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Developmental psychopathology in an era of molecular genetics and neuroimaging: A developmental neurogenetics approach

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Abstract

The emerging field of neurogenetics seeks to model the complex pathways from gene to brain to behavior. This field has focused on imaging genetics techniques that examine how variability in common genetic polymorphisms predict differences in brain structure and function. These studies are informed by other complimentary techniques (e.g., animal models and multimodal imaging) and have recently begun to incorporate the environment through examination of Imaging Gene × Environment interactions. Though neurogenetics has the potential to inform our understanding of the development of psychopathology, there has been little integration between principles of neurogenetics and developmental psychopathology. The paper describes a neurogenetics and Imaging Gene × Environment approach and how these approaches have been usefully applied to the study of psychopathology. Six tenets of developmental psychopathology (the structure of phenotypes, the importance of exploring mechanisms, the conditional nature of risk, the complexity of multilevel pathways, the role of development, and the importance of who is studied) are identified, and how these principles can further neurogenetics applications to understanding the development of psychopathology is discussed. A major issue of this piece is how neurogenetics and current imaging and molecular genetics approaches can be incorporated into developmental psychopathology perspectives with a goal of providing models for better understanding pathways from among genes, environments, the brain, and behavior.

Since its inception, the field of developmental psychopathology has emphasized the complex interaction between the individual and environment in shaping adaptive and maladaptive outcomes (Cicchetti, 1984, 1993; Rutter, 1997; Sameroff, 1995, 2010; Sroufe & Rutter, 1984). The last three decades have brought a wealth of new ways to measure these processes, with particularly notable developments in tools to understand biological processes, such as brain imaging techniques and ever changing approaches to understanding links between the genome and behavior. A burgeoning synergy of disciplines and technologies are providing unique insights into how the dynamic interplay among genes, brain, and experience shapes complex behavior, especially 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 (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010; Caspi & Moffitt, 2006; Hariri, 2009; Meaney, 2010). These new approaches have given us the ability to ask new questions and to answer many age-old questions in new ways (Hyde, Bogdan, & Hariri, 2011).

Fundamental to our understanding of development broadly is identifying mechanisms that link our genetic background and early experience to later behavior. Because brain structure and function are proximal and important mechanisms in understanding differences in risk for psychopathology, researchers have begun to search for ways to understand the predictors of neural variability. One powerful approach that has begun to link genes, brain, and behavior is neurogenetics (Bogdan, Hyde, & Hariri, 2012; Hariri, 2009). Neurogenetics is an emerging field that capitalizes on several different techniques to link genetic variability to variability in brain neurochemistry, structure, and function in order to understand the development of neural circuits at the genetic and molecular levels. By augmenting neurogenetics with an approach that we termed Imaging Gene × Environment (IG × E) interactions (Hyde, Bogdan, et al., 2011), we have recently broadened the focus of neurogenetics beyond measuring only biological pathways to also examining the dynamic interplay between genetic and environmental variability as it affects brain and behavior. Although neurogenetics studies have helped inform our understanding of biological pathways, particularly in relation to psychopathological outcomes, there

This paper builds on work done by many luminaries in developmental psychopathology who are cited throughout the article, as well as specific neurogenetics and IG × E papers (Bogdan, Hyde, & Hariri, 2012; Hyde, Bogdan, & Hariri, 2011). I am greatly indebted to Ahmad R. Hariri and Ryan Bogdan for their major roles in developing IG × E concepts and their seminal work in neurogenetics. I also thank many wonderful colleagues for their insightful comments on this manuscript and the ideas within, including Janet S. Hyde, Arnold J. Sameroff, Christopher S. Monk, Rebecca Waller, and Aidan G. C. Wright. Finally, the integration of these ideas would not be possible without mentorship in developmental psychopathology and neurogenetics from Susan B. Campbell, Stephen B. Manuck, and Daniel S. Shaw, among others.

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has been little focus on development (Viding, Williamson, & Hariri, 2006). Moreover, no work thus far has aimed to integrate perspectives from neurogenetics and developmental psychopathology, despite overlap in concepts between these fields. Integration of these two fields is likely to enrich and strengthen the approach in each field.

Thus, the main goal of the current paper is to examine how neurogenetics and developmental psychopathology can inform each other to build a model and integrative approach for understanding the development of psychopathology. I start by briefly describing a neurogenetics approach. I then consider six core principles (tenets) from developmental psychopathology, particularly as they may inform both neurogenetics models and broad models for understanding the development of psychopathology. In particular, in an age of new tools and methodologies for studying these processes, I focus on considerations for future research that will improve our understanding of development at multiple levels of analysis, including contextual effects, especially IG × E effects. Therefore, my secondary goal is to describe current and future developmental psychopathology approaches that leverage the new tools of the current age through application of neurogenetics and other related techniques. Throughout the paper, I will draw on examples from the empirical adult and child literature to illustrate points and discuss studies that examine specific phenotypes related to psychopathology where researchers are currently grappling with these issues. However, this is not an exhaustive review of neurogenetics studies in general or of developmental neurogenetics studies specifically (for a more in-depth review of developmental neurogenetics approachs to child internalizing see Hyde, Swartz, Waller, & Hariri, 2015). Finally, throughout this paper, I will provide perspectives on how existing approaches and methods could be further used to advance our understanding of the etiology, pathophysiology, and, ultimately, treatment and prevention of psychopathology, particularly from a developmental standpoint. My ultimate goal is to consider conceptual models for understanding developmental psychopathology, and the development of resilience in the face of risk, in an era that has begun to focus more and more on molecular genetics and neuroimaging techniques, with the explicit assumption that incorporating the nuance of a developmental psychopathology approach into biologically focused approaches will help to specify the complex nature of development.

Neurogenetics

A large volume and wide variety of psychological research has documented that individual differences in dimensions of personality and temperament, mood, cognition, and environmental experience critically shape complex human behavior and confer differential susceptibility for psychopathology across development (Belsky & Pluess, 2009; Ellis & Boyce, 2011). The integration of neuroscience and psychology has shown that many individual differences in personality, mood, cognition, and experience are associated with differences in the brain, including its structure (Kempton et al., 2011), connectivity (Gorgolewski, Margulies, & Milham, 2013; Whitfield-Gabrieli et al., 2009), activity at rest (Pizzagalli, 2011), and activity during tasks (Hariri, 2009). Moreover, the associations between brain structure and function and complex behavior are not just correlational: experimental designs, including direct chemical (Bigos et al., 2008; Honey & Bullmore, 2004) and electrical (De Raedt et al., 2010; Holtzheimer & Mayberg, 2011) manipulation of these neural circuits, have been shown to cause behavioral changes. Thus, much current research, particularly research in neuroscience and psychiatry, is aimed at understanding the neural correlates and brain mechanisms involved in the development of psychopathology and other complex behaviors. Although this research has already begun to inform our understanding of the etiology and treatment of various psychopathologies, the field of neurogenetics takes one step back to examine *sources* of these individual differences in neural structure and function (though note, of course, that these are still mostly correlational methods in humans; Bogdan, Hyde, et al., 2012; Hariri, 2009).

Imaging genetics

Neurogenetics as a field can be seen as integrating several complimentary techniques. However, for the most part, neurogenetics is most often associated with imaging genetics, and these terms are often used interchangeably (Hariri, Drabant, & Weinberger, 2006; Meyer-Lindenberg & Weinberger, 2006; Munoz, Hyde, & Hariri, 2009). As I will describe below, neurogenetics also encompasses several other approaches, but imaging genetics is the foundation upon which the field is built. Imaging genetics involves linking common genetic polymorphisms to variability in brain structure, function, and connectivity (Hariri et al., 2002, 2006; Pezawas et al., 2005). This foundation is important for three major reasons. First, by connecting genetic variation to an intermediate biological phenotype (i.e., the brain), a plausible mechanism is provided through which genes affect behavior. For example, several studies have demonstrated a link between the short allele of a repeat in the promoter of the serotonin transporter gene (*5-HTTLP*R) and increased amygdala reactivity to threat (Hariri et al., 2002, 2006), as well as increased functional connectivity between the amygdala and prefrontal regions (Pezawas et al., 2005). Given links between increased amygdala reactivity and anxiety and depression (Fakra et al., 2009; Price & Drevets, 2010), these studies address possible mechanisms through which variation in the *5-HTTLPR* and serotonin signaling more broadly may affect risk for these psychopathologies (Caspi et al., 2010).

Second, imaging genetics studies typically focus on common genetic polymorphisms in genes affecting specific neurotransmitter systems. Genetic polymorphisms are selected based on evidence supporting the functional effects of the polymorphism (e.g., altered gene transcription in a gene

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that codes for a protein important in a neurotransmitter system). Thus, these polymorphisms can serve as a proxy for individual differences in underlying brain chemistry, offering putative molecular mechanisms through which differences in brain function arise at a molecular (i.e., neurotransmitter) level. For example, in the case of the *5-HTTLPR*, the short allele has been linked to decreased transcription of the serotonin transporter (Lesch et al., 1996), which affects clearance of extracellular serotonin from the synapse.

Third, 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., DSM-5 diagnoses) that are often plagued by heterogeneity in symptoms/behaviors or inherent biases in self-report (e.g., Andreasen, 2000). This shift toward more "objective" intermediate and multilevel phenotypes is also more consistent with recent shifts to a research domain criteria (RDoC) approach emphasized by the National Institute of Mental Health. Part of the goal of the RDoC approach is to shift the focus of defining psychopathology at the diagnosis level to a focus on processes at multiple levels of analysis (Insel et al., 2010; Sanislow et al., 2010). Moreover, by using a biological phenotype (i.e., behaviorally relevant brain structure and function) that is more proximal to the direct functional effects of genetic variants, imaging genetics gains power relative to research with more distal behavioral phenotypes (Jonas & Markon, in press), which are presumably the result of multiple interacting neural pathways. As genetically informed neurobiological pathways are identified through imaging genetics, these pathways can in turn be targeted in association studies with behavioral and/or clinical phenotypes (Hasler & Northoff, 2011).

In sum, primary strengths of imaging genetics include testing the brain as a proximal mechanism between gene and behavior, and focusing on genes that specifically affect neurotransmitter pathways, which may give us clues about the underlying neurochemistry of individual differences in behavior, especially psychopathology. Thus imaging genetics can help to understand genetically driven variability in brain function, which may in turn be linked to psychopathology (Hariri, 2009; Meyer-Lindenberg & Weinberger, 2006).

Techniques to probe neurochemistry

Another advantage of leveraging genetic polymorphisms in the context of brain phenotypes is that it allows for synergy with animal models (e.g., transgenic mouse models and optogenetics), which in turn can advance the detailed understanding of molecular and cellular mechanisms, ultimately linking genetic variation to brain and to behavior (Caspi et al., 2010; Holmes, 2008). Animal models allow for many designs that cannot be carried out ethically in humans and enable greater experimental control and more precise and in-depth measurement of molecular biological pathways, particularly in systems or in genes that are conserved across species. Thus, imaging genetics studies are typically built upon results from animal models and can be strengthened through a two-way exchange with this literature (see Bogdan, Hyde, et al., 2012).

Multimodal neuroimaging. A major reason we now refer to this field more broadly as *neurogenetics* instead of *imaging genetics* is to emphasize that several other techniques are critical, and the sole focus is not simply using magnetic resonance imaging (MRI) with genetics (Bogdan, Hyde, et al., 2012; Hariri, 2009). Although imaging genetics has contributed to our understanding of how molecular signaling pathways affect brain structure and function, genes are a very distal and static indicator of these processes. Studies suggest that some genetic variants (e.g., *5-HTTLPR*) may have their effects very early in development (e.g., Jedema et al., 2010). Thus neurogenetics researchers have leveraged other approaches in combination with imaging genetics and animal models to better define these pathways at a molecular level, including the use of multimodal (Fisher & Hariri, 2012) and pharmacological imaging (Honey & Bullmore, 2004). Multimodal imaging studies have used positron emission tomography (PET), or other complimentary imaging modalities, in combination with genetic polymorphisms and functional MRI (fMRI) to directly probe in vivo neurochemistry and link it to brain function (Fisher et al., 2012; Willeit & Praschak-Rieder, 2010).

PET and fMRI used in tandem can be especially helpful because fMRI has excellent temporal and special resolution of blood flow dynamics, and PET can probe neurochemistry directly through the use of radioligands that can illuminate specific aspects of in vivo neurochemistry such as receptor density and binding potential of specific proteins involved in neurotransmission. For example, work by Fisher, Meltzer, Ziolko, Price, and Hariri (2006) using PET and fMRI demonstrated that the density of serotonin 1A autoreceptors (assayed with PET) accounted for 30%–44% of variability in amygdala reactivity to emotional faces in healthy adults (assayed with fMRI). This study identified the importance of serotonin 1A autoreceptors in shaping amygdala reactivity in live adults. These results are even more significant when considered alongside an in vitro study that identified a genetic polymorphism in the serotonin 1A gene (the -1019G allele of 5-hydroxytryptamine (serotonin) receptor 1A [*HTR1A*]) that affects transcription and subsequent amount of protein and binding of this receptor (Lemonde et al., 2003) and an in vivo neuroimaging study linking this same polymorphism to individual differences in amygdala reactivity and trait anxiety (Fakra et al., 2009). Through combining the results of these three studies, we can build a molecular account for the ways in which this genetic polymorphism may affect complex neurotransmitter pathways (e.g., affecting receptors that affect feedback on the serotonin system) to affect neural functioning and subsequent behavior (Fisher & Hariri, 2013). Moreover, through combining PET with fMRI, we are able to examine neurochemistry in the same human participants who are undergoing fMRI scans for a molecular account of

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brain function and behavior (Fisher & Hariri, 2012). This approach can thus probe neurochemistry more precisely than imaging genetics studies, leading to a better understanding of the molecular mechanisms underlying genetic effects on differences in neural functioning.

Pharmacological fMRI. While multimodal studies involving PET can directly observe neurotransmitter binding levels in adults, another technique adopted within neurogenetics is pharmacological fMRI. These direct manipulations of circuits examine neural response after individuals are given drugs that target specific neurotransmitter systems (Honey & Bullmore, 2004; King & Liberzon, 2009; Schwarz, Gozzi, Reese, & Bifone, 2007). For example, studies have used acute administration of selective serotonin reuptake inhibitors in combination with fMRI to demonstrate that these commonly prescribed drugs, which block the reuptake of serotonin, have effects on amygdala reactivity (e.g., Bigos et al., 2008). These findings demonstrate that experimental manipulation of the serotonin system also causes changes in neural functioning and can begin to specify how blocking serotonin transporters affects amygdala reactivity acutely, helping to connect our understanding of the effect of serotonin on brain function as measured by fMRI. Thus, through PET and pharmacological challenge (or even their combination; Buckholtz et al., 2010), neurogenetics researchers are able to probe more precise molecular mechanisms and also experimentally manipulate these pathways. Though the addition of multimodal neuroimaging and pharmacological fMRI are important components of a neurogenetics approach, these techniques cannot be ethically used in minors, and thus they cannot be used directly to examine younger populations or to ask questions about early development. However, using these complementary techniques in adults, along with converging findings from nonhuman animal models, can help to lay the foundation for understanding the molecular pathways connecting genetic variation to neural variation across development, which can help lead to converging evidence with developmental studies. In sum, a neurogenetics approach, informed by nonhuman animal work, uses imaging genetics, along with other complimentary techniques (e.g., multimodal and pharmacological fMRI), to build a more precise and multilevel account of individual differences from gene to neurotransmitter to brain structure and function, and ultimately to behavior.

Until recently, neurogenetics had been solely focused on delineating neurobiological contributions to behavior pathways and had mostly ignored environmental influences on these pathways. However, a convergence of recent studies has begun to highlight ways in which experience affects or interacts with complex biological pathways, underlining the need to consider context in neurogenetics. For example, the rise of the field of epigenetics has led to a greater specification of the molecular mechanisms through which experience affects gene transcription and translation within the nervous system and across generations (Meaney, 2010). Gene × Environment (G × E) interaction studies at the epidemiological level have led to a greater appreciation for the conditional effects of genetic polymorphisms on behavior (Moffitt, Caspi, & Rutter, 2005). In addition, recent neuroimaging studies have emphasized that experiences during development are correlated with differences in brain structure and function (e.g., Ganzel, Kim, Gilmore, Tottenham, & Temple, 2013; Gianaros et al., 2008, 2011; Luby et al., 2013; Tottenham et al., 2011). Therefore, it has become increasingly important to specify the role of the environment within the complex biological pathways examined in a neurogenetics research (Caspi & Moffitt, 2006). Thus, the most recent addition to neurogenetics is an IG × E approach that focuses on modeling the role of experience within imaging genetics studies. To describe IG × E, I will first review G × E interaction research and then articulate the additional layer of adding neuroimaging into this approach.

G × E interactions

A G × E interaction occurs when the relationship between an environmental experience (e.g., exposure to toxins, trauma, or stress) and the emergence of altered physiological or behavioral responses (e.g., psychopathology) is contingent on individual differences in genetic makeup (i.e., genetic polymorphisms) or, conversely, the effect of individual genotype on behavior or health is conditional on an environmental experience (Moffitt et al., 2005). For example, in key early developmental work, Caspi et al. (2003) demonstrated longitudinally that well-established links between life stress and subsequent depressive symptoms were contingent on *5-HTTLPR* genotype. Specifically, individuals with the transcriptionally less efficient short allele 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 relationships are supported by meta-analysis (Karg, Burmeister, Shedden, & Sen, 2011; though see Risch et al., 2009) and animal models (Caspi et al., 2010), and a wealth of other G × E studies have demonstrated similar relationships across other genes, environments, and phenotypes (e.g., Byrd & Manuck, 2014; Caspi et al., 2002, 2005).

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 interactions are instrumental in addressing several major issues that have arisen in behavioral genetics research that examines only direct gene–behavior links. For example, G × E interaction studies may help to tackle the problem of "hidden heritability" raised by the general failure of genomewide association studies (and specific candidate genes) to account for much of the variance attributed to heritable factors in quantitative studies (Maher, 2008). By incorporating differences in environmental exposures, G × E interaction studies may help identify gene–behavior links that are weak across the entire population but

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strong in certain environments (Jaffee et al., 2005; Tuvblad, Grann, & Lichtenstein, 2006). Similarly, G × E interaction studies help to address the generally weak penetrance of polymorphisms in candidate genes (Maher, 2008) and the lack of consistent replication in genetic association studies of complex behavior and psychopathology by identifying environmental exposures that amplify genetic effects (Caspi & Moffitt, 2006; Plomin, 2005).

It is important that G × E interaction research also represents a more plausible model of development in which individual experiences and genetic makeup interact across development to influence relative risk rather than more simplistic models hypothesizing independent effects of particular genetic variants or experiences. Moreover, G × E research is consistent with a growing literature supporting the existence of factors that make some individuals more or less susceptible to certain experiences (Belsky et al., 2009; Belsky & Pluess, 2009; Ellis & Boyce, 2011), and may help identify why only some individuals with the same experience (e.g., abuse) go on to experience psychopathology (e.g., depression or antisocial behavior).

Finally, G × E interaction models have been important in developmental sciences in addressing age-old nature–nurture debates (e.g., Collins, Maccoby, Steinberg, Hetherington, & Bornstein, 2000; Harris, 1998; Vandell, 2000). When combined with epigenetic work that is demonstrating molecular mechanisms through which experience affects the very complex pathways from DNA to behavior (Meaney, 2010; Zhang & Meaney, 2010), the debate should be over: all behavior has a heritable aspect at some level and all behavior has nonheritable aspects (i.e., there are no complex behaviors that have a heritability of 1 and none that have a heritability of 0; Turkheimer, 1998). Even highly heritable and stable complex traits like height (Silventoinen, 2003) and IQ (Dickens & Flynn, 2001; Turkheimer, Haley, Waldron, D'Onofrio, & Gottesman, 2003) are powerfully shaped by experience. Thus, the goal of developmental science now is to specify more nuanced models of how genetic and experiential factors interact across time (Rutter, 1997; Sameroff, 2010) and the mechanisms underlying these interactions as they influence complex behavior. One powerful mediator of G × E interactions is the brain. However, until recently, little work had examined G × E interactions in the context of brain structure and function (Caspi & Moffitt, 2006).

IG × E interactions

Both G × E interaction and imaging genetics research examine potential relationships between genetic variation and individual differences in behavior and risk for psychopathology. In G × E interaction studies, the relationship is conditional (statistical moderation) on experiences that are necessary to unmask genetic effects (or vice versa). In imaging genetics, a biological mechanism is specified (statistical mediation/indirect effects) in which variability in the brain links genes and behavior. Thus, an integration of these approaches within neurogenetics can help understand conditional mechanisms through which genes, environments, and the brain interact to predict behavior and risk for psychopathology through an IG × E framework (Hyde, Bogdan, et al., 2011). Several recent reviews have demonstrated possible IG × E interactions by combining findings from research in animal models, G × E interaction studies, and imaging genetics studies to explain the interactions of genetic variants with environmental variables to predict learning, memory, and psychopathology (Casey et al., 2009; Caspi et al., 2010; Meyer-Lindenberg, 2011). Although these reviews are exciting, empirical studies are only just beginning to test components of IG × E directly (Canli et al., 2006; Gerritsen et al., 2011; Kohli et al., 2011). Here, I briefly review a conceptual model of IG × E as it would be tested in a single study and then review studies that test components of an IG × E interaction. I go on to discuss how a conceptual model of IG × E and a broader neurogenetics approach is primed for integration with developmental psychopathology.

Conceptual models of IG × E. Statistically, the concept of IG × E can be modeled by a moderated mediation framework (also called conditional indirect effects; Preacher, Rucker, & Hayes, 2007) 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, or gene to behavior via brain) may differ depending on the level of a moderator variable (e.g., presence of absence of childhood abuse). As seen in Figure 1, 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 Preacher et al., 2007). However, beyond this statistical specification, a moderated mediation model helps to specify a conceptual approach to understanding the development of psychopathology: (a) examining mechanisms can help us better understand the underlying processes of development, and (b) examining interactions helps specify the contexts in which these mechanisms operate.

A particularly intuitive IG × E model is a G × E interaction in which the interaction term predicts behavior through its effect on brain function (Figure 1, Path 3F). In this case, there may be direct effects of both genetic and environmental variables on brain function. Alternatively, there may be no main effects, but any genetic effect on the brain is present only in some environments (or vice versa, in which environmental effects on the brain only occur in individuals with more susceptible genetic alleles). For example, the *5-HTTLPR* polymorphism predicts increased amygdala reactivity (Hariri et al., 2002), as do experiences, such as early environmental deprivation (Tottenham et al., 2011) and maltreatment (McCrory et al., 2013). *5-HTTLPR* has also been shown to predict later adverse outcomes such as depression, but only in the context of early life stress (Caspi et al., 2003; Karg et al., 2011). Thus, individuals with both this genetic variation and harsh and stressful environmental experiences could

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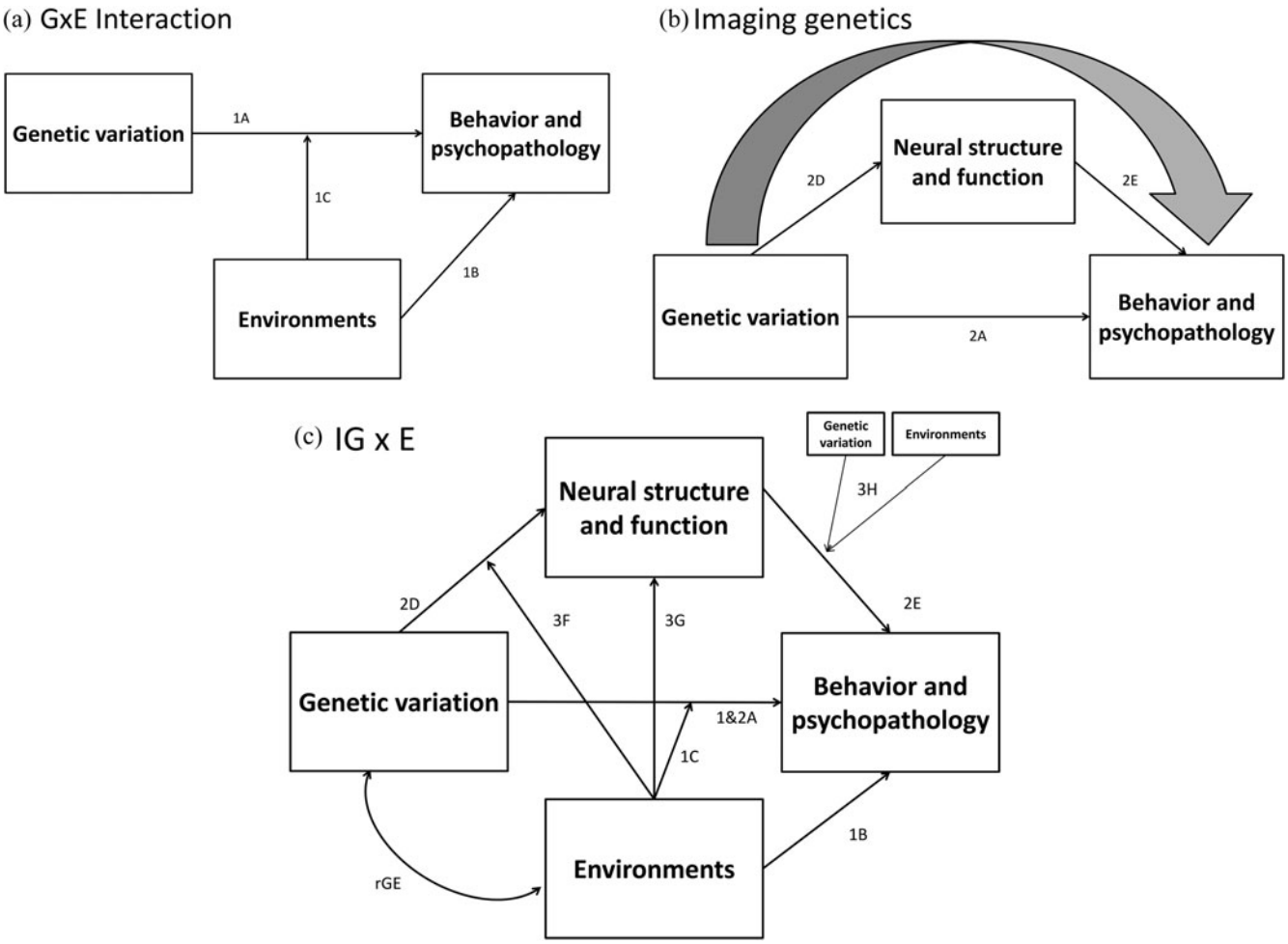

Figure 1. Imaging Gene × Environment interaction (IG × E) models. (a) A Gene × Environment (G × E) framework: genes and environments might each have a "main effect" on behavior (Paths 1A and 1B), but the focus of these studies is on the interaction term, which is modeled as a product of the two variables (1C). (b) An ideal imaging genetics framework: genetic variation to individual variability in neural structure or function (Path 2D) and individual variability in neural functioning leads to differences in behavior or psychopathology (Path 2E). Genetic variation might or might not have a direct impact on distal complex behavior (Path 2A). Genetic variation has an indirect or mediated effect on behavior via its effect on neural functioning (large arrow). (c) An IG × E framework: all paths labeled "1" are paths from G × E interactions studies, paths labeled "2" are imaging genetics pathways, and paths labeled "3" are paths unique to IG × E or other frameworks. The 3F pathway denotes a gene–environment interaction predicting neural functioning (IG × E effect). The 3H paths represent gene or environmental moderation of brain–behavior relations. 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. (For more details describing these pathways see Hyde, Bogdan, & Hariri, 2011.)

show a synergistic increase in amygdala reactivity, which then predicts increased anxiety or depression symptoms. In contrast, these individuals may show strong gene–brain links only when in the context of adversity. Alternatively, a positive environment, such as social support, could negate any relationship between genetic variation in serotonin signaling and amygdala reactivity, and this lowered amygdala reactivity could then predict lower mean levels of anxiety symptoms (Hyde, Manuck, & Hariri, 2011; Kaufman et al., 2004).

This example of an interaction (i.e., G × E predicting brain function) 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 may provide further insight into the conundrum of hidden heritability and provide a mechanism for G × E interaction findings. 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., maltreatment), IG × E may be able to detect this association, particularly with more proximal neural phenotypes. IG × E may also explain why certain environments do not uniformly affect brain and behavior by specifying who is most at risk due to genetic background.

Finally, it is important to note that within an IG × E model, other interesting interaction pathways may exist in which genes or experience could moderate brain–behavior links. Genetic variability may qualify brain–behavior correlations as illustrated by a study that found that a genetic variant

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affecting endocannabinoid signaling moderated the correlation between reward-related brain reactivity and a measure of impulsivity (Hariri et al., 2009). Experience could also qualify brain–behavior correlations, as illustrated by a study that found that those with low social support have a greater relationship between threat-related neural reactivity and trait anxiety (Hyde, Manuck, et al., 2011). Therefore, in thinking through IG × E interactions, we should consider that each pathway is likely to be qualified by both context and biology.

IG × E examples. Approaches testing a "full" IG × E model, in which a G × E interaction predicts brain function, which in turn predicts behavior through a mediated pathway, are exciting but only just beginning to emerge (Funderburk et al., 2013; Glaser et al., 2014). Several studies have been published testing G × E interactions that predict brain function, a critical first step in this emerging field (e.g., Cousijn et al., 2010; Drabant et al., 2012; Gerritsen et al., 2011; Ursini et al., 2011). In the first study, testing portions of an IG × E model, Canli et al. (2006) reported that *5-HTTLPR* genotype interacted with life stress to predict resting-state activity in the amygdala. More specifically, this study found that short allele carriers, who are more susceptible to the "depressogenic" effects of stress (Karg et al., 2011), had elevated amygdala activity at rest, but only among those who had experienced more life stress. This finding therefore provides a neural mechanism through which short allele carriers may be more susceptible to the environment at the neural level.

In another example, in two separate studies, Bogdan, Williamson, and Hariri (2012) and White et al. (2012) have shown, in relatively large samples of adolescents ($N = 279$ and 139), that variations in genes that affect hypothalamic–pituitary–adrenal (HPA) axis function (i.e., variation in mineralocorticoid receptor and FK506 binding protein 5 [*FKBP5*] genotype, respectively) moderate the association between childhood emotional neglect and threat-related amygdala reactivity. Finally, in an example of a full IG × E model, a very recent study examined another gene affecting HPA axis functioning (corticotropin-releasing hormone receptor 1 [*CRHR1*]) and demonstrated an indirect pathway from genotype to neural reactivity in the right ventral–lateral prefrontal cortex to negative emotionality. It is interesting that the path from geneotype to neural reactivity was moderated by childhood stress, consistent with a full-moderated mediation IG × E pathway (Glaser et al., 2014). Overall, these studies are beginning to demonstrate that gene effects on the brain are moderated by experience (or vice versa, that experience effects on the brain are moderated by genotype), a major component to an IG × E model. Moreover, like imaging genetics studies, they examine genetic variants that have specific effects on molecular pathways of interest. For example, in the studies by Bogdan, Williamson, et al. and White et al., as well as in the study by Glaser et al., the authors focused on variation in genes that affect HPA axis function and the stress response because these are critical pathways in understanding the neural effects of childhood maltreatment and child stress (Gunnar & Quevedo, 2007). Although these studies are beginning to identify a potential neural mechanism for G × E interactions, future studies that examine G × E interaction effects on behavior that are *mediated* by neural reactivity (i.e., Glaser et al., 2014) would strengthen inferences to how these processes affect behavior. Of course, such studies would need ample sample sizes for this relatively complex model, and neuroimaging studies have previously lacked the requisite power to test these associations. However, studies are emerging that combine neuroimaging and genetics in much larger samples with a greater ability to test complex mediation pathways with more appropriate levels of power (e.g., Ahs, Davis, Gorka, & Hariri, 2013; Paus, 2010; Thyreau et al., 2012; Whelan et al., 2012). Moreover, pushes for more MRI data sharing and open access neuroimaging data is likely to result in larger and larger studies of youth that contain neuroimaging and molecular genetics, with many of these data sets being open access, allowing for greater access by researchers with a wider variety of skills and areas of expertise (Mennes, Biswal, Castellanos, & Milham, 2013; Milham, 2012).

Neurogenetics summary

In summary, neurogenetics is an exciting approach to understanding neurobiological pathways that link genetic variability to neural structure and function and subsequent complex behavior and psychopathology. The core technique of neurogenetics is imaging genetics, which seeks to link candidate genes in relevant neurotransmitter systems to differences in neural structure and function. Imaging genetics findings are strengthened by building upon animal models and through additional studies testing molecular pathways more directly using techniques like multimodal and pharmacological imaging. By combining G × E interaction studies with imaging genetics, through an IG × E model, neurogenetics studies are now able to focus on the brain as a mechanism linking G × E interactions to the development of psychopathology. These models provide a framework for testing and understanding the complex interaction of genetic background and experience that influences the development of psychopathology across the life span.

Although IG × E models were inspired by some common approaches within developmental psychopathology (i.e., a focus on mechanisms and conditional relationships), there has been little integration of IG × E or neurogenetics more broadly with developmental psychopathology or any examination of how these approaches may inform each other. Therefore, I next describe some core tenets of developmental psychopathology, give examples of these areas of emphasis, and discuss how neurogenetics and developmental psychopathology can inform each other.

Tenets of Developmental Psychopathology in an Era of Molecular Genetics and Neuroimaging

The field of developmental psychopathology fundamentally aims to provide a developmental and ecological systems-based

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approach to understanding the development of psychopathology, adaptation, and maladaptation (for various descriptions of the field, see Cicchetti, 1984, 1993; Cicchetti & Rogosch, 1996; Cummings, Davies, & Campbell, 2000; Rutter, 1997; Sameroff, 1995; Sroufe & Rutter, 1984). Original goals in the field included bringing a more interdisciplinary approach to understanding child psychiatric disorders and focusing on a developmental systems approach to defining, conceptualizing, and studying the development of risk and resilience across the life span (Sroufe, 2013). These goals are no less important today, and as each year passes, we have a greater range of tools with which to examine development (Cicchetti & Toth, 2009; Rutter, 2013). Because it would be difficult to give a comprehensive account of this field, I focus my conceptualization of developmental psychopathology based on what I believe are core tenets or major areas of emphasis within the field (Cicchetti, 1993), with a focus on tenets that are particularly important and applicable to neurogenetics. My goal is to help build a model that involves a nuanced understanding of the development of psychopathology (and resilience in the face of risk) with a particular focus on integrating across multiple levels of analysis (for other models bridging across levels of analysis, see Bilder, Howe, & Sabb, 2013; Marshall, 2013; Patrick et al., 2013; Wiggins & Monk, 2013).

Tenet 1: Precise and complimentary phenotypic measurement is essential as psychopathology is dimensional, hierarchical, and likely contains unique and homogenous subgroups.

Developmental psychopathology researchers have been at the forefront of designing ways to conceptualize and measure "disordered" phenotypes. Recent evidence suggests that psychopathology, at both a construct and a measurement level, is dimensional rather than categorical in nature (Krueger & Markon, 2011; Plomin, Haworth, & Davis, 2009). Moreover, research has highlighted that most psychopathologies have high comorbidity and overlap with other psychopathologies (Krueger & Markon, 2006). In addition, within diagnostic categories, diagnoses contain great heterogeneity in terms of symptoms, prognosis, and development (Clark, Watson, & Reynolds, 1995; Tsuang, Lyons, & Faraone, 1990). Thus, simply measuring individuals in one diagnostic category versus "control" participants in which the diagnosis is considered to be categorical, nonoverlapping with other diagnoses, and a homogenous construct, ignores the fundamental structure of psychopathology. In an age of trying to map genetic and neurobiological correlates to these outcomes, studies of the structure of psychopathology may take on increased importance (Ofrat & Krueger, 2012; Plomin et al., 2009). Developmental psychopathology approaches have offered several ways to address these complex conceptual and measurement problems, which is important to neurogenetics because imaging and genetic approaches can only be as strong as the measurement of the phenotypes they seek to explain.

Dimensional and hierarchical models of the structure of psychopathology

Early pioneering work in children (Achenbach, 1966), for whom comorbidity is particularly high (Caron & Rutter, 1991), found that many childhood disorders could be mapped onto broadband factors (i.e., internalizing and externalizing). Research in adults has confirmed these findings and has identified that the dimensional and hierarchical structure of psychopathology suggests that much of the problem of comorbidity may come from a metastructure involving several broad domains (e.g., externalizing) that contain specific disorders as subfactors (e.g., conduct disorder or substance use disorders) that share general and specific risk factors (Krueger & Markon, 2006; Krueger, Markon, Patrick, Benning, & Kramer, 2007). Recent work even suggests that there may be a "p" metafactor (similiar to the metafactor "g" in the structure of intelligence; Carroll, 1993; Pedersen, Plomin, & McClearn, 1994) that indicates an overall latent risk for increased distress, greater overall symptomatology, and greater lability to psychopathology across all diagnoses (Caspi et al., 2013; Lahey et al., 2012), though research is only just emerging on this broadest metafactor.

Applying this metastructure to neurogenetics studies, or even neuroimaging studies in general, is particularly important given that many neural and genetic risk factors seem to be rather broad in their effects. For example, in children and adults, amygdala reactivity has been linked to several different disorders, including anxiety (Fakra et al., 2009; Monk et al., 2008) and depression (Price & Drevets, 2010), as well as some externalizing disorders (Blair, 2013; Hyde, Shaw, & Hariri, 2013). Results have been similar for genetic variants, such as the *5-HTTLPR*, which has been associated with these same internalizing and externalizing outcomes, though sometimes in opposite directions (Glenn, 2011; Karg et al., 2011; Sadeh et al., 2010). When considered in the context of research examining the hierarchical nature of psychopathology, neural and genetic studies suggest that variability across many individual genes or brain structures likely predicts multiple disorders due to the shared etiological structure of disorders at multiple levels (i.e., at the neural, genetic, and symptom levels). Applying models of general (i.e., general internalizing factor) versus specific (i.e., depression, anxiety, or substance use) factors as an outcome when undertaking neurogenetics studies may help identify which risk factors are general versus specific, or even *how* specific these risk factors are. This type of modeling approach, often referred to as a *bifactor*, or *general–specific model*, examines which risk factors predict multiple outcomes and the shared variance among these outcomes, and which risk factors predict only one disorder (and only its unique variance), and have the potential to explain why some individuals show a predominance of symptoms for one versus another related disorder (see Figure 2). These types of bifactor models have been applied in

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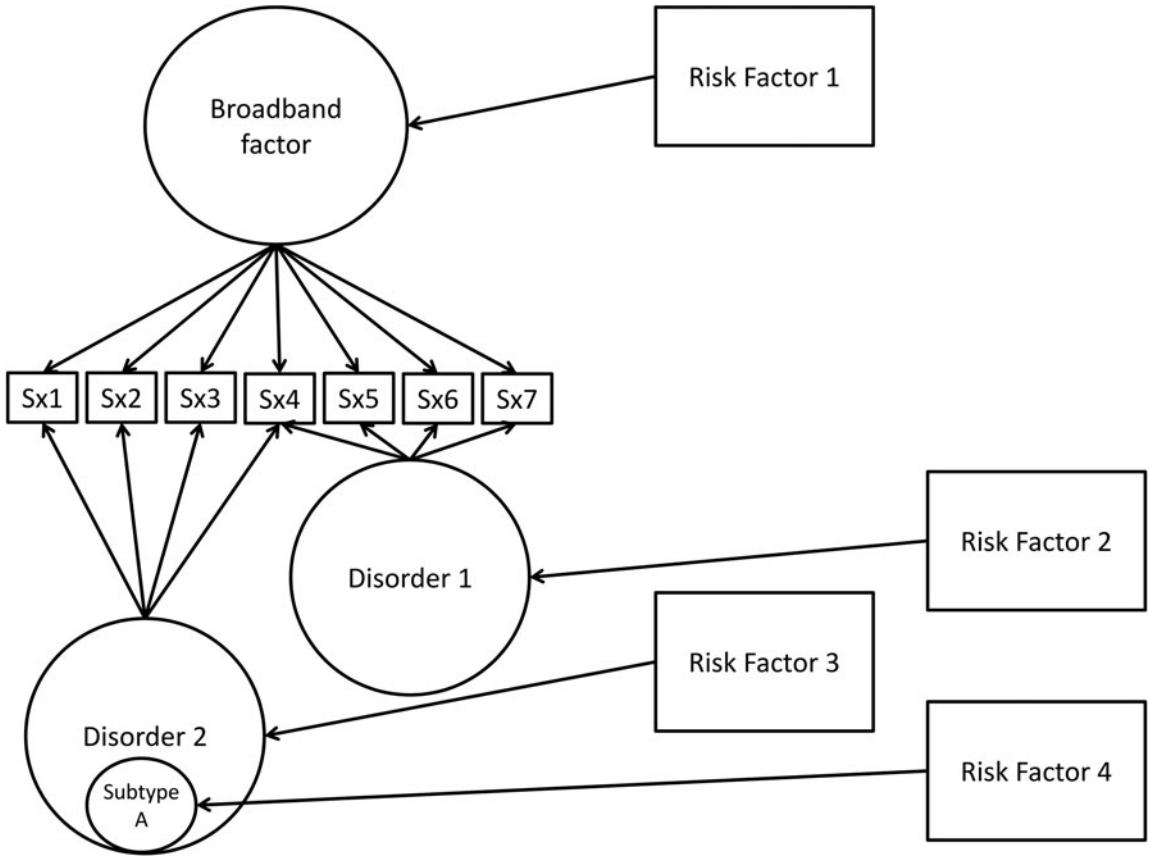

Figure 2. A hypothetical multilevel bifactor model. A graphical depiction of a hypothetical bifactor model for modeling general and specific effects of risk factors. In this model, *Sx* represents symptoms of a disorder. The broadband factor represents a latent factor underlying shared variance among the symptoms (the "general" factor). Risk Factor 1 represents a general risk that may have broad effects on symptoms that are related to Disorder 1 and 2. Disorders 1 and 2 represent comorbid and correlated disorders that may even share some symptoms (*Sx*4). Risk Factor 2 is specific to Disorder 1 and thus can be seen as a unique risk factor that does not contribute to shared variance among symptoms. Risk Factor 3 is similar in predicting specificity to Disorder 2 but broadly predicts all subtypes of Disorder 2. Risk Factor 4 represents a risk factor that even distinguishes a subtype within Disorder 2. As an example, the broadband factor could represent externalizing broadly with Disorder 1 representing attention-deficit/hyperactivity disorder and Disorder 2 representing conduct disorder. Subtype A could represent those high on callous–unemotional traits. Risk factor 1 might represent a risk factor for general disinhibition and externalizing, Risk Factor 2 would represent risk for poor attentional control more specific to attention-deficit/hyperactivity disorder, Risk Factor 3 would represent risk for opportunities to break rules (e.g., deviant peers), and Risk Factor 4 would represent risk for decreased empathy for others (for a more realistic example of externalizing, see Beauchaine & McNulty, 2013). Note that this model could represent many different levels (i.e., the broadband factor could represent a general "p" factor, with Disorder 1 representing externalizing and Disorder 2 representing internalizing and *Sx*s representing individual disorders; Caspi et al., 2013; Krueger et al., 2007; Lahey et al., 2011, 2012). The general factor or other mediating factors could also represent the "building blocks" described above, particularly if Disorder 1 and Disorder 2 share some specific building block (e.g., emotion dysregulation).

other areas, such as intelligence (Pedersen et al., 1994) and psychopathy (Patrick, Hicks, Nichol, & Krueger, 2007), but are still scarce in genetic and neuroimaging studies of psychopathology despite their promise (Banaschewski et al., 2005; Lahey, Van Hulle, Singh, Waldman, & Rathouz, 2011).

Bifactor models help to explain high levels of comorbidity between disorders and explain why many risk factors are shared across disorders. Instead of understanding genetic and neural variation as specific correlates or part of an etiology for one disorder, with further bifactor and transdiagnostic research, we may instead conceptualize neural and genetic variables as factors contributing to dimensions that may be shared or unique to various psychopathologies (Insel et al., 2010; Sanislow et al., 2010). For example, in the case of both the short allele of the *5-HTTLPR* and high amygdala reactivity, these risk factors may instead contribute to broad risk for psychopathology, particularly internalizing. It may be that this risk is underpinned by a dimension of neuroticism, emotionality, or emotional dysregulation (Lahey, 2009). Being greater on amygdala reactivity may make one more prone to being emotional, emotionally dysregulated, or sensitive to emotional stimuli, which could increase risk for anxiety and depression, thus explaining the lack of specificity of amygdala reactivity in predicting anxiety versus depression. This same risk of high amygdala reactivity could even be linked to some types of externalizing that involve higher levels of emotion dysregulation, such as oppositional defiant disorder (Pardini & Frick, 2013). In contrast, having very low

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amygdala reactivity and emotionality could increase risk for other pathologies, including some types of externalizing that are low on emotionality such as psychopathy (Hyde, Byrd, Votruba-Drzal, Hariri, & Manuck, 2014; Hyde et al., 2013). In this case, basic neural functioning, when examined transdiagnostically and within a bifactor framework, may explain why some disorders overlap and how they overlap (e.g., through greater amygdala reactivity and emotional reactivity; Buckholtz & Meyer-Lindenberg, 2012). Thus bifactor models involving neurogenetics could help to identify factors associated with a general increased level of risk for psychopathology, as well as identifying why risk in some people leads to different outcomes (i.e., why do some people with high amygdala reactivity show anxiety versus depression? Why are some people resilient to high amygdala reactivity?).

Identifying the mediators and building blocks of these processes

One extension of this idea, a major foundation of the RDoC initiative, is that psychopathology research should be focusing more on individual building blocks to these broader domains, rather than focusing only on one specific disorder. Whether these building blocks are conceptualized as domains in the RDoC (Sanislow et al., 2010) or even components of personality and temperament, it seems likely that variability in genes and the brain will map more directly to more narrow and homogenous building blocks rather than directly and simply onto complex, overlapping, and heterogeneous clinical diagnostic constructs (Insel et al., 2010; Ofrat & Krueger, 2012; Plomin et al., 2009). Thus, one day, we may think more of various clinical diagnoses in terms of their building blocks (e.g., high emotionality or low reward), which may explain their overlapping and hierarchical structure as well as why certain neural, genetic, and experiential variables map on to general versus specific psychopathology outcomes (e.g., Dillon et al., 2013). Of course, it is important to consider that much of this work has focused on adults, and there has been less consideration of how these building blocks might differ or develop over time and what that development would look like (see points about homotypic and heterotypic continuity below). In addition, examination of general versus specific risk factors is not unique to biological approaches. One major thrust in developmental psychopathology has been to understand why the same risk factor (e.g., child maltreatment) can often lead to many different outcomes in different individuals (e.g., depression, anxiety, or antisocial behavior; see Equifinality and Multifinality below).

Overall, models of the structure of psychopathology among youth and adults demonstrate the need for advances in neurogenetics for several reasons. First, psychopathology at the measurement and construct levels should be considered as dimensional and overlapping in nature. Thus, examining specific versus general correlates of genetic and neural variability may help to identify how these genetic, neural, and environmental variables fit together and how they contribute to the developmental of psychopathology. Second, examining mediators of brain–psychopathology and gene–psychopathology links may help to identify the "building blocks" of psychopathology at multiple levels (e.g., Brammer & Lee, 2013; Dillon et al., 2013). For example, would level of neuroticism or negative affectivity help explain links between amygdala reactivity and pathological outcomes, such as anxiety and depression? Third, from a developmental perspective, we may begin to think about what these building blocks would consist of at different ages to help specify the dynamic interplay of genes and experience early in development. For example, might early difficult temperament, later emotional dysregulation, and adult mood lability be differing manifestation of the same underlying neurobiological processes? Understanding the building blocks of psychopathology at multiple levels early in development will then be important because their development may set the stage for increased risk for later psychopathology. As such, an examination of these building blocks early in life (e.g., early temperament and early behavioral response to reward) may also help to identify those children at highest risk for later disorders, even before the onset of diagnosed psychopathology when preventative interventions may be most successful and behavior may be less entrenched.

Person-centered approaches

Although these dimensional and hierarchical models appear to fit the data well, they also ignore the usefulness of categories in clinical practice and the marked heterogeneity even within individual diagnoses (i.e., it focuses more on what disorders share at the broad level or which symptoms are important transdiagnostically, rather than addressing the heterogeneity within each disorder). Bifactor models may uncover broad, general risk factors for psychopathology, but it is also important to identify why different individuals have different symptom profiles within a specific diagnosis. Further, identification of symptom profiles or other attributes of an individual may help to identify subgroups of individuals with a more similar development, course, and etiology of psychopathology, and may even identify individuals who need different treatments. This idea of drilling down into smaller and more homogenous groups is akin to specifying a third level in the metastructure of psychopathology (i.e., externalizing contains conduct disorders that contain subgroups within this disorder; see Figure 2). Developmental psychopathology as a field has long championed using person-centered approaches to augment variable-centered analyses. This emphasis is important because finding statistical relations with a dimensional outcome can result in very different interpretations relative to interpretations arising from results with a small group of individuals who are particularly extreme on certain variables that are associated with etiology, development, or prognosis (e.g., consider Sebastian et al., 2012; vs. Viding, Sebastian, et al., 2012). Moreover, a person-centered analysis can help to uncover groups of youth that may look

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similar on one measure (e.g., diagnosis), but may differ in many important ways on other measures (e.g., symptom onset, duration, or age of onset).

One major example illustrating the importance of person-centered approaches is that the age of onset of antisocial behavior (AB) defines groups of youth with a different course and outcome to their behaviors (Moffitt, 1993). Many group-based trajectory modeling studies have supported the delineation of these subgroups (e.g., Broidy et al., 2003; Shaw, Hyde, & Brennan, 2012), and theoretical work has supported the idea that youth in these groups come to AB via different developmental processes (Moffitt, 1993; Patterson, DeBaryshe, & Ramsey, 1989; Patterson, Reid, & Dishion, 1992): early-starting AB is associated with greater antecedent risk, including neurocognitive deficits, harsher parenting, more difficult temperament, and higher comorbidity (Moffitt, Caspi, Harrington, & Milne, 2002; Patterson et al., 1992), a more chronic and escalating trajectory of behavior (Shaw & Gross, 2008), and worse outcomes in adulthood (Moffitt et al., 2002). In contrast, AB that begins in adolescence has been linked to deviant peer affiliation (Dishion, Patterson, Stoolmiller, & Skinner, 1991), fewer proximal family risks, and a less elevated and less chronic trajectory of AB, with fewer problematic outcomes during adulthood (Moffitt, Caspi, Dickson, Silva, & Stanton, 1996). This body of research emphasizes that examining the age of onset may help to uncover important subgroups of youth who may appear similar at one point in time (e.g., midadolescence) but differ in both risk profile and developmental course (an example of equifinality, described in more detail below), which has implications for prevention and intervention (i.e., early starting youth are at most at risk for worse outcomes, and thus interventions should target these youth and start early).

Neurogenetics research could benefit from examining specific subgroups of more similar individuals, which may produce more consistent and robust findings than do studies that examine broad diagnostic classifications that contain substantial heterogeneity. For example, although age of onset has received relatively little attention in the fMRI literature on youth AB (though see Passamonti et al., 2010), a second major subtyping approach for delineating more homogenous subgroups of youth high on AB has been to examine the presence or absence of callous–unemotional (CU) traits (Frick, Ray, Thornton, & Kahn, 2014). This subtyping approach has been particularly helpful in the application of fMRI to the study of youth AB (Viding, Fontaine, & McCrory, 2012). For example, early results from studies examining heterogeneous groups of youth with conduct disorder yielded inconsistent findings (for a review, see Hyde et al., 2013), whereas more recent studies that have examined CU traits as a subtyping approach for youth AB appear to identify two subgroups with different profiles of neural reactivity: youth with AB and CU traits appear to have behavior that is more highly heritable (Viding, Jones, Paul, Moffitt, & Plomin, 2008), associated with deficits in emotion recognition (Marsh & Blair, 2008), and exhibit *reduced* amygdala reactivity to emotional paradigms (Jones, Laurens, Herba, Gareth, & Viding, 2009; Marsh et al., 2008). In contrast, youth high on AB and low on CU traits appear to have AB that is much less highly heritable, more associated with emotional dysregulation (Pardini & Frick, 2013), and exhibit *exaggerated* amygdala reactivity to the same emotional paradigms (Viding, Sebastian, et al., 2012). Given that youth with AB and CU traits are low on amygdala reactivity, whereas youth with AB and without CU traits are higher than control youth, neurogenetics studies that ignore these subgroups may find very conflicting findings depending on the levels of unmeasured CU traits within them, particularly when examining neural and genetic correlates.

Beyond neurogenetics needing to consider subgroups that may have different biological correlates, neural and genetic studies may also eventually help to identify heterogeneity in diagnoses and possible ways to identify those who are more biologically similar within a diagnostic group. That is, these studies may uncover more homogenous groups that were not evident when only examining behavior at the symptom level. For example, within G × E interaction studies, particularly studies examining the *5-HTTLPR* × Stressful Life Events interaction predicting depression, depression itself appears to be a heterogeneous outcome because empirical research suggests that stressful life events are predictive of *early* depressive episodes (Bogdan, Agrawal, Gaffrey, Tillman, & Luby, 2013), but less predictive of its future *recurrence* (Kendler, Thornton, & Gardner, 2000). This interaction may predict some types or patterns of depression, but not others, particularly in the sense that depression cannot be conceived of as a single or simple outcome. Studies can address this issue by exploring subtypes of disorders (e.g., child vs. adult onset depression) and phenotypes within a disorder (e.g., anhedonia within depression), by narrowing criteria for a disorder (e.g., only those with recurrent rather than a single depressive episode), or by exploring specific symptoms clusters within a disorder. These studies illustrate how G × E interaction studies are likely to benefit from examining potential subgroups, and also how the G × E literature may help to emphasize or identify factors that delineate more homogenous groups of individuals within a single diagnosis.

The promise of examining subgrouping and person-centered approaches within studies of psychopathology, particularly those examining neural and genetic correlates, is that if these studies identify a group of youth or adults with a distinct etiology (e.g., those high on CU traits and AB, or those with early onset depression), then we may be better able to tailor interventions to these individuals based on our understanding of their differential neural correlates (e.g., Dadds et al., 2013; Hyde, Waller, & Burt, 2014). Moreover, if empirical studies identify factors (i.e., early starting AB or certain genetic polymorphisms) that predict a different course of a disorder, then these factors may be important in identifying those at highest risk and most in need of early preventative interventions (e.g., Dishion et al., 2008). Genetic variation and brain function may also help to predict treatment

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response, and in the future these factors could be considered before interventions are started (e.g., Bryant et al., 2008; Uhr et al., 2008). Thus, as medicine moves toward both a more tailored and a personalized model of care at the individual level and a preventative model of care at the population level, identifying factors that delineate subgroups of individuals that need different treatments or that can be targeted earlier with preventative interventions is increasingly important and may help to increase the effectiveness of both prevention and intervention models (Simon & Perlis, 2010; Willard & Ginsburg, 2009).

Summary of phenotypic consideration

In sum, models of the development of psychopathology are beginning to benefit from examining the dimensional and hierarchical structure of psychopathology, as well as links between risk factors and general versus specific outcomes, but these models have not yet been applied to neuroimaging or molecular genetics research. Moreover, though evidence supports a dimensional and hierarchical approach, research is also needed that specifies these risk processes at a person level by identifying groups of individuals that are more homogenous in development, symptoms, outcomes, and treatment response. Neural and genetic studies have already helped to support the notion that, within some psychopathologies, subgroups exist that have different biological correlates. However, broad and person-centered approaches have not been a major focus in neurogenetics yet. Thus, further integration of these concepts into neurogenetics is needed to help uncover how neural and genetic processes might operate to predict broad and general outcomes, as well as specific subgroups of youth within existing diagnoses. Moreover, by providing more accurate outcomes (with less error), these outcomes may help increase the precision of neurogenetics studies.

Tenet 2: Mechanistic research informs our understanding of how risk affects outcomes.

A second major theme in developmental psychopathology has been the importance of specifying mechanisms that link risk to outcomes. For example, knowing that harsh parenting or deviant peer interactions are correlated with youth AB is helpful, but it does not specify how or why these experiences lead to greater levels of AB at subsequent time points (e.g., Hyde, Shaw, & Moilanen, 2010). Behavioral studies that have uncovered mechanisms underlying these associations (e.g., coercive parent–child interactions or rewards within microinteractions as part of peer deviancy training) have helped to better inform our overall understanding of these risk processes (e.g., Dishion, Spracklen, Andrews, & Patterson, 1996; Patterson et al., 1989, 1992), which have in turn helped inform more effective theory-based interventions (e.g., Dishion & Kavanagh, 2003; Dishion et al., 2008; Webster-Stratton & Reid, 2003). In a second example, research in both internalizing disorders (Abramson, Seligman, & Teasdale, 1978) and externalizing disorders (Dodge, 1993; Huesmann, 1998) emphasized the mechanistic role of cognitions in the development of psychopathology and helped to inform important current treatment approaches for depression and conduct problems that involves targeting maladaptive cognitions as part of treatment (Beck, 1976; Conduct Problems Prevention Research Group, 2002). These are only a few of many examples demonstrating that the examination of mechanisms underlying risk–outcome relationships can better inform our understanding from a basic science approach, as well as informing intervention research.

Applying mechanisms to neurogenetics

As described above, a first major implication of an emphasis on mechanisms is in delineating building blocks (or RDoC domains) of more basic behaviors or temperamental profiles that may underlie links between brain and psychopathology. Just as identifying these building blocks may help to explain overlapping symptoms and comorbidity between diagnoses (Beauchaine & McNulty, 2013; Buckholtz & Meyer-Lindenberg, 2012), these building blocks may also be seen as more proximal mediators linking genetic and environmental risk to more basic behavioral processes that underlie later psychopathology symptoms (see also work on endophenotypes, e.g., Gottesman & Gould, 2003). Thus, neurogenetics studies can examine narrower and more homogenous constructs as described by temperament, personality, or domains described in RDoC, rather than heterogeneous, comorbid, and complex diagnostic categories. Neurogenetics studies can formally examine these building blocks as *mediators* between genetic, neural, and environmental risk and psychopathology (see also earlier descriptions of similiar pre-RDoC approaches; Carter et al., 2008). Though this approach has taken on a new form with neural and genetic tools, the idea of examining more basic behaviors or tendencies to understanding the components of psychopathology is not completely new (Costa & McCrae, 1995; Lahey, Waldman, & McBurnett, 1999; Widiger & Lynam, 1998). However, neural and genetic tools may help to better define these more proximal behavioral phenotypes and better examine building blocks at multiple biological levels, and through mediation analyses we can actually test the hypotheses that these building blocks are the underlying mechanisms. For example, in models of externalizing, recent work has emphasized that externalizing is composed of latent disinhibition and impulsivity (Zucker, Heitzeg, & Nigg, 2011), as well as mood lability and emotion dysregulation components (Beauchaine & McNulty, 2013), and emerging work may help to revise our understanding of these constructs and their relation to different externalizing disorders at multiple levels (e.g., symptom, psychometric, physiological, genetic; Patrick et al., 2013).

Mediation models linking gene–brain–behavior

A second way in which neurogenetics can use more focus on mechanisms is in applying mediation analyses to imaging

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genetics. The emphasis on mechanisms is important because, fundamentally, imaging genetics focuses on linking variability in genes to variability in the brain as this pathway affects behavior. However, a majority of imaging genetics studies have only established links between genetic polymorphisms and brain structure or function but have failed to link these variables directly to meaningful differences in behavior (e.g., Hariri et al., 2002; Pezawas et al., 2005). Imaging genetics studies have recently begun to establish such meaningful links by modeling *indirect* or mediated pathways from genes to behavior via the brain (see Figure 1b), but only a few studies thus far that have actually tested these relationships statistically (Fakra et al., 2009; Furmark et al., 2008; Glaser et al., 2014). In one of these studies, we examined the impact of common functional variation in the gene coding for the serotonin 1A receptor, *HTR1A* (Fakra et al., 2009). Building on previous research described above (Fisher et al., 2006; Lemonde et al., 2003), we found that a genetic variant in *HTR1A* predicted amygdala reactivity to threat, and amygdala reactivity in turn predicted level of trait anxiety in a sample of healthy adults. It is important that, though the main effect of this gene on trait anxiety was small and not statistically significant, a path analysis revealed a significant indirect effect from the genetic polymorphism to trait anxiety via its effect on amygdala reactivity. This study illustrates how imaging genetics studies can probe indirect and mediated gene–brain–behavior pathways and can even find indirect pathways between gene and behavior through the brain, when no direct gene–behavior link exists. Moreover, these models specifying the brain as a mechanism between gene and behavior emphasize the importance of using statistical approaches common in developmental psychopathology (but perhaps not as common in neuroscience) that can model indirect or mediated pathways (Preacher et al., 2007). Although this study demonstrates the potential of combining quantitative approaches to testing mechanisms and imaging genetics, more imaging genetics studies (and IG × E studies) are needed that actually draw out the gene–brain relationships. Thus, common conceptual and quantitative approaches that emphasize and test mechanisms within developmental psychopathology (e.g., mediation and structural equation modeling) could help to better test important neurogenetics models.

Mechanisms across levels of analysis

Finally, a mechanistic emphasis applied to current neural and genetics studies illustrates how complex these multilevel models will be. Scholars in developmental psychopathology have written cogently about the application of multilevel (e.g., Cicchetti & Toth, 2009) and complex systems (Bronfenbrenner & Ceci, 1994; Sameroff, 1995, 2010) frameworks to understanding these complex, reciprocal, and cascading pathways, and thus have much to offer theoretically and empirically to neurogenetics studies. As ecological and complex systems theories that have been described in developmental psychopathology are applied to neural and genetic studies, better models can be proposed and tested that contain multiple mechanistic (and interactive) pathways that reach from molecules to cells to brain circuits to traits to symptoms to outcomes (e.g., Beauchaine & McNulty, 2013; Hankin, 2012). These multilevel developmental systems models will help lead to well-defined molecular mechanisms specifying both the genetic and the environmental precursors to psychopathology (Meaney, 2010; Roth, 2013). In other words, developmental scholars have spent much time conceptualizing the integration of nature and nurture across multiple levels and across time, and thus these theories can and should inform neurogenetics studies that are becoming more or more complex.

In sum, an emphasis on mechanisms in developmental psychopathology can help to shape neural and genetic studies of the development of psychopathology. These models can be applicable in conceptualizing the links between levels of analysis, as well as quantitative approaches to testing these relationships. It is important that developmental psychopathology's emphasis on adopting an interdisciplinary approach, particularly in its adaptation of ecological and complex systems models, can help inform changing views of the structure of psychopathology and maladaptive behaviors.

Tenet 3: Interactions: Gene, brain, experience, and behavioral mechanisms are conditional.

Another important area of emphasis within developmental psychopathology is that each risk or protective factor does not operate alone but rather within a complex system of interactions. This point is vital to IG × E models and certainly underlies G × E interaction and differential susceptibility models (Belsky & Pluess, 2009; Ellis & Boyce, 2011). Thus, the most straightforward way that an emphasis on complex interactions has influenced, or can influence, neural and genetic studies of development is to highlight that large main effects of either biology or experience are unlikely; rather, these influences will be conditional. This notion is important in countering popular culture understandings that when an outcome is heritable or genetic or hard-wired in the brain, it is somehow immutable, unchangeable, or not subject to interaction with experience, nor that it will change through development. As noted throughout this paper, gene–behavior (Moffitt et al., 2005), brain–behavior (Hyde, Manuck, et al., 2011), and gene–brain (Canli et al., 2006) relationships have all been shown to be moderated by experience. Moreover, research has shown thus far that we will not find a depression gene or a violence gene, just as we have not found a height or weight gene. Rather, such complex behaviors will be the result of multiple interacting genes and experiences (Plomin & Simpson, 2013). Of course, specifying these interactions is one of the major challenges for the field. Though this point may not seem novel to developmental psychopathologists, it is a critical point as neural and genetic variables take on an increased emphasis and are interpreted by the media and general public.

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One good example of a way that theory and research in developmental psychopathology can help to address complex models is the recent advance in understanding conditional effects. Previously, the dominant model of psychopathology was a diathesis–stress model (Rosenthal, 1963) positing that some individuals had a latent propensity toward a certain psychopathology, which could be unmasked under certain conditions (e.g., high stress). Recent work in the field has brought more nuance to this idea through the proposal and testing of models of differential susceptibility that posit that some individuals are more susceptible to their environment for better (vantage sensitivity) or worse (vulnerability factors or diathesis), or both (differential susceptibility; Belsky & Pluess, 2009; Ellis & Boyce, 2011). Many of these models have focused on genes as markers for individuals who are most vulnerable to negative environments (Belsky & Pluess, 2009), those who may benefit the most from positive experiences (Pluess & Belsky, 2013), and those who are more sensitive to both good and bad environments (Belsky et al., 2009). Although more research is needed to provide empirical support for these models and the range of effects (Manuck, 2013), they provide conceptual models that are important for thinking through the interactions among genes, brain, and experience in the prediction of current and future behavior. Further, the emphasis that some "risk" factors may actually be factors that make individuals more susceptible to both bad *and* good experiences and outcomes is critical to consider in IG × E models.

G × E × E and G × G × E interactions in neurogenetics

Beyond "simple" G × E interactions, recent evidence has also shown that even greater complexity likely exists in the form of G × E × E and G × G × E (Kaufman et al., 2004; Rutter & Dodge, 2011; Wenten et al., 2009) interactions. For example, in an interesting G × E × E study, the authors report that the *5-HTTLPR* Genotype × Maltreatment interaction predicting depressive symptoms originally reported by Caspi et al. (2003) was further moderated by social support. In this study, only short allele homozygotes with a history of childhood maltreatment *and* low social support showed increased depressive symptoms (Kaufman et al., 2004). In an example of a G × G × E interaction, researchers using the Children's Health Study found that G × G interactions predicting respiratory-related school absence in youth (i.e., related to asthma) are most evident in communities that have higher ozone (i.e., pollution) levels. Similarly, in another example of a G × G × E interaction predicting maladaptive outcomes, Cicchetti, Rogosch, and Oshiri (2011) found that the combination of "risky" *CRHR1* and *5-HTTLPR* genotypes predicted the highest levels of internalizing symptoms among children who had been maltreated versus those who had not. These types of studies emphasize the complex and multifaceted nature of the relationship among genes, experiences, and behavior, in which some experiences exacerbate risk (e.g., maltreatment), while others are protective (e.g., high social support). These complex interactions are likely present in imaging genetics studies as well. For example, G × G interactions have been shown to predict neural structure and function, emphasizing that simple imaging genetics studies examining only one gene may be underestimating the inherent complexity of these systems (e.g., Buckholtz et al., 2007).

Cumulative risk models

It is interesting that, in recent neurogenetics studies, researchers have begun to address G × G interactions and the likely cumulative nature of different genetic variants by constructing cumulative/polygenic genetic profiles (Cicchetti & Rogosch, 2012; Holmes et al., 2012; Nikolova, Ferrell, Manuck, & Hariri, 2011; Purcell, 2002). This approach harkens back to the major impact that cumulative risk models of environmental exposures have made within developmental psychopathology (Sameroff, Seifer, Zax, & Barocas, 1987). Thus both fields have shown that an accumulation of risk, whether genetic or environmental, is often more important than any single risk factor by itself in predicting poor outcomes (Plomin & Simpson, 2013). No studies to my knowledge have combined cumulative genetics models with cumulative experiential models, but these models seem imminent and important. Beyond cumulative risk models, more data-driven and hypothesis-driven quantitative approaches are needed to model complex gene and environmental risk models that may involve several genes and experiences. These models will likely require new methodology to be developed or the application of previously used quantitative approaches to quantitatively combine multiple interacting genetic variants (e.g., Bentley et al., 2013; Gruenewald, Seeman, Ryff, Karlamangla, & Singer, 2006; Hizer, Wright, & Garcia, 2004; Holmes et al., 2012). Although these models will be challenging, they appear to be more consistent with the complexity inherent in nature.

Tenet 4: Pathways are complex and probabilistic.

As noted above, developmental psychopathology research has consistently conceptualized and tested complex pathways in the development of psychopathology. Research testing these complex pathways has emphasized that children take a variety of different paths to or from the same point, that interactions between risk factors are likely to be complex and probabilistic, and that the conceptualization and focus only on risk may leave out an understanding of processes important in the pathways to adaptive and maladaptive outcomes. These conclusions have implications for neurogenetics, particularly as neurogenetics studies are applied to studies of development.

Equifinality and multifinality

Children can arrive at the same point or diagnosis from many different risk factors (equifinality), and children with the same risk factor(s) may end at very different points or

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diagnoses (multifinality; Cicchetti & Rogosch, 1996). These concepts help to emphasize that many risk factors are not specific to one outcome, that there are likely multiple pathways and etiologies to any single disorder, and that the effects of risk on outcome are probabilistic. In an example of equifinality, multiple different risk factors can influence the development of the same behaviors: a child with early abusive parenting and a child with early warm parenting but later deviant peer affiliation may both exhibit the same symptoms of conduct disorder in adolescence. Alternatively, as an example of multifinality, two children with the same initial risk factor may end up with very different outcomes (Hankin et al., 2011). For example, a child high on sensation seeking and testosterone may be at greater risk for externalizing in a dangerous neighborhood (Dabbs & Morris, 1990; Trentacosta, Hyde, Shaw, & Cheong, 2009), but these same risk factors may lead him to become a competent firefighter in another context (Fannin & Dabbs, 2003). These same pathways likely apply to neurogenetics findings because the same genetic variant or neural profile may lead to a variety of different outcomes, and there may be multiple different biological pathways to the same diagnosis (Hyde et al., 2013).

Probabilistic predictors and complex systems

Although observations of equifinality and multifinality have led to an understanding of the probabilistic nature of risk in complex systems in developmental psychopathology, in applying these principles to neurogenetics studies, it is important to highlight that the effects of genetic and neural variability are also likely to be probabilistic, as highlighted by much of the research described thus far. Thus, understanding biological differences between groups high or low on a certain psychopathology only helps us understand *biases* toward certain behaviors. Any single experience, single gene, or functioning in a single brain area is unlikely to be *deterministic* or to be *the* major factor in the development of complex psychopathology. Rather, each risk, across all possible domains, is likely to bias an individual toward or away from risk via interaction with other factors. For example, studies of the serotonin system and the amygdala have shown that certain genes in the serotonin system (e.g., the short allele of *5-HTTLPR*) and increased amygdala activity to threat are linked to anxiety and depression (Fakra et al., 2009; Hariri et al., 2006; Monk et al., 2008; Price & Drevets, 2010). However, many people with both increased amygdala activity to threat and risk alleles in the serotonin system are not depressed or anxious (Hyde, Manuck, et al., 2011). These variables simply reflect one small part of a complex probabilistic chain. As noted above, this point is important in communicating science to the public and in not privileging genetic or neural variables as more real, deterministic, or stable than other variables.

At the same time, we must also consider that a small risk factor or a push toward one outcome in a complex system can lead to larger changes (Kauffman, 1996; Sameroff, 1995). In the case of specific neural or genetic profiles, small pushes to a system (e.g., a slightly greater tendency toward or away from anxiety and attention to threat) in one direction may lead to developmental cascades toward or away from risk as the child and environment begin to shape each other over time (Masten & Cicchetti, 2010). For example, literature in early child behavior problems has shown that children shape their environment as much as they are being shaped by it: more difficult infants tend to be more difficult to parent, leading to harsher parenting, which in turn may promote further difficultness and behavior problems (Bell, 1968; Patterson et al., 1989; Shaw, Gilliom, Ingoldsby, & Nagin, 2003). Thus, though the effects of many genetic and neural variables may be small and probabilistic, they may, in some youth and in some contexts, have larger effects due to their role in a developmental cascade over time.

Moreover, consistent with research showing gene–environment correlations (*r*GE), children at the highest genetic risk for psychopathology are also those likely to live in environments that put them at the most risk for psychopathology (Jaffee, 2011; Jaffee & Price, 2007). For example, children inheriting genes that may impact brain functioning to make them more impulsive are more likely to have parents with genes that are related to impulsivity, who may model this behavior, and because of their own behavior, live in more dangerous neighborhoods. Thus, given work on *r*GE, at the epidemiologic level, children with the riskiest genetic loading are more likely to have riskier environmental exposures as well. The context in this case is likely to reinforce whatever underlying biological predisposition is present, leading to further developmental cascades.

In addition, as some authors have pointed out, children with early deficits such as poor emotion regulation may learn strategies that work in these risky environments, only to have these strategies lead to later problems in other environments (Thompson & Calkins, 1996). Thus, *r*GE may lead to a double-edged sword: their emotion regulation strategies may initially be protective but may lead to more problems later in life when in a different context. For example, early aggression may actually keep a child safer from peers in a dangerous neighborhood (Belsky, 1997), but it may eventually lead to poor outcomes outside of this neighborhood. Gene–environment correlations are important to consider in developmental neurogenetics because genes and environments are not randomly distributed, and small effects of genetic or neural measures can lead to larger consequences across development through more risky environments and potential cascading effects.

Studies of equifinality and multifinality also provide important future directions for neurogenetics. Now that studies have begun to establish more robust relationships between risky genetic and neural variables and psychopathology, a next major step will be to help define why these risks predict poor outcomes for *only some people*. In other words, what pathways contribute to normal functioning for many with risky genetic or neural profiles? Why do some individuals who carry the *5-HTTLPR* not have elevated amygdala

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reactivity? These questions have major treatment and prevention implications in identifying who is protected from the negative effects of risk and how they are protected. For example, if protective effects can be found in neural or environmental domains, then these variables can be targeted in interventions. In the example of social support moderating the relationship between amygdala reactivity to threat and trait anxiety (Hyde, Manuck, et al., 2011), a treatment for more severe anxiety, particularly for those with greater amygdala reactivity, might be to increase social support because this appears to protect against the risk posed by heightened amygdala reactivity to threat (though obviously much more research is needed to support this particular example). Thus, one major way forward for neurogenetics research, as suggested by work in developmental psychopathology, is to identify factors that buffer risk or that explain why only some individuals with neural or genetic risk go on to show psychopathology.

Resilience

Further, the study of resilience in developmental psychopathology could also inform neurogenetics models (Cicchetti & Blender, 2006; Cicchetti & Curtis, 2007; Curtis & Cicchetti, 2003; Masten, 2001; Rutter, 2006). Much neurogenetics research has focused on risk and maladaptive outcomes, but these same tools could be leveraged by positive psychology. Studies of resilience within a neurogenetics framework could help to identify neural and genetic profiles of individuals who are resilient under circumstances of great risk (e.g., child maltreatment or high stress; e.g., Cicchetti & Rogosch, 2012; Feder, Nestler, & Charney, 2009). Alternatively, these studies could help to identify factors that buffer the risk posed by risky genes or neural profiles. Little research or theory within neurogenetics has explored these questions (though for insights on this approach and an overview of the merging of these approaches, see Cicchetti & Blender, 2006; Cicchetti & Curtis, 2007; Curtis & Cicchetti, 2003), whose answers may help to identify potential avenues for novel treatment and help us to understand more about success, rather than focusing solely on risk and maladaptive outcomes.

Definition of risk

Finally, it may be important to consider whether many of the neural and genetic variables being studied in neurogenetics can really be cast as risky versus protective. Developmental psychopathology has emphasized questions that we must ask in neurogenetics: risky for what and under what circumstance? The same may be true in neurogenetics. Without question, major neural or genetic insults, such as head trauma or gene deletion, will almost always result in poor outcomes because they affect many processes. However, many common polymorphisms examined in studies to date likely code for more basic and normative processes that are risky in some settings but not in others. For example, the short allele of the *5-HTTLPR* has been identified as the risk allele due to its correlation with internalizing outcomes. However, there is now mounting evidence that the other allele (the long allele) may be correlated with externalizing outcomes, particularly psychopathy in adults and CU traits in youth (Glenn, 2011; Sadeh et al., 2010). Moreover, others have argued that the short allele itself may confer advantages in other domains outside of risk for internalizing disorders (Homberg & Lesch, 2011). Similarly, elevated amygdala reactivity to threat has been correlated with internalizing outcomes (Price & Drevets, 2010), whereas low amygdala reactivity has been correlated with psychopathy (Blair, 2013). These results also highlight the point made previously that examining temperamental variables as mediators of these processes can help to explain neurogenetics relations with psychopathology. In this case, it may be that the short allele of the *5-HTTLPR* and greater amygdala reactivity are related to greater neuroticism and trait anxiety. Individuals higher on this dimension may be at greater risk for some internalizing outcomes but may also thrive in situations where greater attention to threat is adaptive, whereas individuals lower on this dimension may be at greater risk for some poor outcomes involving low fear and anxiety, such as psychopathy (particularly primary psychopathy; Hyde, Byrd, et al., 2014; Lahey, 2009; Lykken, 1957). The intermediate variable of trait anxiety highlights that neither *5-HTTLPR* genotype nor amygdala reactivity defines risk for all outcomes in all settings, but rather these variables may push toward one outcome more than another, especially in certain environments.

Tenet 5: Development is a critical factor in understanding risk and resilience.

A major thrust when developmental psychopathology was first conceptualized was to add a clear emphasis on the role of development in psychiatric conceptualizations of disorder. Though neurogenetics is certainly poised to answer questions about development, much of the neurogenetics literature has focused on adults, with little work carried out among developing populations, nor testing the role of development in findings. However, there have been some studies across imaging and genetics that point to the need for a developmental focus in neurogenetics, including studies of normative brain development and a handful of imaging genetics studies done with youth (Hyde, Swartz, et al., 2015; Viding et al., 2006).

Developmental neuroimaging

Neuroimaging studies of normative brain development have shown that brain structure and function change dramatically across development and highlight the importance of conceptualizing the brain as an ever changing variable (e.g., Giedd et al., 1999). Moreover, developmental neuroimaging studies help to explain developmental trends in behavior that may be driven by specific aspects of brain development. For example,

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structural MRI studies have shown that the brain has major periods of growth and then pruning during the toddler and adolescence years, though this rate of change is not uniform across brain areas. Subcortical brain structures mature relatively quickly, whereas prefrontal areas of the brain have a more protracted maturation, particularly during adolescence (Giedd, 2008). It is interesting that adolescence is also a peak time for environmental change and risk for behavior problems and psychopathology, particularly risky behaviors. Several scholars have proposed that the differences in growth across different brain areas may underlie normative developmental change in risky behavior (Casey & Jones, 2010; Steinberg, 2007). These prominent theories posit that during adolescence an imbalance emerges between early maturing bottom-up subcortical structures associated with emotion and sensitivity to reward (e.g., the amygdala and striatum) and later maturing top-down cognitive and affective control structures (i.e., the prefrontal cortex). The imbalance of these areas leads to a window in adolescence of increased risk-taking behavior due to heightened activity in bottom-up versus top-down control systems, leading to increases in emotional and reward-dependent behaviors (Casey & Jones, 2010; though see Crone & Dahl, 2012; Pfeifer & Allen, 2012). These theories and the empirical support for them highlight how studying normative brain development can inform models of behavior as it changes throughout development. Moreover, this area has not been limited to structural brain imaging, because fMRI studies have also shown marked developmental differences in mean levels of activation and connectivity over time across different ages groups (Durston et al., 2006; Hare et al., 2008; Swartz, Carrasco, Wiggins, Thomason, & Monk, 2014), often with complex relationships among age, function, and connectivity (Gee et al., 2013).

These studies also support the notion that individual differences in brain maturation trajectories may predict differences in risky maladaptive behavior (De Brito et al., 2009; Luna et al., 2001). Developmental psychopathology studies have emphasized conceptual and statistical models for identifying groups of individuals that differ on longitudinal trajectories over time. Growth mixture modeling has been used quantitatively to identify individuals with different trajectories of behavior over time (Nagin & Tremblay, 2001). Accordingly, an interesting future direction for developmental neuroimaging and neurogenetics may be to model *trajectories* of brain structure and function (and groups with similar longitudinal trajectories; e.g., Ordaz, Foran, Velanova, & Luna, 2013), which can then be tested as a mediator of gene, environment, and behavior links. Such studies would require longitudinal neuroimaging data, but they could test how the individual shape of neural structure and function across areas of the brain predicts the developmental course of behavior. For example, studies could test if adolescents or young adults with more severe risk-taking behaviors have a delayed trajectory of top-down control neural areas (i.e., areas that mature in the same way, but later in the development) or if these areas mature less or in a different way in these individuals. Beyond future directions, developmental neuroimaging clearly supports the notion that we cannot interpret neurogenetics findings in youth without considering age and developmental stage.

Developmental imaging genetics

Although relatively understudied, there have been some imaging genetics studies conducted in youth. Several of these studies have shown similar results to those found in adults, such as those linking the short allele of the *5-HTTLPR* to greater amygdala reactivity (Battaglia et al., 2012; Furman, Hamilton, Joormann, & Gotlib, 2011). Though mean levels of neural reactivity are changing across childhood and adolescence, these few studies suggest that well-replicated imaging genetics findings may apply to youth, at least at some ages (for more details see Hyde, Swartz, et al., 2015). Though examining if imaging genetics findings generalize to individuals at different ages is important, very few studies have examined *the role of development* in imaging genetics, such as exploring age as a potential moderator of gene–brain–behavior relationships (Dick et al., 2013). Those that have, paint a complex picture. For example, Wiggins et al. (2014) found cross-sectionally that in short allele (or in this case low-expressing) carriers of the *5-HTTLPR*, there was a positive correlation between amygdala activation from age 9 to 19, whereas in long allele carriers, there was no correlation between age and amygdala activation. These same investigators have shown similar genotype-dependent age effects on functional neural connectivity as well (Wiggins et al., 2012). Thus, age may moderate gene–brain relationships, or in this case, genotype may moderate age–brain relationships, adding further complexity to the picture. Fundamentally, we still need to know much more about how imaging genetics findings may vary across development as the brain and gene expression are both changing, particularly because nonhuman animal models have emphasized the different effects of genes and neurotransmitter levels at stages of brain development (e.g., Jedema et al., 2010; Yu et al., 2014). Again, longitudinal imaging in cohorts that contain molecular genetic information and have well-measured phenotypes will be key to addressing these emerging issues. However, simply having this data will not be enough if these data are not explored through a developmental lens.

$G \times E \times D$

Although G × E interaction studies have been prominent in the developmental psychopathology literature, there has not been a large focus on the role of development in these models. For example, are there sensitive periods for specific environments measured in G × E interactions? Much work in developmental psychopathology has suggested that environmental predictors of later outcomes are dependent on developmental stage, and thus, as described above, we would expect G × E interactions to vary by the timing of the environment and the outcome.

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For example, harsh parenting may only be a potent moderator of certain genotypes (e.g., monoamine oxidase A) when measured in early childhood and when the behavioral outcome (e.g., AB) is measured in adolescence when rates of the outcome are higher (Choe, Shaw, Hyde, & Forbes, 2013). In contrast, interactions between genotype and peer experiences may only be significant in predicting AB when peer experiences and outcomes are measured in adolescence, when peers have the greatest effect on behavior. Thus future studies that examine three-way G × E × D (development) interactions will be key to uncovering developmental pathways within G × E interactions (Banaschewski, 2012; Vrieze, Iacono, & McGue, 2012).

Moreover, given developmental trajectories of brain maturation, we would not expect IG × E findings to be uniform across development either. Rather, one might ask if there are critical periods in the development of specific brain regions that might be associated with specific G × E interactions at one developmental stages but not others (Lenroot & Giedd, 2011). Casey et al. (2009) have argued cogently for just this sort of developmental stage-dependent IG × E interaction by combining studies in nonhuman animal models and neuroimaging of children. Specifically, they have argued that variation in the gene coding for brain derived neurotrophic factor is likely to have developmentally dependent effects on brain structure and function and subsequent behavior, and thus is a good example of how development will impact G × E interaction effects on the brain and behavior. Furthermore, though animal models of G × E interactions clearly show sensitive periods in effects on brain function (Meaney, 2010), including periods in which specific neurotransmitters may have different effects on different areas of the brain and subsequent behaviors (Yu et al., 2014), longitudinal IG × E studies will be needed to test these pathways in humans, ideally with multiple measures of environmental exposures, neural structure and function, and well-specified outcomes. As alluded to above, a particularly compelling model may be to examine IG × E relationships in cascade models in which specific experiences may interact with specific genes at specific developmental periods, which may in turn affect later brain functioning and subsequent behavior (which could in turn lead to different environmental experiences). For example, harsh parenting in early childhood could interact with specific alleles in dopamine genes to predict greater reward-related brain activity and impulsivity, which could in turn predict drug use and deviant peer affiliation, leading to more environmental exposures (e.g., more drug use or more deviant peers) and an exacerbation of earlier G × E interactions and further sensitization of the neural systems involved in reward seeking (Dodge et al., 2009; Hyman, Malenka, & Nestler, 2006; Sitnick, Shaw, & Hyde, 2013; Starkman, Sakharkar, & Pandey, 2011).

Heterotypic and homotypic continuity

A final important point in considering the role of development in these pathways is to consider what these pathways might "look like" behaviorally across development. One major challenge to understanding developmental trajectories is that the same behavior has different meanings, underlying causes, and outcomes at different ages. A temper tantrum at age 2 is quite normative, may reflect typical brain and behavior development in the training of emotional regulation, and may have relatively minor consequences for the child (e.g., a time-out). The same temper tantrum at age 15 could have very different underlying causes, or be caused by the same underlying neural profile that is now nonnormative at this age (e.g., emotional dysregulation that is atypical for this stage in development), and thus lead to different consequences (e.g., being expelled from school or arrested) and be related to different neural development (e.g., delayed maturation of prefrontal areas or exaggerated limbic reactivity). It is important to consider which behaviors, and at which ages, we expect *homotypic* continuity versus *heterotypic* continuity. For some behaviors, such as temperament or later personality, we might expect continuity in the same behavior or trait over time (i.e., homotypic continuity). For example, though the behaviors involved change a bit throughout development, level of aggression in a child at one point typically predicts aggression at a later time point.

In contrast, many behaviors we are most interested in when studying risk and resilience show heterotypic continuity. That is, the same underlying process or disorder may have differing manifestations at different developmental stages. For example, childhood depression may present as irritability and without cognitive symptoms, whereas adult depression may present more with low mood and pessimism. Within the study of youth AB, scholars have mapped behaviors that may be age-specific presentations of the same underlying psychopathology: early difficult temperament in early childhood, attention-deficit/hyperactivity disorder and oppositional defiant disorder in middle childhood, escalation to conduct disorder in adolescence, and substance use disorders and antisocial personality disorder in adulthood (Beauchaine & McNulty, 2013; see also Loeber & Stouthamer-Loeber, 1998). Inherent in these types of models is the assertion that these different behaviors reflect the same underlying vulnerability or trait (in this case, it may be impulsivity or disinhibition), which is likely to be produced by specific neural and genetic profiles. Developmental psychopathology research on heterotypic continuity could start examining if these behaviors truly are heterotypic behavioral manifestations of a relatively constant, homotypic neural or genetic profile. Might these different antisocial behaviors be the developmental manifestations of the relatively constant building blocks of trait impulsivity and emotion dysregulation that arise from reward and threat neural reactivity, respectively (for more on this type of model see Beauchaine & McNulty, 2013)? Neurogenetics could be leveraged by developmental psychopathologists to test the assumptions under our models of heterotypic continuity within various psychopathologies. Are certain neural or genetic profiles the "sameness" that underlies the hypothesized differing manifestations of these

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disorders over time? Could brain reactivity or individual differences in neural networks help to identify the stable, underlying biological signature of continuity while behaviors are changing across development or even within shorter periods of time? Of course, the pathways noted above are not likely to be simple or linear. As emphasized throughout this paper, the brain and genome are unlikely to map directly onto psychopathology or even these more narrow building blocks, but rather will predict these outcomes probabilistically in interaction with experience, other brain regions, and other genes.

One final thought to consider in applying models of heterotypic continuity to neurogenetics: do we expect the brain or genetic effects to be homotypic or heterotypic? Within neuroscience, we often treat some variables like level of amygdala reactivity as a relatively traitlike variable. However, developmental neuroimaging has shown that the means of this variable change across development and suggests that individuals may have different trajectories as well. Moreover, the test–retest stability of neural reactivity may vary by brain region and method, and is likely not quite as high as we might expect for a trait (e.g., Johnstone et al., 2005). Thus, we may need to make different hypotheses about the relation of neural structure or function to the same behavior at different developmental stages. For example, prefrontal cortex functioning may be key to individual differences in impulsivity in childhood and adulthood, but given its development, it may be less predictive of impulsivity during adolescence. This point is quite speculative but helps to identify how applying concepts of developmental psychopathology to neurogenetics may raise new questions that challenge some assumptions.

Summary of the role of development

The major focus of the role of development in developmental psychopathology will be key to understanding neurogenetics pathways across development. Studies of typical neurodevelopment emphasize that different brain areas mature at different rates, and thus neurogenetics findings may be moderated by age but could also benefit from examining individuals differences in brain structure and function as trajectories, rather than a static variable. Moreover, emerging studies of imaging genetics and G × E interactions suggest that development may moderate these pathways as well and that developmental stage is critical to consider in interpreting the results. Finally, neurogenetics may help to find the "sameness" underlying possible heterotypic manifestations of psychopathology across development. Though researchers have noted the likely heterotypical continuity for many years, being able to measure more proximal phenotypes and links with genetics may offer new ways to identify the stable characteristic that is driving the developmentally variable heterotypic behavior. Clearly, neurogenetics and developmental psychopathology can both contribute to pushing each field forward, though with a substantial amount of added complexity to models of psychopathology.

Tenet 6: Attention to *who* is studied is critical to interpreting and translating developmental research.

Equally important to considering what age or developmental stage is being studied is to consider *who* is being studied in neurogenetics studies, who should be studied, and how this decision affects the interpretation of the results.

Examining the dimensions of behavior between normative and disordered

A major point made very early in the history of developmental psychopathology was that studies of normative development could and should inform the study of psychopathology, and in turn that the study of development gone awry could inform an understanding of development more broadly (e.g., Cicchetti, 1993; Rutter, 2013). Much of neurogenetics has been done on healthy samples in youth and adults, and helps to demonstrate how these studies of typical development can help inform models of psychopathology. Furthermore, studies of normative brain function and adolescent risk taking, as well as studies emphasizing the dimension nature of behavior and psychopathology, support the idea that much of the neurogenetics work done on normative samples will be dimensionally applicable to understanding the development of psychopathology. Moreover, because neurogenetics has also been applied in clinical samples of youth, these complimentary samples can begin to map relationships across the dimension of psychopathology.

One major study design (using high-risk samples), frequent in developmental psychopathology, could be very important in developmental neurogenetics. Within high-risk samples, youth or families either are often chosen on a dimension that may increase risk (e.g., lower socioeconomic status) or are oversampled for some risk or outcome (i.e., the sample may be representative but contain an additional amount of youth with greater level of behavior problems). This type of design can test gene–brain–environment–behavior questions dimensionally while still containing enough power to find those that would be clinical cases and thus be applicable to understanding more severe psychopathology. Though in neuroscience and psychiatry the reigning models are either of normative (which often means ultrahealthy with psychopathology screened out) or dichotomous clinical samples, high-risk and enriched samples are better suited for the assessment of neurogenetics and IG × E relationships across the spectrum of symptoms (e.g., Bogdan, Williamson, et al., 2012; Morgan, Shaw, & Forbes, 2014). High-risk samples contain a distribution of behavior that often includes normative, at-risk, and clinical levels of behaviors in enough quantity to assess the continuum between normative and disordered. Overall, neurogenetics seeks converging evidence across species, type of approach (e.g., multimodal neuroimaging, fMRI, or G × E), and sample, and thus the addition of different types of sampling approaches may help to add to

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greater nuance in our understanding of the convergence (or lack of convergence) across different ages or cohorts.

Sampling

High-risk samples may add a lot to understanding neurogenetics, as they have to developmental psychopathology. However, I also think it is important to point out the importance of sampling in neurogenetics and in neuroscience more broadly. As noted throughout this paper and developmental psychopathology, one brain is not the same as the next brain. Much of the knowledge built up in neuroscience has been on samples of convenience that may differ in many drastic ways from typical adults in this country or others. The idea that a small collection of college students can provide representative brains or provide data that can generalize to individuals outside of college students is problematic and may be leading to well-replicated findings in neuroscience that are interpreted as universal truths that really only apply to a very select group of people (Chiao & Cheon, 2010; Henrich, Heine, & Norenzayan, 2010). In other words, much of what we know about neuroscience is based on a group of individuals (i.e., college students) that may not generalize more broadly. Neurogenetics and neuroimaging studies, more broadly, would be strengthened considerably through the use of more sophisticated sampling and an emphasis on using representative samples. (Note that the high-risk samples described above can be generated by carefully oversampling within a weighted representative sample.) These types of approaches will lead to a better generalization from sample to population (for much more on this point, see Falk et al., 2013). This point is especially true when considering that many of the neuroimaging studies done of pediatric psychiatric disorders often contrast those with superhealthy controls who have been screened for any possible past or present psychopathology (for additional important considerations and limitations of the pediatric psychiatric neuroimaging literature, see Castellanos & Yoncheva, 2014; Horga, Kaur, & Peterson, 2014).

Better sampling and attention to the sample itself will allow for more accurate assessment of potential moderators of developmental neurogenetics effects such as gender, race, and ethnicity. Careful attention to these variables is critical in neurogenetics because biological pathways, particularly genetic ones, have been shown to be moderated by these variables. For example, monoamine oxidase A is an X-linked gene, and thus studying this gene in women leads to further complication because one allele is likely inactivated. Beyond X-linked genes, genetic pathways may also be differentially affected by different hormones in men versus women (Byrd & Manuck, 2014; Pinsonneault, Papp, & Sadée, 2006). In addition, the direction of imaging genetics findings has been shown to be opposite in those of different racial background (e.g., Long et al., 2013), leading to further complexity in understanding how universal imaging genetics findings may be. We probably know very little about how neurogenetics mechanisms may operate across race and ethnicity, and thus much of the work done cannot be generalized beyond primarily Caucasian and middle-class samples (Falk et al., 2013). Whenever researchers are examining genes, they must carefully address the possibility of genetic substructure and the impact of ancestry and different allele frequencies across races/ethnicities in interpreting findings (Cardon & Palmer, 2003; Shriver & Kittles, 2004).

In sum, neurogenetics and neuroimaging, in general, have focused primarily on Caucasian samples of convenience or on clinical samples that contrast highly selected cases versus superhealthy controls. An emerging focus on using more sophisticated techniques to yield samples that are more representative of a specific population, as well as further focus on samples that are high risk, may yield new insights and, at the least, would help us to understand how generalizable the current knowledge in the field is and/or if third variables (e.g., socioeconomic status or comorbidities) may be driving previous findings. As developmental neurogenetics aims to explore more complex and dimensional phenotypes, larger and more carefully sampled studies, especially those with greater risk, will be critical.

Conclusion

By emphasizing converging evidence across species and methods, neurogenetics has helped to define genetic pathways to differences in neural structure and function, which in turn have been linked to psychopathology. With the addition of IG $\times$ E approaches, neurogenetics is beginning to specify the complex contextual biological pathways toward increased risk for psychopathology. Though several neurogenetics studies have emerged over the last decade in youth, there are many ways in which concepts from developmental psychopathology can improve neurogenetics. Moreover, through the careful and thoughtful use of neuroimaging and molecular genetics approaches, neurogenetics represents appealing new tools being applied in developmental psychopathology. Both fields certainly overlap in some ways, but they could be further integrated. This integration can happen through new empirical studies that are longitudinal, sampled carefully, use neuroimaging, collect other pertinent biological information at multiple time points across development, and measure constructs of interest in multiple ways (e.g., self-report, observation, official record, and interview) and from multiple reporters (e.g., parents, teachers, and youth). These types of studies are emerging through piggybacking neuroimaging onto existing longitudinal studies (e.g., Morgan et al., 2014), as well as newly started studies with molecular genetics and repeat MRI scans (Bogdan, Williamson, et al., 2012). These types of studies could also collect other neuroimaging data (e.g., event-related potentials or near infrared spectroscopy) very early in development, before fMRI is possible, and could also collect epigenetic, gene expression, and other biomarker (e.g., hormone levels) data at multiple time points to add further ability to test mediating and moderating developmental neurogenetics mechanisms. Decreasing costs

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in molecular genetics, as well as increased collaboration across disciplines make these types of studies more possible with each passing year. However, simply exploring or replicating neurogenetics findings in samples of youth will not take the field forward in the same ways as applying complex models from developmental psychopathology will. RDoC and other multilevel perspectives are pushing forward integration from genes to molecules to cells to brain structure and function to behavior, but without understanding complex systems and the role of experience and development, these models will be limited.

Ultimately, the great promise of developmental neurogenetics is to inform our understanding of conditional mechanisms that will identify who is at most risk for psychopathology and when this risk may emerge, how risk is transmitted, and further points in the etiological chain that can be targeted for intervention (Bogdan, Hyde, et al., 2012). Thus, through greater understanding of who, when, and how individuals are at most risk for maladaptive outcomes, or who, when, and how some individuals are resilient, studies can push forward more targeted and personalized prevention and intervention strategies (Simon & Perlis, 2010; Willard & Ginsburg, 2009). Clearly more work is needed to begin to translate developmental neurogenetics findings into a better understanding of psychopathology and prevention and intervention strategies. As these findings are usefully translated, interventions can feed back into the knowledge base of neurogenetics (e.g., Brody, Beach, Philibert, Chen, & Murry, 2009), as interventions, as well as natural experiments (Costello, Compton, Keeler, & Angold, 2003; Kilpatrick et al., 2007), and genetically informed designs (e.g., twin and adoption designs; Reiss & Leve, 2007) can help separate correlated environments and genotypes, leading to better causal inferences within neurogenetics and developmental psychopathology more broadly. In the long run, the models to be tested are quite complex, but they are necessary in order to understand the interaction of biology and context from gene to brain to behavior.

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