects of genes on neural functioning, it is helpful to specify how genes and environments might interact at a conceptual level to bring out the statistical relationships that could be found in IG × E studies. **(a)** A synergistic model. Both genes and environments directly act on one brain area on similar mechanisms at the synapse. For example, short carriers of 5-HTTLPR could have increased 5-HT signaling in the amygdala [47], leading to greater reactivity to threat, and abuse or extreme neglect could increase the transcription of nonindividually varying sequences in genes that affect amygdala function [72] causing parallel increases in amygdala reactivity to threat. Thus the amygdala could have two pushes towards being more reactive to threat and show a multiplicatively exaggerated response. **(b)** A buffering model. Although a carrier of the short allele of the 5-HTTLPR has increased amygdala 5-HT signaling, high levels of social support cause changes in areas of the prefrontal cortex which are able to downregulate amygdala reactivity leading to normal reactivity to threat (alternatively abuse could affect the prefrontal cortex diminishing its ability to regulate the amygdala [84]). In both (a) and (b) interactions could occur within the same brain area or across multiple brain areas within a related circuitry (e.g. a corticolimbic circuitry). Note: it is also important to keep in mind that all of these relationships are 'probabilistic', not deterministic, and thus these models offer possibilities as a way of understanding IG × E.

latent variables, and common statistical packages have recently made estimation of continuous latent interactions possible [58]. Continuous interactions are likely to provide more power and reflect the dimensional nature of many of the variables (e.g. environmental experiences, neural function), as well as allow for the modeling and evaluation of the rGE between the specific genetic and environmental variables in the model (Figure 2).

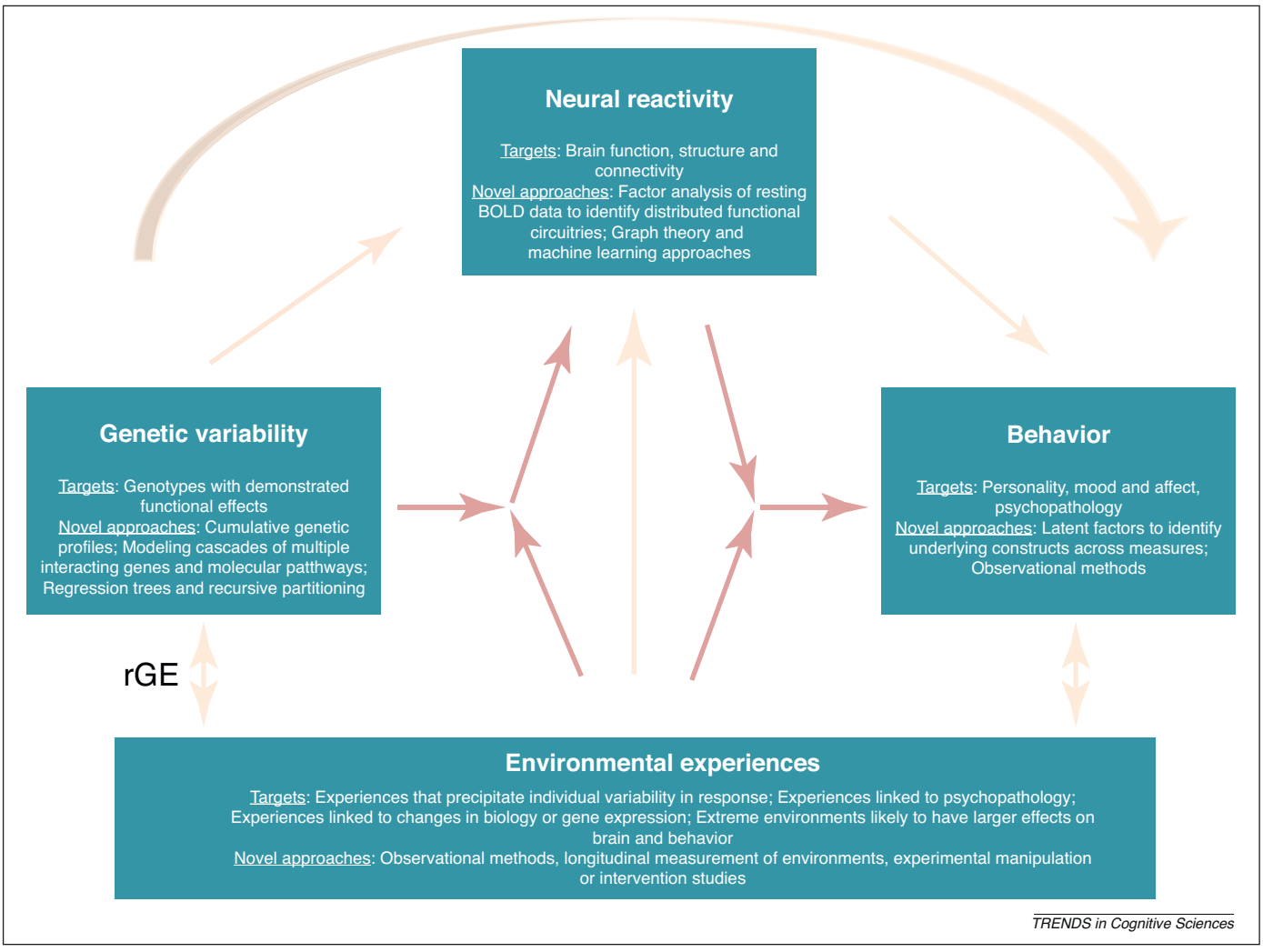

Figure 4. Specific targets for G × E, imaging genetics and IG × E studies. Importantly, novel approaches across each domain are needed to help progress understanding across all models. Moreover, similar to Figure 2, this model emphasizes the interaction between the environment and biology (genes, neural reactivity) as these variables predict behavior. More transparent arrows signify links made in traditional research. Bolded arrows represent newly proposed paths specific to IG × E models. BOLD: blood oxygen level-dependent.

Considerations

The above promise of IG × E, like that of its parent strategies, is not without challenges. First, the challenges noted in the G × E and imaging genetics sections generally apply to IG × E models (Box 1; Figure 4). Second, IG × E models test statistical correlations in humans specifying possible relationships and thus need to be paralleled by work in animal models or with experimental designs (e.g. drug treatment protocols, adoption studies) that can infer causality [4]. Moreover, as we discuss below, these models should be guided by biologically plausible relationships between variables. Third, these complex models require significantly larger samples than those currently available to have acceptable levels of power. Moderated mediation models require starting sample sizes in the range of 500–1000 subjects to examine the expected small to moderate effects of each variable [58]. Moreover, this estimate does not include issues such as low minor allele frequencies and environmental exposure rates, which could necessitate even larger samples. Although samples of this size might sound untenable in neuroimaging, there are already published studies with samples of this size (e.g. [73]) and consortium projects are addressing this issue by pooling data across sites/studies (e.g. [74]). Fourth, it is important to understand that development plays a large role in the unfolding of gene–environment–brain–behavior relationships. For example, many studied genetic variants (e.g. *MAOA*, 5-HTTLPR) likely function *in utero* or very early in development [75–77]. Moreover, environmental experiences differ in their impact depending on the developmental stage of the individual (e.g. types of stressors for a child might differ from those for an adult) [78,79] and epigenetic studies demonstrate that certain experiences have a greater biological impact during 'sensitive periods' of development [4]. Finally, just as G × E and imaging genetics studies required researchers to bridge several areas and/or work in multidisciplinary teams, IG × E studies require even greater knowledge and collaboration. We hope that the conceptual models introduced in IG × E will garner even greater appreciation for the work of colleagues in disparate fields (e.g. animal neurophysiology, biostatistics, epidemiology, experimental psychology).

Box 1. Challenges to progress and outstanding questions

- **Genes**
  - Challenges: single polymorphisms are of small effect. Issues such as epistasis and developmental regulation of genes have not been addressed in most studies.
  - Solutions: genetic risk profiles representing the cumulative impact of multiple functional polymorphisms within a system (e.g. dopamine) and statistical models combining polymorphisms within and between systems (recursive partitioning, regression trees) can identify small genetic effects and their interactions. Longitudinal studies of genetic effects in animals and humans can inform when and how each genetic variant might affect brain and behavior.
  - Outstanding questions: when and how do most genes of interest have their effect on brain and behavior? Are there more complex mechanisms or organized ways in which genes interact across development?
- **Environments**
  - Challenges: many G × E studies have relied on self-report or other measures with substantial error (e.g. retrospective reports). For many environmental variables it is not clear when certain experiences might have their effect on brain or behavior. For many experiences, G × E studies have not paid attention to whether it is the objective account or the subjective report that matters.
  - Solutions: observational measures and multiple well-validated measures of the same construct can help decrease error of measurement, as can modeling latent constructs of these variables. Prospective longitudinal studies can address developmental cascades and determine 'sensitive periods' during which certain experiences might have the greatest impact. Studies with multiple informants and methods can compare the impact of subjective versus objective accounts of experiences.
  - Outstanding questions: are there certain experiences that have an impact no matter when they occur? Are there experiences that interact differently with genetic polymorphisms depending on when they occur? Are there experiences for which objective or subjective reporting is more important?
- **Brain**
  - Challenges: much imaging genetics research focuses on a single brain region or the simple relationships between two regions whereas behavior reflects complex interactions within and across multiple brain regions. fMRI studies are relatively indirect measures of cellular activity.
  - Solutions: exploratory statistical techniques such as machine learning, factor analysis and graph theory analysis use a data-driven approach to identify complex circuit function and whole-brain network organization. Multimodal human and animal studies can help address cellular and molecular mechanisms underlying brain activity. Mediation analyses can be used in multimodal studies to provide plausible pathways (e.g. does brain structure mediate gene–brain function relationship? Do receptor levels, assayed with PET, mediate the gene–brain function relationship?). In addition, experimental studies (e.g. experiments that manipulate the environment, pharmacological studies to manipulate neural chemistry) and animal studies can address mechanisms from a causal perspective.
  - Outstanding questions: are studies finding relationships between single brain areas (e.g. the amygdala) and behavior the result of more complex interactions between multiple brain structures we do not yet understand? How does the interaction between brain regions map onto behavior? To what extent do genetic variants affect behavior through their influence on function versus structure versus connectivity in the brain?
- **Outcome behavior/psychopathology**
  - Challenges: our conceptualization and resulting measurement of psychopathology is still rudimentary and based on observable behavior, which can lead to increased error in diagnosis. Dichotomous diagnoses limit statistical and inferential power, and miss the likely dimensional nature of most psychopathology.
  - Solutions: imaging genetics and IG × E provide intermediate continuous phenotypes, which might be more objectively measured and more powerful. Continuous and hierarchical models of broad psychopathology can increase power and model the high comorbidity found in studies of psychopathology. Observational methods of behavior can provide more reliable measures particularly when combined in latent constructs with multiple converging self-report measures.
  - Outstanding questions: how do we account for the high levels of comorbidity across most psychopathology? Can intermediate phenotypes and, ultimately, the genetic polymorphisms by which they are predicted, usefully inform diagnosis and treatment? How can we define and delineate subgroups within broad diagnostic categories (e.g. Antisocial Personality Disorder) that express more homogeneous alterations in behavior and, by extension, brain dysfunction?

Plausible biological mechanisms

Imaging genetics studies in humans and non-human primates (e.g. [26,77]) as well as studies of strain differences in laboratory mice (e.g. [52]) convincingly link interindividual genetic variability to differences in brain and behavior. What about the environment: does it alter biology in ways that affect brain and behavior? For many biologists, including neuroscientists, the obvious answer might be 'yes', but given the 'nature–nurture' debates in some areas of psychology [4] it is important to specify models whereby experiences are transduced into functional biological signals that affect brain function and subsequent behavior. A fundamental example of such transduction comes from molecular studies demonstrating that learning is supported by long-term changes (i.e. long-term potentiation and depression) in synaptic physiology, which are mediated by changes in gene expression [80,81]. Thus, activity-dependent gene regulation drives changes in protein expression and adaptations in the molecular machinery for neurons and neuronal circuits supporting behavior. Importantly, such environmentally induced changes ultimately manifest in the reorganization of brain circuits and their functional responses [80,81].

Another fundamental mechanism governing the transduction of experience into changes in biology and behavior is epigenetics [4,82,83]. Reviews of epigenetic regulation of brain and behavior are available elsewhere [e.g. 4,82–84]. Briefly, epigenetic regulation refers broadly to the local (i.e. cell specific) modification of gene expression of the DNA-histone complex and resulting accessibility of specific genes for transcription. Studies have demonstrated that early experience can alter epigenetic markers and subsequent patterns of transcription in a way that affects brain structure and function as well as behavior [4].

Chief among studies of epigenetic regulation of behavior are those conducted by Meaney and colleagues demonstrating that in rats, maternal care of offspring affects later adult behavior through epigenetic regulation of hypothalamic–pituitary–adrenal (HPA) axis reactivity to stress. Specifically, higher levels of maternal licking and grooming and arched-back nursing (LG-ABN) of rat pups during the first week of life leads to increased serotonin levels, which drive the expression of nerve growth factor-inducible protein A

(NGFI-A). Increased NGFI-A, in turn, leads to decreased methylation and increased acetylation of the promoter region of the glucocorticoid receptor (GR) gene in hippocampal neurons. This pattern of decreased methylation and increased acetylation results in increased gene expression and higher GR numbers in the hippocampi, which mediate negative feedback regulation of the HPA axis response to stress. These changes persist throughout the lifespan and promote adult behavior that is characterized by relative stress resilience and increased subsequent maternal care. Thus, through this epigenetic mechanism, high LG-ABN mothers beget relatively stress-resilient pups that become high LG-ABN mothers by experience-dependent mechanisms [4,85].

In these and similar studies, early experience affects epigenetic modifications triggering a cascade of changes in cellular signaling (particularly in the brain), which shape adult behaviors. In a compelling extension of this research to humans, a study of postmortem hippocampal tissues from individuals who committed suicide (compared to others who had accidental deaths) found increased methylation of the human GR promoter and decreased GR mRNA. However, this difference was only observed in a subset of suicide completers who had been abused as children and not in completers without history of abuse. Thus, there could be a remarkable conservation of epigenetic mechanisms regulating brain and behavior across species, which gives us confidence in developing plausible biological models of IG × E in humans based on findings in animal models [86]. Similar epigenetic effects have been documented in other genes and brain regions associated with psychopathology [84,87].

Collectively these studies suggest that the environment has a very direct and long-lasting effect on biology at the epigenetic and neural level and that these effects translate into differences in behaviors, thus emphasizing that G × E is the rule rather than the exception when understanding variability in behavior [4]. Trying to parse main effects of genetic versus environmental variables is to ignore that the genome and environment are in constant interaction [4]: the biological primacy of G × E is apparent from the realization that transcription factors can be and often are controlled by environmental signals [82]. Thus, these biological mechanisms indicate that the impact of genetic variation on relative risk and resilience for psychopathology will be experience and context dependent [88]. It is unclear, however, if such changes can be examined in the context of human IG × E research because data demonstrating that epigenetic markers in peripheral human tissue (e.g. blood cells) are faithful proxies for changes in the brain is lacking ([83,84], although see [87,89]). Moreover, future studies are needed that examine the impact of epigenetic mechanisms on genetic polymorphisms, especially promoter variants, to test true epigenetic G × E relationships [84,90].

Looking forward

With the emergence of detailed measures for both genes and brain, IG × E research is poised to accelerate the pace of scientific discovery by fueling novel exchanges between studies in humans and those in animals. Specific brain substrates (e.g. amygdala reactivity), environments (e.g. childhood neglect) and genes (e.g. *5-HTT*) identified through human IG × E research can generate the next set of targets in animal models that can delve into the detailed molecular mechanisms that link these larger elements. Likewise, research in animals, especially studies that identify novel molecular and genetic factors in the regulation of brain and behavior, can generate targets for human research, which can model these factors through common polymorphisms in the genes of interest and fMRI probes of the relevant brain circuits. Dynamic exchanges across human studies and animal models promise to elucidate tractable biological mechanisms that can inform the etiology and pathophysiology of psychopathology.

Within human studies, an IG × E approach connects the pieces of the puzzle: whereas G × E studies of the past have implied that the mechanism through which G × E affects behavior is the brain, and whereas imaging genetics studies have missed the interaction of biology with experience, IG × E studies can elucidate conditional mechanisms through which genes and experience interact to affect neural structure and function and ultimately behavior and psychopathology. Specifying these models through careful statistical and methodological approaches in well-characterized samples is crucial for the ability of IG × E to inform our understanding of psychopathology.

The treatment implications of such work are critically important as medicine moves towards greater personalization [91]. For example, IG × E studies could lead to intervention and prevention trials that target those at specific genetic and/or environmental risk [4,27] by identifying more homogenous subgroups of individuals within the same diagnosis [92]. Thus, future IG × E research might inform the development of frameworks for determining when and for whom certain treatments will work (e.g. which environments could sabotage the treatment process, which genes could predict treatment success, which combinations of genes and environments could be the targets of early preventative intervention projects) and might help to refine diagnostic criteria. Overall, IG × E can provide a more nuanced and complex model of human nature in health and disease by extending beyond nature–nurture debates and revealing specific mechanisms through which the constantly interacting environment and genome can be understood at the level of brain function and behavior.

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