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EXPERT REVIEW

A neurogenetics approach to understanding individual differences in brain, behavior, and risk for psychopathology

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Neurogenetics research has begun to advance our understanding of how genetic variation gives rise to individual differences in brain function, which, in turn, shapes behavior and risk for psychopathology. Despite these advancements, neurogenetics research is currently confronted by three major challenges: (1) conducting research on individual variables with small effects, (2) absence of detailed mechanisms, and (3) a need to translate findings toward greater clinical relevance. In this review, we showcase techniques and developments that address these challenges and highlight the benefits of a neurogenetics approach to understanding brain, behavior and psychopathology. To address the challenge of small effects, we explore approaches including incorporating the environment, modeling epistatic relationships and using multilocus profiles. To address the challenge of mechanism, we explore how non-human animal research, epigenetics research and genome-wide association studies can inform our mechanistic understanding of behaviorally relevant brain function. Finally, to address the challenge of clinical relevance, we examine how neurogenetics research can identify novel therapeutic targets and for whom treatments work best. By addressing these challenges, neurogenetics research is poised to exponentially increase our understanding of how genetic variation interacts with the environment to shape the brain, behavior and risk for psychopathology.

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More than a century of psychological and psychiatric research has robustly documented that individual differences in personality, mood, cognition and environmental experience critically shape complex human behavior and confer differential susceptibility for psychopathology. The integration of neuroscience, psychology, and psychiatry has shown that variance in brain circuit structure,[1] connectivity,[2,3] resting activity[4,5] and task-elicited activation[6] as well as peripheral indices of circuit function (for example, hormone levels)[7] are reliably associated with individual differences in behavior and psychopathology. Moreover, direct chemical[8,9] and electrical[10,11] manipulation of these circuits causes behavioral and clinical changes, further grounding our understanding of the biological origins of complex behavior and psychopathology. Such mechanistic knowledge facilitates the development of not only quantifiable etiologically based diagnostic descriptors, but also treatments targeting links within the etiologic chain.[12–14] Thus, a deeper, more nuanced and more complete understanding of psychopathology can emerge, leading to improved treatment and prevention.

A logical step to developing a mechanistic understanding of complex behavior (encompassing not only overt behavior but also emotion, cognition and any other manifest change of an individual) is to identify sources of individual variability in neural signaling pathways (for example, neurotransmitter systems) and to understand how such variability influences brain function, and ultimately, behavior. Because differences in protein availability and function shape variability in emergent neural pathways, developing links between brain chemistry and circuitry is critical for understanding the biological basis of behavior and psychopathology. Building upon non-human animal research,[15] as well as positron emission tomography ligand,[16] and pharmacologic challenge[8] studies, molecular genetics provides noninvasive and cost-effective tools to tap into variability in brain chemistry through the identification of common DNA sequence variation, referred to as polymorphisms. These polymorphisms allow for the modeling of individual differences in brain chemistry and neural signaling pathways, and further represent the first step in a cascade that leads from genetic differences to neural differences to behavioral differences.[6,17–19]

Neurogenetics, which integrates the fields of genetics, neuroscience, psychology and psychiatry, attempts to link genetic polymorphisms to variability in protein expression and/or function, brain structure, function and connectivity and, ultimately, behavior and psychopathology.[6] We use the term neurogenetics as opposed to 'imaging genetics', which we used previously, to be more inclusive of the research conducted within this domain (that is, not solely based on neuroimaging). A neurogenetics approach provides several key elements that are especially important for gaining a more complete understanding of the origins of individual differences in personality and the etiology of psychopathology. First, by connecting genetic variation to intermediate biological phenotypes (for example, brain chemistry or circuit function), a plausible, observable and testable mechanism is provided through which genes influence behavior.[14,18] Second, when the target polymorphism is of known functionality (for example, altered gene transcription and/or function), the variant serves as a proxy for individual differences in brain chemistry and can thus inform our understanding of molecular mechanisms through which differences in the brain arise at the genetic and molecular levels.[6] Third, by focusing on dimensional and relatively

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objective intermediate phenotypes, neurogenetics research largely escapes the limitations of broad nosological psychiatric definitions that often comprise heterogeneous symptoms/behaviors and/or inherent biases in self-report.[14,18]

A rapid growth of neurogenetics research has begun to link genetic variation to individual differences in brain chemistry, function, behavior and related psychopathology.[6] Building upon non-human animal research documenting the effects of environmental experience on gene expression,[20,21] emerging epigenetics[22] and gene-by-environment interaction (G × E)[23] research have made evident the necessity of including measures of environmental experience alongside genetic polymorphisms to fully develop a mechanistic understanding of complex human behavior.[24] This interdisciplinary neurogenetics approach has led to unprecedented growth in our understanding of how genetic differences and environmental experiences interact to shape the vast array of human behavior, as well as the molecular mechanisms underlying these relationships. Such research has also encountered several key challenges familiar to genetics, neuroscience, psychology, and psychiatry including: (1) small effects of individual variables, (2) absence of detailed mechanisms and (3) the need to translate findings to the clinic. In this review, we discuss and exemplify the utility of an integrative neurogenetics approach for understanding complex human behavior and psychopathology and showcase techniques and emergent developments that may be used to confront these challenges.

THE CHALLENGE OF SMALL EFFECTS

Neurogenetics research has reliably linked several polymorphisms to differences in brain function, behavior and psychopathology.[6] For instance, key early work demonstrated that threat-related amygdala reactivity is dependent upon serotonin-transporter-linked polymorphic region (5-HTTLPR) genotype.[25] Specifically, individuals with the less transcriptionally efficient short allele (fewer transporter proteins available to clear serotonin from the synapse)[26,27] had heightened threat-related amygdala reactivity relative to individuals with the long allele. Subsequent neuroimaging studies[28–30] as well as meta-analyses[31] and non-human animal research[32] have supported this association and suggest that 5-HTTLPR genotype may account for as much as 2–5% of the variance in amygdala reactivity to threat,[33] which, when considering the complexity of neurochemical signaling, is quite substantial. Moreover, emerging research suggests that these genetically conferred differences in amygdala reactivity may mediate some of the association between this polymorphism and depression, especially subsequent to life stress.[33,34]

Similarly, a common polymorphism of the *catechol-O-methyltransferase* gene (*COMT* Val158Met; rs4680) that affects enzyme function and resulting synaptic catecholamine concentrations[35,36] has been shown to reliably predict variability in emotion, cognition and related brain function.[37–40] In relation to cognition, Egan *et al*.[41] were the first to link the 158Met allele to increased working memory capacity and more efficient prefrontal information processing (that is, less extensive activation but equivalent or better performance) relative to the Val158 allele. Much like the 5-HTTLPR findings, this association has been widely replicated,[42,43] supported by meta-analyses,[38] and informs understanding of biological risk pathways related to psychopathology.[41,44]

Despite such relatively robust and reliable findings, research suggests that individual common polymorphisms will have, at most, only a small effect on brain function and behavior, presenting a major challenge to the field; such weak penetrance is difficult to detect and likely to result in nonreplications, especially in small samples characteristic of neurogenetics research.[31,38,45] Such nonreplications may represent original false-positive associations but may also arise from a lack of standards in neurogenetics research. Indeed, many studies assessing similar constructs use slightly or even vastly different paradigms and different analysis methods. When there is convergence across these different methods, greater faith can be gained in the reported associations. When a lack of replication is observed, it may not necessarily represent a false positive but may reflect differences in experimental paradigms and analysis strategies as well as study populations. However, the neural phenotypes in neurogenetics studies are both more proximate and more objectively measured than behavioral or clinical phenotypes, and there has been consistent replication of core genotype–phenotype associations (for example, 5-HTTLPR and amygdala reactivity; *COMT* rs4680 Val158Met and prefrontal activation).[31,33,38]

The challenge of small effects has prompted the development of large-scale studies,[46–50] multisite data pooling protocols[51,52] and data-sharing networks[53] that promise to more completely capture even the small effects of common genetic variation on brain and behavior. Alongside and within such large-scale efforts, neurogenetics research must develop novel strategies to better detect relatively small effects and understand the complex circumstances under which they arise. Below, we illustrate how incorporating environmental and epistatic relationships into neurogenetics research can improve our ability to detect molecular genetic effects and help clarify the detailed biological pathways of such relationships.[24] Moreover, building upon existing neuroscience knowledge linking specific brain circuitry to behavior,[6,54] as well as research linking specific polymorphisms to differences in brain chemistry,[27,35] it is now possible to construct biologically informed multilocus profiles that more holistically represent genetically driven variability within a specific neural system (for example, subcortical dopamine function) than do single variants.[55]

Considering the environment

G × E occurs when the relationship between an environmental experience (for example, exposure to trauma) and a phenotype (for example, psychopathology) is contingent on individual differences in genetic make-up (for example, polymorphisms).[56,57] Alternatively, G × E is observed when the association between genetic make-up and a phenotype is dependent upon environmental experience. As such, G × E research does not presuppose a main effect of either single polymorphisms or environmental experiences, but rather emphasizes an interaction between genetic variation and experience. This approach holds particular promise to confront the problem of small effects in neurogenetics research whereby inclusion of environmental factors may inform the effects of polymorphisms on a phenotype. G × E research also provides face validity as it represents a more plausible model of disease in which individual experiences and genetic background interact across development to influence relative risk rather than more simplistic models hypothesizing independent effects of particular polymorphisms or experiences.

The utility of a G × E approach can be best exemplified by the influential work of Caspi *et al*.[23] who demonstrated that the depressogenic effects of stress are contingent upon 5-HTTLPR genotype. Specifically, short allele carriers had a strong and positive relationship between life stress and depression, whereas long allele homozygotes had little or no relationship between stress and depression. This finding has been well replicated[33,58] and is supported by meta-analytic data[59] (but see also Refs. 60,61) as well as extensive rodent and non-human primate models.[33] Inspired by G × E studies and epigenetics research (discussed below), we next demonstrate how including measures of environmental experience in neurogenetics research can improve our power to detect effects and help clarify our understanding of the mechanisms through which such relationships occur.

In one of the first human neurogenetics studies incorporating environmental measures,[22,24,62–66] we have shown that genetic variation affecting hypothalamic–pituitary–adrenal (HPA) axis

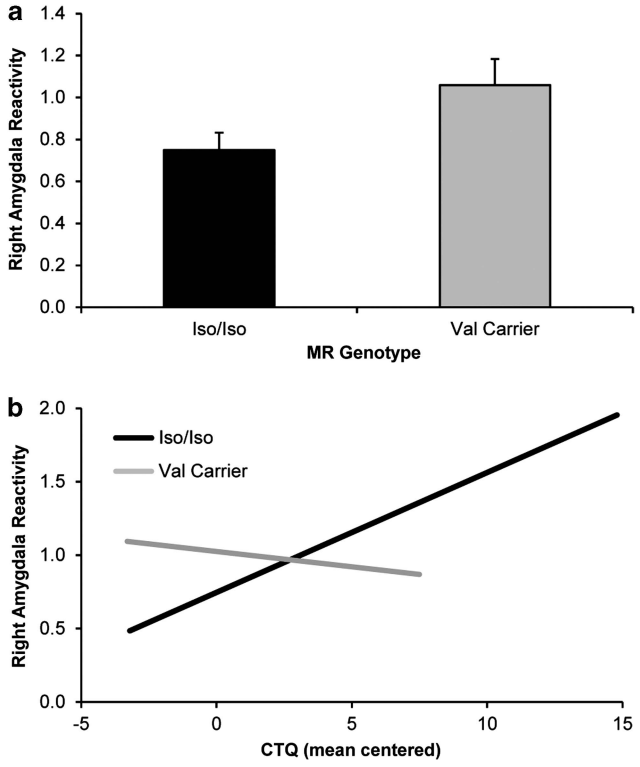

Figure 1. Threat-related amygdala reactivity is predicted by mineralocorticoid receptor (MR) Iso/Val (rs5522) genotype as well as its interaction with prior childhood emotional neglect. (**a**) Main effect of MR genotype. Val carriers have elevated threat-related amygdala reactivity relative to Iso/Iso homozygotes. (**b**) MR genotype interacts with prior childhood emotional neglect to predict additional variability in threat-related amygdala reactivity. Childhood emotional neglect is only positively associated with amygdala reactivity in Iso homozygotes. Val carriers display heightened amygdala reactivity in the context of low neglect but the genotype groups do not differ at high levels of neglect. CTQ, Childhood Trauma Questionnaire Emotional Neglect.

function moderates the association between childhood emotional neglect and threat-related amygdala reactivity in a relatively large sample ($n = 279$) of youth.[67] In this imaging G × E (IG × E) study, we examined a functional missense Iso/Val polymorphism (rs5522) located in exon 2 of the mineralocorticoid receptor (MR) gene (*NR3C2*). Prior work has demonstrated that the Val allele is associated with a loss of function with regard to cortisol and hence reduced MR-cortisol binding that inhibits the HPA axis.[68] Much like extreme forms of childhood emotional neglect,[69] the Val allele has also been associated with blunted cortisol upon awakening[70] as well as heightened stress reactivity as indexed by endocrine[68] autonomic[68] and self-report measures.[71,72] Even after controlling for main effects documenting that childhood emotional neglect and MR rs5522 Val allele carrier status independently confer heightened amygdala reactivity, an interaction between prior childhood emotional neglect and MR genotype emerged (Figure 1). Specifically, there was a positive association between emotional neglect and threat-related amygdala reactivity in Iso allele homozygotes only. In contrast, Val allele carriers displayed heightened amygdala reactivity relative to Iso allele homozygotes only in the context of low prior childhood emotional neglect. Thus, Val allele carriers have an HPA axis profile mirroring that of maltreated individuals[69] and also show similar patterns of heightened amygdala reactivity to threat,[73,74] even in the context of no prior maltreatment. This may reflect a physiological ceiling in Val allele carriers whereby maltreatment cannot further exacerbate amygdala reactivity, and further suggests that Iso allele homozygotes may be more sensitive to environmental circumstances, for better or worse.[75] The dysregulated HPA axis profile and heightened amygdala reactivity of Val allele carriers may leave them more vulnerable to the development of stress-related illness, even in the absence of actual stress experience.

This IG × E study highlights several advantages of carefully incorporating measures of environmental experience into neurogenetics research.[24] Even after accounting for main effects of genotype and prior emotional neglect, the G × E interaction explained additional variance in amygdala reactivity. With IG × E, inclusion of an environmental measure and its interaction with genotype adds explanatory variance not captured within a traditional neurogenetics approach, consistent with the generally enhanced predictive validity of G × E research over that investigating only main effects of genetic variants.[22,23] More importantly, modeling G × E informs us about how genetically driven variation in brain shapes individual differences in risk for psychopathology across different environments. Ideally, more neurogenetics studies will begin to include manipulations of the environment to exert greater experimental control and minimize potential issues such as gene-by-environment correlation or self-report biases.[64,65] Last, the incorporation of experiential measures into neurogenetics research also offers the potential to detect masked effects, such as when a genetic variant only has an association with a phenotype under specific circumstances (for example, 5-HTTLPR and depression only in the context of stressful life events).[23]

Despite such promise, recent influential reports suggest that traditional G × E psychiatric research (that is, studies with psychiatric diagnosis/symptoms as a dependent variable) suffers from significant publication bias, low power and a high false-discovery rate (but see also Refs. 33,59).[61,76] Such reports emphasize the importance of not only sample size, but also replication within this field. With multiple large studies currently ongoing,[46–53] neurogenetics research is finally approaching sample sizes that will allow for adequate testing and, ideally, replication of G × E. Moreover, because neurogenetics G × E research examines continuous and quantifiable phenotypes that are inherently more homogenous and proximal to gene function than psychiatric disorders,[18] the effects studied are likely to be larger and less sensitive to scaling artifacts.[76] Nonetheless, given evidence of publication bias and a high false-discovery rate of traditional psychiatric G × E research,[61] replication of neurogenetics G × E research is critical.

Our ability to research any given construct is dependent upon how precisely it can be measured.[77] Assessing environmental exposure is fraught with difficulties ranging from cognitive biases associated with mood within individuals to inconsistency of measurement across studies.[78] As is true for all G × E research, neurogenetics should carefully select measures of environmental exposure and, when possible, use controlled manipulations of exposure. The use of prospective designs combined with repeated environmental exposure and neurogenetics assessments, as new large studies are designed to do,[46] will be particularly useful. Moreover, recent developments in self-reported[79] and biologically based[80] naturalistic experience sampling methods may be particularly useful techniques to employ within prospective G × E neurogenetics studies. Alongside such attention to methods, it is also important to consider recent influential theoretical developments within G × E research,[75] which have begun to receive empirical support,[81] suggesting that polymorphisms traditionally conceptualized within the diathesis stress model as markers of 'risk' may more accurately be conceptualized as markers of 'plasticity' to the environment, for better or worse. Thus, the inclusion of not only measures of adversity, but also of enrichment, such as social support,[82] will be particularly useful to include within neurogenetics G × E research.

The importance of epistasis

Epistasis refers to the interaction between two or more polymorphisms such that the observed phenotype differs from what would be expected by either polymorphism alone. Much like the incorporation of the environment into neurogenetics research, capturing epistatic (that is, gene-by-gene, G × G) interactions has the potential to clarify relationships between genetic variation and brain function. For example, if an individual possessed a monoamine transporter variant that resulted in reduced reuptake (that is, enhanced synaptic neurotransmitter concentrations) and also a genetic variant of a presynaptic inhibitory autoreceptor that conferred a loss of binding (that is, less presynaptic inhibition), the effects of enhanced synaptic neurotransmitter concentrations conferred by the transporter variant would be compounded by the reduced negative feedback conferred by the autoreceptor variant, resulting in greater postsynaptic signaling than either variant would confer alone. On the other hand, if an individual had polymorphisms conferring reduced transporter availability but enhanced inhibitory autoreceptor function, there may be no net effect on synaptic signaling because the inhibitory autoreceptors would be more sensitive to the elevated neurotransmitter available in the synapse. However, these types of interactions have not been addressed in most studies, though examples below emphasize the importance of these interactions within neurogenetics research.

Several epistatic relationships have been documented with the *COMT* Val158Met polymorphism in relation to prefrontal function and working memory performance.[83–87] In one such case, Buckholtz *et al*.[88] reported an interaction between the rs951436 polymorphism of the gene encoding regulator of G-protein signaling 4 (*RGS4*), which regulates striatal dopaminergic signaling, and the *COMT* polymorphism, such that the effects of one genotype was dependent on the other. Specifically, the A allele of rs951436 was associated with working memory-related prefrontal *inefficiency* in Val158 allele homozygotes, but with *enhanced efficiency* in 158Met allele carriers. Thus, by examining genetic variation within two genes coding for distinct proteins influencing dopamine function, greater clarity was gained regarding the conditional relationship between genetic variation and behaviorally relevant brain function. These results highlight how significant effects at one polymorphic locus can be moderated and potentially even masked by genetic variation in a disparate locus within a common signaling pathway. Critically, had this epistatic relationship not been modeled, this study may have found no relationship between genetic variation across either gene and neural function.

Importantly, however, the majority of epistatic relationships have yet to be replicated. For example, despite several different epistatic relationships documented with the *COMT* Val158Met polymorphism and working memory function/prefrontal cortex efficiency (for example, *COMT* × *RGS4*, *COMT* × *DRD2*), none have been replicated to our knowledge. Replication is especially important for epistasis because of the statistical instability resulting from small groupings of genotype combinations. With the development of large-scale neurogenetics studies,[46–53] the near future should produce data sets that are adequately powered to ascertain whether these interactions are false positives or simply understudied. In fact, a recent report suggests that additive genetic effects are positioned to dominate variability in emergent biological and behavioral phenotypes even if epistatic interactions occur at the level of individual genes.[89]

Biologically informed multilocus profiles

The vast majority of neurogenetics research has examined single polymorphic loci to predict differences in brain, behavior and psychopathology. Importantly, a single functional polymorphism confers differences in a single protein's function and/or expression within the backdrop of multiple genes and resulting proteins comprising a neural system. With increasing knowledge of the effects of polymorphisms on basic brain chemistry, it is now possible to construct biologically informed multilocus profiles that represent the cumulative effect of multiple polymorphic loci of known functionality on a specific signaling mechanism.

The utility of such an approach was recently demonstrated in a study showing that five functional dopaminergic polymorphisms (that is, *DAT1* nine-repeat, *DRD4* seven-repeat, *DRD2*-141C Del, *DRD2* Taq1A C (A2) and *COMT* 158Met alleles) predicted nearly 11% of the variance in reward-related ventral striatal reactivity when combined into a single variable, whereas none of the variants alone significantly contributed to reward-related reactivity.[55] Thus, the use of profile scores representing multiple polymorphisms without independent significant effects can account for significant proportions of variability, presumably by better characterizing genetically driven variability in overall signaling. A biologically informed multilocus profile approach holds tremendous potential for neurogenetics research whereby known functional polymorphisms may be collectively harnessed to represent function across a specific neural system and could relatively easily be applied across neural systems. For example, this approach could be used to understand how individual differences in HPA axis function influence brain activation, behavior and psychopathology (see Figure 2) and applied to examine interactions across systems (for example, dopamine × HPA).

Importantly, however, this approach is limited by our functional understanding of polymorphisms, the vast majority of which have unknown functional consequences or have not been well replicated. As such, there are a limited number of neural systems that have adequate documented functional polymorphic effects (for example, dopamine, serotonin, HPA axis) to interrogate at present. As our broad understanding of basic gene function and our specific understanding of polymorphic effects on functioning increases, we will be able to more completely capture genetic variability in these and other neural systems. Moreover, following replication, it may even be possible to move beyond simple additive approaches to have differentially weighted polymorphisms based upon known functional consequences.

Complementing this hypothesis-driven biologically informed strategy are data-driven profiles derived from genome-wide association studies (GWASs; that is, the summation of all variants reaching a threshold of significance; see GWAS section below)[90–93] as well as hypothesized gene-group analyses (that is, clustering polymorphisms of unknown biological function within genes of similar function—for example, those involved in intracellular signal transduction).[94–96] Although these approaches may inform who is at risk for certain phenotypic expressions, they will not, without follow-up research, reveal mechanisms underlying these individual differences as biologically informed approaches do. Indeed, such profiles are likely to collapse across a host of neural systems that collectively influence a phenotype via different mechanisms. These different polymorphic-pooling approaches emphasize the polygenic nature of complex traits and highlight the benefit of more completely modeling genetic variation to capture the small effects conferred by single polymorphisms. Moreover, novel statistical approaches such as regression trees,[97] recursive partitioning[98] and machine learning[99] provide researchers with tools to evaluate multiple sites of genetic variation and offer potential to identify genetic interactions empirically (without hypotheses).[100]

FURTHERING OUR UNDERSTANDING OF MOLECULAR MECHANISMS

Because functional genetic polymorphisms can represent individual differences in brain chemistry and associated neural signaling pathways, neurogenetics can inform our ultimate goal of

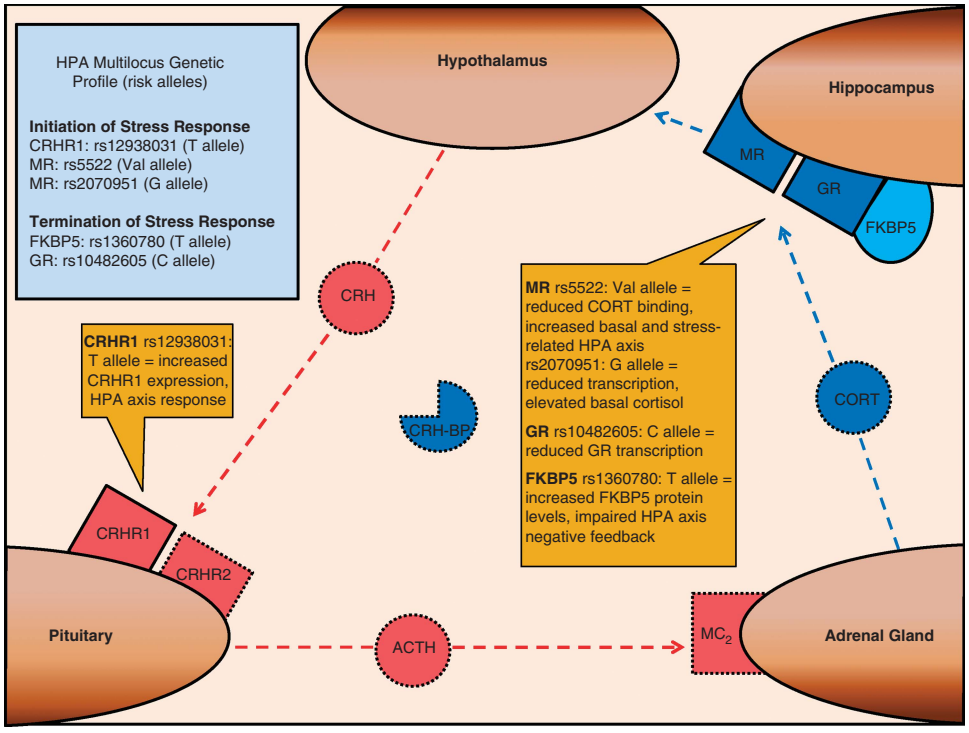

Figure 2. Functional polymorphisms in genes coding for regulatory components of the hypothalamic–pituitary–adrenal (HPA) axis can be combined into biologically informed multilocus genetic profiles. Because the HPA axis is a central regulator of the body's biological response to stress,[154] it is an ideal candidate for gene-by-environment (G × E) research. Briefly, in response to environmental challenge, the hypothalamus secretes corticotropin-releasing hormone (CRH) that binds to type 1 (CRHR1) and type 2 (CRHR2) receptors located in the pituitary gland (among other locations). CRH binding stimulates the secretion of adrenocorticotropin hormone (ACTH) that travels to the adrenal gland and stimulates cortisol (CORT) release. CORT binds to mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs) in the hippocampus (among other locations) to shut down activation of the HPA axis and return the body to homeostasis. Genetic variants in CRHR1, MR, GR and FK506 binding protein 5 (FKBP5) may be integrated into a single multilocus genetic profile representing enhanced stress responsiveness (for example, CRHR1 rs12938031T allele, MR rs5522 Val allele, MR rs2070951 G allele) and impaired negative feedback (that is, return to homeostasis) of the HPA axis (for example, FKBP5 rs1360780T allele; GR rs10482605 C allele). [72,163,164] Additionally, it is important to note that the GR was recently shown to also have an excitatory role on HPA axis activity, suggesting attention is warranted based on the neural phenotypes of interest.[165] There are many other proteins that affect this system that are not included (for example, AVP, NE). Moreover, there are other variants within included genes (for example, FKBP5: rs9296158, rs9470080, rs3800373, rs7748266, rs9394309, all in high linkage disequilibrium (LD) with rs1360780;[163,166] CRHR1 rs110402, rs242924)[167] that have been shown to influence HPA axis function that are also not included. The minor allele of GR polymorphisms shown to impact HPA axis function are relatively rare.[72] As research characterizes other polymorphisms, this profile can be expanded and/or refined. Red represents excitatory mechanisms, and blue represents inhibitory mechanisms (note however that although MR binding inhibits HPA axis function, research suggests that differences in binding here are critical to the onset of the stress response). Dashed lines represent pathways. Dotted boundaries represent proteins for which there are not convincing data linking polymorphisms to HPA axis function. CRH-BP, corticotropin-releasing hormone-binding protein (can block CRH-mediated secretion of ACTH); CRHR1, corticotropin-releasing hormone type 1 receptor; CRHR2, corticotropin-releasing hormone type 2 receptor; MC_2, melanocortin receptor type 2 (ACTH receptor).

identifying the detailed and complex biological mechanisms that give rise to the diversity of human behavior and related risk for psychopathology. However, to truly gain mechanistic knowledge, a more comprehensive neurogenetics approach needs to more widely incorporate assessments (for example, ligand positron emission tomography)[101] and/or manipulations (for example, pharmacological challenge)[102] of brain chemistry in humans and work alongside non-human animal research, which allows for even more detailed and controlled assessment and manipulation of such brain chemistry. Below, we first illustrate how non-human animal research is uniquely positioned to target specific molecular mechanisms that would otherwise be inaccessible in humans. We then discuss recent developments in the field of epigenetics, which are already informing one of the major questions of modern science: how does experience shape biology? Last, we touch upon the promise of GWASs to identify novel or understudied proteins critical to neural and behavioral phenotypes of interest.

Integration with non-human animal models

Traditionally, non-human animal research within psychiatry has sought to model psychopathology and related intermediate behaviors by documenting changes in response to a behavioral, environmental, pharmacologic and/or genetic manipulation. Because of the ability to manipulate and directly measure brain chemistry and gene function, studies using animal models can target specific molecular mechanisms otherwise inaccessible in human studies. In addition, neurogenetics research in non-human animal models offers unique opportunities to control both genetic background and environmental experience, neither of which is practical or ethically feasible in humans.[103] The presence of orthologous genetic variants and the development of novel manipulations (for example, transgenic lines, optogenetics) provide researchers using non-human animal models with opportunities to identify specific molecular mechanisms for behaviors related to human psychopathology, which also represent potential novel treatment targets.[104–106]

Orthologous genetic variants, which are similar but not identical to human polymorphisms, allow for more direct comparison of non-human animals and humans based on shared genetic differences that confer similar effects on gene transcription and/or protein function. For instance, an ortholog of the 5-HTTLPR exists in rhesus macaque monkeys (that is, rh5-HTTLPR) and, like the human variant, the short allele of rh5-HTTLPR is associated with relatively decreased transcription.[107] This functional genetic ortholog has allowed researchers to examine how various factors, such as maternal separation[108] and chronic selective serotonin reuptake inhibitor administration,[109] influence behavior and brain chemistry in experimentally controlled settings.[106] For instance, it has been shown that following maternal separation, monkeys carrying the rh5-HTTLPR short allele display greater anxiety, agitation and exaggerated HPA axis response.[33,108] Moreover, much like humans, rh5-HTTLPR short allele carriers have greater metabolic activity in the amygdala,[32] engage in less eye contact with high-status conspecifics (for example, dominant male monkeys) and are more risk averse in their presence.[33,110] Emerging neuroimaging work with the 5-HTTLPR has begun to establish mechanisms by which these associations may emerge. For instance, results from human studies suggest that the behavioral consequences of the short 5-HTTLPR allele may arise via neurodevelopmental influences on brain morphometry,[111,112] which has been confirmed in the rhesus model.[113] Moreover, the rhesus model also has confirmed human findings indicating that the effects of the 5-HTTLPR on adult brain function and behavior may be mediated by downstream modulation of other serotonin (5-hydroxytryptamine; 5-HT) signaling mechanisms (for example, 5-HT_{1A} autoreceptor downregulation).[114,115] Thus, the availability of orthologous genetic variants allows for testing and validation of observed neurogenetic pathways of individual differences in behavior, genetic disease risk in the context of environmental exposure and, perhaps most importantly, the discovery of specific molecular mechanisms mediating neurogenetic effects on behavior and psychopathology.

Similarly, transgenic mouse models have provided an invaluable insight into the genetic and molecular components of complex behavior and related psychopathology. For example, serotonin transporter (5-HTT) knockout mice have informed our understanding of how the short allele in humans may contribute to depression. A series of studies using this knockout model have demonstrated that loss of 5-HTT function results in a multitude of downstream effects including regionally specific up- and down-regulation of both pre- and post-synaptic 5-HT receptors, which ultimately determine the modulatory effects of 5-HT on neuronal signaling.[116] Moreover, conditional transgenic models, which unlike the constitutive (that is, from birth) 5-HTT model allow experimenters to control the exact timing of gene knockout, have demonstrated that similar differences in 5-HT signaling (but conferred by autoreceptor negative feedback and not transporter reuptake) must occur early in development to alter adult brain function and behavior.[15] These latter results suggest that 5-HTT function and resulting effects on brain and behavior vary substantially across development. Thus, consistent with monkey research reviewed above, these rodent data suggest that the short allele of the 5-HTTLPR may exert its influence on behavior and risk for depression through neurodevelopmental mechanisms influencing downstream 5-HT signaling mechanisms as well as corticolimbic structure that may be exacerbated by stressful experiences. These convergent patterns across mouse, monkey, and man help detail the molecular mechanisms that shape the effects of the 5-HTTLPR on brain chemistry, circuitry, behavior, and risk for psychopathology.[33]

Non-human animal research has provided excellent convergent data with human studies and has allowed for more precise detailing of molecular mechanisms and the influence of developmental timing. However, it is also constrained by the phenotypes available for study, which cannot always model complex human behavior and psychopathology. For example, in relation to anxiety, constructs such as separation anxiety can be modeled with ultrasonic pup vocalizations in mice; however, feelings of losing control during a panic attack, a key symptom of panic disorder, cannot be modeled in a non-human animal model.[117] Similarly, with regard to depression, anhedonia can be modeled with social withdrawal in non-human animal models and degree of intracranial self-stimulation, but feelings of worthlessness or suicidal ideation are impossible to model.[117] Thus, although non-human animal research can be used to detail molecular mechanisms of some psychiatrically relevant constructs, it cannot be used to model all aspects of disorders. Moreover, although some non-human animal studies allow for the dissection of constructs similar to human neurogenetics research (for example, reward anticipation, consumption and learning),[118] the direct translation of such work to paradigms assessing these constructs in humans[119,120] is not fully understood and likely to be influenced by variables inaccessible in non-human animal models (for example, cognitive rumination). However, a focus on neural phenotypes (for example, amygdala reactivity), as opposed to diagnostic/behavioral phenotypes, provides a phenotype that is highly conserved across humans and non-human animal models and can be measured with comparable techniques (for example, blood oxygen level-dependent functional magnetic resonance imaging).

Epigenetics

Broadly, epigenetics refers to cell-specific changes in gene expression that are caused by factors (for example, methylation affecting gene transcription accessibility) other than the underlying static DNA sequence.[21,121,122] Studies conducted primarily in non-human animals have shown that experiences, especially those occurring early in life, can elicit epigenetic modifications that trigger a cascade of cellular signaling changes that more broadly affect brain structure and function as well as behavior. Paramount among epigenetics research is that conducted by Meaney and colleagues,[21] who have shown that in rats, maternal care of offspring affects later adult behavior through epigenetic regulation of HPA axis reactivity to stress.[123,124] Specifically, rat pups that receive elevated maternal licking and grooming and arched-back nursing (LG-ABN) have increased serotonin levels, which leads to elevated nerve growth factor-inducible protein A expression. Increased nerve growth factor-inducible protein A expression leads to decreased methylation and increased acetylation of the promoter region of the glucocorticoid receptor (GR) gene in hippocampal neurons. This decreased methylation and increased acetylation increases GR gene expression, resulting in more GRs in the hippocampus. Because negative feedback regulation of the HPA axis (that is, return to homeostasis) is achieved through GR-cortisol binding in the hippocampus, the increased GR expression characteristic of rats who received elevated LG-ABN care results in a stress-resilient phenotype that is better able to return to homeostasis following the extinction of a stressor. Interestingly, these epigenetic changes persist throughout the rat's lifespan and promote adult behavior that is characterized by relative stress resilience and increased subsequent maternal care, whereby high LG-ABN mothers beget relatively stress-resilient pups that become high LG-ABN mothers by experience-dependent mechanisms.[21,123] Results from a recent human post-mortem study[63] are remarkably consistent with this rodent work suggesting striking conservation of epigenetic mechanisms across species and highlighting the synergy between non-human animal and human neurogenetic research.

Evidence that epigenetic factors are dependent upon genotype has also begun to emerge.[22] The Val158 allele of *COMT* rs4680, which is described above, results in a CpG island (a cytosine–guanine pair connected by a phosphate backbone) that is absent

in the 158Met allele. Because methylation typically occurs at CpG islands, the Val158 allele confers a methylation site that is absent in 158Met alleles. Interestingly, Ursini *et al.*[22] show that methylation at this site is negatively associated with lifetime stress and positively correlated with working memory performance; moreover, an interaction between stress and methylation occurs wherein greater stress and lower methylation is associated with reduced COMT mRNA and protein expression as well as less efficient prefrontal cortex activation. These results suggest that the high COMT activity conferred by the Val158 allele can be reduced through stress-related methylation and show, for the first time in humans, that environment-related methylation within functional genetic variants is an important regulator of gene expression and behaviorally relevant brain function, thus demonstrating true G × E effects via epigenetic influence. More broadly, in concert with epistatic relationships documented with *COMT*, these findings also suggest that even more complex relationships (for example, G × G × E) are likely to exist and be mediated by epigenetic mechanisms.

Collectively, studies of epigenetic regulation inform the mechanisms through which experiences can have direct, long-lasting and even heritable effects on biology. In turn, such effects can translate into important differences in brain circuitry and behavior. These biological mechanisms indicate that the impact of genetic variation on relative risk and resilience for psychopathology will be experience and context dependent.[125] One major question currently confronting human epigenetics research is how faithfully peripheral blood measures of methylation, which are readily accessible in humans, map onto regionally specific patterns of methylation in the brain. Although there is some evidence that these peripheral measures correlate with brain methylation in non-human animal models,[22] how well they represent methylation in the human brain, which can be regionally dependent,[126] is uncertain.

GWAS: identification of novel proteins and pathways

GWASs, which test for associations between a phenotype and genetic variation across the entire genome, are hypothesis-free investigations unconstrained by prior evidence that have the potential to identify novel genes that could play important, potentially unexpected, mechanistic roles within distinct neural systems.[127] Because of the focus on targets that are more proximal to functional genetic variation expressed in the brain than related behavioral or clinical phenotypes, neurogenetics GWAS has the potential to overcome some of the impedances to traditional psychiatric GWAS (for example, low penetrance, diagnostic heterogeneity, self-report bias). Moreover, the potential mechanistic role of any novel genes identified would be more tractable because of their direct association with known neural systems. The real potential of neurogenetics GWAS is only now being revealed[120–135] and, unlike the vast majority of psychiatric GWASs,[136] half of neurogenetics GWASs have identified single-nucleotide polymorphisms reaching stringent genome-wide significance (that is, 10×10^{-8}), with positive replication in some cases.[130,131,133,134] Such promising findings are consistent with speculations that the effect of genetic variation on neural phenotypes will be larger than the effects of behavioral or clinical phenotypes including psychiatric nosology.[18,137]

This potential also comes with tremendous challenge. Obtaining adequate sample sizes to detect the small effects of common polymorphisms at genome-wide significance levels (usually $P < 5 \times 10^{-8}$) is a herculean task that only the largest ongoing investigations approach.[46–52] Moreover, such a stringent statistical approach will likely not identify most, if any, causal variants, even in the largest studies because of these small effects. As such, some of the suggestions provided for confronting the challenge of small effects in neurogenetics research may be particularly useful for integration with GWAS.

For instance, much like the biologically informed multilocus profile approach suggested above, data-driven profiles (for example, the summation of all variants reaching an *a priori* threshold of significance) could be developed from GWAS data and applied to independent data sets for replication. Indeed such approaches have been shown to at least partially address the conundrum of hidden heritability, suggesting that genetic variance may simply be 'hidden' below the threshold of genome-wide significance (but see also Ref. 138).[90–93] Moreover, for research designed to inform our understanding of stress-related psychiatric disorders (for example, depression, post-traumatic stress disorder) and related neural phenotypes, the inclusion of environmental measures of stress experience may aid the detection of polymorphic variants that are only associated with individual differences under certain circumstances (for example, a promoter polymorphism affects transcription only after methylation occurs subsequent to a stressor). Evidence highlighting this potential comes from other fields: for example, the inclusion of environmental factors into GWASs has uncovered novel insights regarding genetic variation and asthma.[139] In this case, novel associations were detected only after modeling farming exposure, which is presumably necessary to unmask the otherwise latent differences in genetic sequence. In other words, many polymorphisms may only exert a functional effect (and a detectable signature) by biasing the response of a system to environmental input (for example, epigenetic regulation). Although to our knowledge neurogenetic GWASs have yet to include environmental effects, this approach promises to be fruitful given consistent links between stress, brain-related phenotypes and psychopathology as well as candidate G × E studies and epigenetic regulation research (see above). Given the increasing economy of genome-wide genotyping, investigators of even underpowered studies may wish to collect DNA to pool with other investigators for GWAS analyses and/or to use for candidate gene investigations based upon new findings introduced by future GWASs.

Last, with regard to mechanisms, it is important to mention recent developments in our basic understanding of gene transcription and translation that will undoubtedly affect all research in genetics. Challenging canonical models of how DNA is ultimately translated to proteins, recent work has documented widespread sequence differences between RNA and DNA.[140] Thus, it is less clear how DNA sequence variation, which is the foundation of neurogenetics research, affects protein function and downstream neural and behavioral phenotypes. However, this work has sparked much controversy among geneticists with concerns that these findings may have resulted from sequencing or other errors.[141] Indeed, an independent study and a reanalysis of these data with more stringent criteria for detecting DNA–RNA differences found much less widespread differences in the transcriptome.[142,143] Moreover, the majority of reported differences are predicted by our current understanding of RNA editing; however, given that not all of these differences could be predicted, there may yet be an unknown mechanism of RNA editing at work. Further complicating our understanding of the transcriptome, emerging expression quantitative trait loci research suggests that gene transcripts can be influenced by multiple and even distal genomic regions and that transcript expression is in general moderately heritable with significant variability in heritability estimates across transcripts.[144–148] In parallel to this research, a number of studies have documented that epigenetic fingerprints are themselves heritable.[21,121,122] Thus, sequence variation may not necessarily affect biology as would be predicted simply from the DNA to RNA to protein chain. Maintaining awareness of such paradigmatic shifts in basic genetics and other biological phenomena is paramount for conducting neurogenetics research that will usefully advance our understanding of genes, brain, behavior and psychopathology.

CLINICAL RELEVANCE

The ultimate unrealized goal of neurogenetics research is to generate knowledge that can be used to improve mental health. The clinical relevance of neurogenetics research lies in its ability to predict individual differences in brain, behavior, risk for psychopathology, and treatment response and to inform the development of novel strategies for treatment and prevention. As a first step toward such clinical utility, emerging neurogenetics research has begun to show that genetically conferred differences in brain function mediate relationships between polymorphisms and variability in behavior conferring risk for psychopathology.[149,150] By establishing specific pathways mediating relationships between genes, behavior and, possibly, clinical symptoms, neurogenetics research can then usefully inform and even direct the search for novel therapeutic targets. Because these targets are born of genetic polymorphisms, they can be further tailored to specific individuals in the broader context of personalized medicine. Indeed, this potential has recently been recognized by the National Institute of Mental Health that has launched the Research Domain Criteria (RDoC) project in an attempt to integrate findings from neurogenetics research into future diagnostic systems and treatment options.[151,152]

Predicting behavior

Traditionally neurogenetics research has shown that genetic differences are associated with differences in brain that have previously been linked to behavioral differences and/or risk for psychopathology. For example, in early neurogenetics work, the short allele of the 5-HTTLPR was linked to relatively increased threat-related amygdala reactivity; in other studies, not incorporating a genetic component, elevated amygdala reactivity has been consistently associated with behavioral responsiveness to stress and threat as well as the pathophysiology of mood and anxiety disorders.[6] Thus, these independent results suggest that elevated amygdala reactivity associated with the 5-HTTLPR short allele may lead to increased stress/threat responsiveness and, especially in the context of provocation (for example, trauma), contribute to the emergence of mood and anxiety disorders.[33]

The application of appropriate statistical techniques, such as mediation analyses,[153] in neurogenetics research holds promise for establishing meaningful links between genes, brain, and behavior by modeling indirect pathways between genetic variation and behavior (or psychopathology) via the brain.[24] We are aware of only two human neurogenetics studies that incorporate mediation analyses.[149,150] In one recent study by our research group,[149] we examined a common functional single-nucleotide polymorphism (rs6295) in the promoter region of the 5-HT_{1A} gene (*HTR1A* C-1019G). The G allele of rs6295 is associated with increased gene expression and resulting 5-HT_{1A} autoreceptor density, and hence increased capacity for negative feedback inhibition and subsequently decreased serotonin signaling.[154–156] In our study, path analyses revealed rs6295 indirectly accounted for over 9% of the variance in trait anxiety through its effects on threat-related amygdala reactivity. Consistent with the effects of other functional polymorphisms resulting in relatively increased serotonin signaling (for example, 5-HTTLPR short allele),[25] individuals homozygous for the C allele of rs6295, which presumably results in increased serotonin via decreased negative feedback, exhibited greater amygdala reactivity in comparison with G allele carriers. Importantly, however, there was no direct link between polymorphism and anxiety.[149] Thus, this example provides evidence of how neurogenetics research can detect indirect associations between genes and behavior through the brain, even when no direct gene–behavior link is evident. As such, the indirect pathway, that is, gene–brain–behavior, inherently contained within neurogenetics research can uniquely advance our understanding of both etiologic and pathophysiologic mechanisms in psychiatry.[24]

Treatment and prevention

By deconstructing the molecular mechanisms underlying gene–brain–behavior pathways, especially in collaboration with non-human animal models and *in vitro* research, neurogenetics can identify novel therapeutic targets. For example, combining the above evidence linking *HTR1A* rs6295 with anxiety through amygdala reactivity with prior work demonstrating effects of the polymorphism on the capacity for negative feedback inhibition suggests that targeting 5-HT_{1A} autoreceptors, perhaps as an adjuvant to selective serotonin reuptake inhibitor treatment, may produce greater clinical effect. In fact, a recent study in a transgenic mouse model of 5-HT_{1A} autoreceptor function demonstrated that reducing autoreceptor levels before selective serotonin reuptake inhibitor administration converted nonresponders into responders.[157] Thus, neurogenetics research with *HTR1A* rs6295 has not only identified a novel therapeutic target (that is, antagonism of 5-HT_{1A} autoreceptors), but also a marker that could be used to individually tailor treatment (that is, C allele homozygotes).

Another example of how neurogenetics can inform treatment and prevention comes from research on TREK1, a background potassium channel. Inspired by a TREK1 knockout mouse study showing that deletion of TREK1 results in a depression-resistant phenotype,[158] human studies have linked variation in the human TREK1 gene (*KCNK2*) to depression,[159] blunted striatal response to reward (a neural profile associated with depression)[160] as well as antidepressant treatment response.[161] More recently, this has led researchers to develop antidepressant medications that antagonize TREK1. One such compound designed to inhibit TREK1 has been associated with a positive antidepressant response, hippocampal neurogenesis, and increased serotonergic signaling in rodents.[162] However, the potential of this novel treatment mechanism has yet to be tested in humans. Nevertheless, this work further documents how neurogenetics research can spur therapeutic advancements by identifying novel targets.

SUMMARY

The field of neurogenetics has informed our understanding of the neurobiological pathways that lead to differences in brain, behavior and risk for psychopathology. We reviewed three challenges currently confronting neurogenetics research above: (1) conducting research on individual variables of small effects, (2) absence of detailed mechanisms, and (3) a need for clinical translation of research findings. We discussed how incorporating the environment and epistatic interactions into neurogenetics models as well as the construction of multilocus genetic profiles can more accurately represent biological function to confront challenges of small effects. We examined how non-human animal and epigenetics research can shed light on detailed molecular mechanisms and biological pathways through which the environment interacts with genotype to shape brain, behavior, and psychopathology. We also touched upon the promise of GWASs to further our basic neuroscience understanding by identifying novel proteins involved in neural function. Last, we demonstrate how neurogenetics research is beginning to provide clinically informative findings that have promise to inform ongoing efforts to improve treatment. Collectively, we hope to have clearly illustrated that if neurogenetics research can overcome the challenges it faces, it is uniquely positioned to revolutionize our understanding of the emergence of individual differences in genes, brain, behavior, and psychopathology, as well as our ability to manipulate these systems for the benefit of individuals and society.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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