Functional Magnetic Resonance Imaging in Developmental Psychopathology: The Brain as a Window into the Development and Treatment of Psychopathology

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Rather than resolving the classic debate of nature versus nurture, advances in developmental psychopathology have illuminated the complex interactions between nature and nurture across development. The transactional model of development highlights the interdependent nature of these interactions; the model proposes that development is the product of reciprocal interacting influences between the child and environment over time (Sameroff, 2010). The complexity of these interactions at the biopsychosocial level is delineated in Gottlieb's theory of probabilistic epigenesis (Gottlieb, 2007a, 2007b). Rejecting the traditional notion that genes lead to psychological or behavioral outcomes in a unidirectional fashion, Gottlieb argued that the environment also alters gene expression and that gene–environment interactions are fundamental to understanding development.

Within this framework, the field that encompasses the neuroscience of developmental psychopathology must consider the bidirectional influences between genes, brain, behavior, and environment. Genes code for the synthesis of proteins that then influence brain development, organization, structure, and function. However, the environment also influences neural development and alters the influence of genes through epigenetics (Meaney, 2010), a set of biological mech-

anisms that permit the environment to modify gene expression. Importantly, the brain is at the intersection of many of these genetic and environmental influences on mental health outcomes and, as a mediator of these reciprocal interacting influences, provides a unique window into the development and treatment of psychopathology (Cicchetti & Dawson, 2002; Hariri & Weinberger, 2003; Hyde, Bogdan, & Hariri, 2011; Monk, 2008).

Throughout this chapter, we emphasize that the inclusion of the brain as a level of analysis in conjunction with genetic, epigenetic, and environmental measures can provide important insights into the development of psychopathology and contribute to the development and testing of novel treatments. In order to illustrate the importance of considering brain function in developmental psychopathology research, we focus our review on two types of psychopathology: anxiety disorders and autism spectrum disorder (ASD). These disorders share common abnormalities in emotion processing and are both associated with alterations in neural circuitry related to emotion processing and regulation (Monk, 2008). Anxiety disorders encompass a range of conditions characterized by excessive fears or anxiety such as social anxiety disorder, which involves excessive anxiety in social situations. ASD is characterized by social interaction deficits, language and communication impairment, and stereotyped or repetitive behaviors. As we will discuss, some evidence suggests it may also be associated with heightened anxiety in response to social stimuli. We begin with a brief

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review of the current state of knowledge regarding abnormalities in brain function in anxiety disorders and ASD. We then discuss how this knowledge of brain abnormalities can be combined with genetic, epigenetic, and treatment research to increase progress in our understanding of the development and treatment of these disorders.

The Role of the Amygdala and Ventral Prefrontal Cortex in Anxiety Disorders and ASD

Anxiety disorders and ASD are associated with abnormal activity in multiple neural regions, including the amygdala and ventral prefrontal cortex. These two regions are implicated in face processing, social cognition, and emotion processing (Adolphs, 2010). The amygdala is a bilateral structure located deep inside the brain, and the ventral prefrontal cortex encompasses the lower portion of the prefrontal cortex (above it is the dorsal prefrontal cortex). The amygdala is involved in the experience of anxiety and fear and may be more broadly involved in detecting any positively or negatively valenced social stimuli in the environment. The ventral prefrontal cortex is associated with a range of functions related to receiving and interpreting signals from other brain regions about conditions in the external environment and internal psychological states. In addition, the ventral prefrontal cortex can modify or inhibit responses in other regions in order to allow an individual to flexibly respond to current contextual or task demands.

The amygdala and ventral prefrontal cortex communicate with one another through reciprocal connections that allow for neural signaling between the regions. Signals from the amygdala to the ventral prefrontal cortex can communicate information regarding the emotional significance of stimuli, whereas signals from the ventral prefrontal cortex to the amygdala can modify amygdala activation (Ghashghaei, Hilgetag, & Barbas, 2007; Sarter & Markowitsch, 1984; Ray & Zald, 2012). Research from animal models and human

neuroimaging data suggests that the ventral prefrontal cortex plays an important role in emotion regulation by regulating amygdala activity via signals to the amygdala that inhibit activation. The dorsolateral prefrontal cortex may also be involved in emotion regulation, but because it has fewer direct connections to the amygdala, its role in emotion regulation is likely mediated through the ventral prefrontal cortex (Ray & Zald, 2012). The ventral prefrontal cortex can be further divided into subregions including the orbitofrontal cortex, the ventromedial prefrontal cortex, the ventral anterior cingulate cortex, and the ventrolateral prefrontal cortex. These regions can be associated with different cognitive functions depending on the tasks that participants perform while undergoing scanning, but frameworks have suggested that medial regions (the ventromedial prefrontal cortex, the subgenual anterior cingulate cortex, and the medial orbitofrontal cortex) may be involved in more automatic processes (e.g., generating expectations of reward or punishment, fear extinction) whereas lateral regions (the ventrolateral prefrontal cortex and lateral orbitofrontal cortex) may be more involved in voluntary processes (e.g., inhibiting prepotent responses, voluntarily controlling attention) (Phillips, Ladouceur, & Drevets, 2008; Ray & Zald, 2012). Because both automatic and voluntary emotion regulation processes involve regulation of the amygdala by the ventral prefrontal cortex, abnormalities in this circuitry likely play an important role in psychopathology characterized by disturbances in emotion regulation such as anxiety disorders and ASD. It has been proposed that there exists a further subdivision within the ventromedial prefrontal cortex: the posterior region of the ventromedial prefrontal cortex is posited to be involved in amplifying negative affect and amygdala response, whereas more anterior regions are involved in inhibiting amygdala response and reducing anxiety (Myers-Schulz & Koenigs, 2012). Thus, psychopathology characterized by disturbances in emotion regulation may reflect a combination of under-regulation of negative affect and amplification of negative affect by different prefrontal regions.

Examining Neural Activation and Functional Connectivity with fMRI

Functional magnetic resonance imaging (fMRI) is a tool to probe brain function in vivo and can be used to relate neural function to specific cognitive and emotional tasks performed during scanning. FMRI relies on measuring changes in oxygenated blood flow as an indirect measure of neural activity in the brain. In addition to the advantage of providing indirect measurement of neural activity, fMRI has good spatial resolution and the ability to examine activation in subcortical regions that cannot be localized through other methods such as electroencephalography (EEG).

One analytic approach of fMRI is functional connectivity, which is used to examine the correlation in activation across regions. If two regions show correlated increases and decreases in activity across a task, it is said that they demonstrate functional connectivity. Such findings would be consistent with the concept that the regions are interacting during the performance of the task. As highlighted in the conceptual framework above, understanding how neural regions communicate with one another will likely be crucial to fully understanding abnormal neural function in psychopathology. However, it is important to note that functional connectivity is limited in that it does not directly assess neural signaling and cannot be used to determine whether signals between regions are excitatory or inhibitory. Additionally, as with all correlational research, direction of causation (i.e., whether one region is modifying activity in the other or vice versa) cannot be determined. Despite these limitations, functional connectivity analyses can provide important information regarding differences in the strength of connectivity between regions such as the ventral prefrontal cortex and amygdala in patient and typically developing populations. This knowledge can be used in the context of research with animal models that can more invasively examine structural and functional connectivity, and in the context of the tasks performed in fMRI experiments, in order to draw inferences regarding the functional consequences of differences in connectivity strength between patients and controls. In the following sections we briefly discuss

fMRI research that has characterized prefrontal cortex-amygdala circuitry in anxiety disorders and ASD. For more extended reviews, see Monk (2008), Pine (2007), and Philip et al. (2012).

Theoretical Considerations for Developmental Neuroimaging Research

Three general theoretical principles have been put forth for examining development with fMRI (Johnson, Halit, Grice, & Karmiloff-Smith, 2002). First, rather than the notion that development may reflect the maturation of one area specialized for one cognitive process, current research suggests that development also reflects the reorganization and integration of activity across distributed networks of regions. Thus, it is necessary for researchers to examine how the connectivity across different regions changes over development.

Second, the regions associated with a cognitive task in adults may not correspond to the regions recruited by children or adolescents during the same task, either because the participants use different strategies or because the functional organization of neural networks differs from that of adults. Therefore, rather than extrapolating findings from fMRI studies in clinical adult samples, it is necessary to conduct research with pediatric samples if we are interested in answering questions about how psychopathology develops.

Third, in line with Gottlieb's probabilistic epigenesis, theoretical views of the role of neural development in psychopathology must move beyond a unidirectional influence from brain to psychopathology and consider that the environment and behavior (such as symptoms or abnormal cognitive patterns) can also influence the neural activity observed when scanning clinical populations.

Prefrontal-Amygdala Function in Anxiety Disorders

One of the most consistent findings in clinical neuroimaging is that anxiety disorders are

associated with heightened amygdala activation to threatening stimuli, such as fearful or angry faces, both in children and adolescents (Guyer et al., 2008; McClure, Monk, et al., 2007; Monk et al., 2008; Thomas et al., 2001) and in adults (Etkin & Wager, 2007). Moreover, there is increasing evidence for altered ventral prefrontal cortex activation and connectivity with the amygdala in youth with anxiety disorders (Guyer et al., 2008; McClure, Monk, et al., 2007; Monk et al., 2006, 2008) and adults with anxiety disorders (e.g., Etkin, Prater, Hoeft, Menon, & Schatzberg, 2010), consistent with the hypothesis that ventral prefrontal regulation of the amygdala may be weaker and amplification of negative affect may be stronger in anxiety disorder patients. Because the amygdala is associated with arousal and the experience of fear, reduced regulation from the prefrontal cortex to the amygdala may relate to the cognitive and emotional biases posited to contribute to the development and maintenance of anxiety disorders, including increased fear conditioning and difficulty extinguishing conditioning, heightened attention to threat, and interpretation of ambiguous stimuli as threatening (Britton, Lissek, Grillon, Norcross, & Pine, 2011; Daleiden & Vasey, 1997).

Developmental frameworks suggest that the transition to adolescence and the adolescent period may involve heightened risk for the development of affective disorders because the balance between amygdala and prefrontal cortex activity is still in flux (Casey, Jones, & Hare, 2008; Steinberg et al., 2006). Specifically, research examining the function and the structure of the prefrontal cortex (including both the volume of gray matter and the volume of white matter, representing long-range connections with other regions) has indicated that this region and its connections may develop along a relatively protracted time course across the period of childhood through adolescence and into adulthood (Giedd & Rapoport, 2010; Gogtay et al., 2004; Hare et al., 2008; Monk et al., 2003; Rubia et al., 2000; Yurgelon-Todd & Killgore, 2006). During this time, the amygdala may be relatively under-regulated, creating a risk for disturbances in emotion processing. An important point for

developmental psychopathologists is that this may also be a sensitive period for environmental influences on the development of this circuitry and potentially a window for intervention. Understanding genetic and epigenetic influences on this neural circuitry across the child and adolescent developmental periods as well as how treatments during these periods alter this circuitry may have the potential to improve preventions and treatments for these disorders, with potentially long-lasting results.

Prefrontal-Amygdala Function in Autism Spectrum Disorders

Although many have suggested that the socioemotional impairments of ASD are related to abnormal amygdala function (Dawson et al., 2005; Schultz, 2005), the results of fMRI studies have been inconsistent regarding the nature of this dysfunction. Many studies have found decreased amygdala activation in individuals with ASD relative to controls (e.g., Ashwin, Baron-Cohen, Wheelwright, O'Riordan, & Bullmore, 2007; Baron-Cohen et al., 1999), whereas others have found evidence for amygdala hyperactivation in ASD (Dalton et al., 2005; Kliemann, Dziobek, Hatri, Baudewig, & Heekeren, 2012; Kleinhans et al., 2009; Monk et al., 2010; Weng et al., 2011).

Whether individuals with ASD exhibit amygdala hypo-activation or hyperactivation to social stimuli relative to controls may depend on the type of task used during fMRI scanning. Studies that found amygdala hypo-activation in ASD generally used relatively long presentation times of face stimuli. In contrast, those utilizing brief presentation times and behavioral tasks to verify that subjects were attending to the stimuli produced evidence for amygdala hyperactivation in ASD (Monk et al., 2010; Weng et al., 2011). Because individuals with ASD attend away from faces (Klin, Jones, Schultz, Volkmar, & Cohen, 2002), studies with long presentation times afford participants the opportunity to attend away from faces in the scanner, resulting in amygdala hypo-activation due to reduced attention toward the

stimuli. In contrast, studies with brief stimulus presentation times minimize differences in attention between participants with ASD and controls, producing evidence of amygdala hyperactivation to faces. In line with this, an fMRI investigation that incorporated eye tracking found a correlation between the amount of time spent fixating on eyes and amygdala activation in individuals with ASD (Dalton et al., 2005). Similarly, in a study that manipulated participants' initial fixations on either the eye or mouth region, participants with ASD showed heightened amygdala response when fixating the eyes relative to controls (Kliemann et al., 2012). Based on these results, we suggest that individuals with ASD avoid social stimuli because these stimuli induce over-arousal, indexed by amygdala hyperactivation (Dalton et al., 2005; Joseph, Ehrman, McNally, & Keehn, 2008; Kliemann et al., 2012; Kliemann, Dziobek, Hatri, Steimke, & Heekeren, 2010; Monk et al., 2010; Neumman, Spezio, Piven, & Adolphs, 2006; Weng et al., 2011). Reduced attention to social stimuli over the course of development could prevent infants and young children with ASD from acquiring the same level of social experiences as typically developing children, which could lead to a cascade of abnormal development of regions associated with social processing.

Some research has also detected abnormal ventral prefrontal cortex activity or ventral prefrontal cortex-amygdala connectivity in individuals with ASD (Dalton, et al., 2005; Monk et al., 2010; Swartz, Wiggins, Carrasco, Lord, & Monk, 2013). For example, Swartz et al. (2013) found evidence for reduced ventromedial prefrontal connectivity with the amygdala while youth with ASD viewed sad faces, as well as heightened amygdala response in the ASD group. Therefore, initial evidence suggests that amygdala hyperactivation in ASD may be the result of or compounded by altered prefrontal connectivity.

ASD emerges much earlier than anxiety disorders, typically before age 3, sparking increased interest in examining neural development across infancy and early childhood as well

as at later ages (Giedd & Rapoport, 2010; Courchesne et al., 2007). However, because very young children cannot typically perform task-based fMRI studies, much of this research has examined changes in brain structure. Overall, there is evidence for an altered trajectory of brain development characterized by increased brain volume, including the amygdala and prefrontal cortex, in infancy and early childhood compared to typically developing controls and then decreases in volume later in development, often resulting in smaller volumes of brain structures such as the amygdala in adolescents and adults with ASD compared to controls (Courchesne et al., 2007; Schumann et al., 2004). A key theme emerging from this research is that ASD is associated with differences in the timing and trajectory of brain development. For example, Carmody and Lewis (2010) found that young children with ASD showed overdevelopment of white matter in the medial prefrontal cortex and underdevelopment of white matter in the left temporoparietal junction, a region associated with the development of self-representation in typically developing children (Lewis & Carmody, 2008). Moreover, degree of deviation from typical levels of development associated with ASD symptoms. In older children and adolescents, fMRI research has suggested that amygdala activation to emotional faces may decrease with age (Weng et al., 2011). Further research will be necessary to examine how prefrontal cortex-amygdala connectivity changes with age and whether this developmental pattern relates to changes in ASD symptoms across childhood and adolescence.

Having outlined the current state of research on brain function in anxiety disorders and ASD, we now consider how neuroimaging may be used to further our understanding of the development and treatment of psychopathology. We focus on three specific examples: imaging genetics, imaging epigenetics, and treatment studies. These examples are not meant to be exhaustive, but rather to illustrate various areas in which neuroimaging research can help achieve advances in this field.

The Brain as a Mediator of Genetic and Epigenetic Influence on the Development of Anxiety Disorders and ASD

Genes and Gene × Environment Interactions in Anxiety Disorders

Investigators have examined the relation between a number of different gene variants and anxiety disorders, but some of the most studied genes are those regulating serotonin (5-hydroxytryptamine; 5-HT) levels in the brain. Serotonin-related genes have been considered important candidates when investigating anxiety disorders for several reasons. First, serotonin is a neurotransmitter involved in signaling and modulating the signals between different neural regions, including the ventral prefrontal cortex and amygdala (Nordquist & Oreland, 2010; Pinto & Sesack, 2003) which, as we have discussed above, have been shown to function abnormally in anxiety disorders. Second, a first-line pharmacological treatment for anxiety disorders is a class of medications called selective serotonin reuptake inhibitors (SSRIs), which affect serotonin levels in the brain. Thus, serotonin may play a key role in the development of anxiety disorders.

Serotonin levels within the brain are influenced by genetic variation. Serotonin is released into the synapse to signal other neurons and afterwards must be cleared from the synapse by serotonin transporters, which reuptake serotonin back into the presynaptic neuron. The rate at which serotonin is cleared from the synapse can influence the strength and duration of serotonin signaling (Daws & Gould, 2011). The amount of serotonin transporters available for this process is regulated by the serotonin transporter gene. Genetic variation in the promoter region for this gene, referred to as the serotonin transporter-linked polymorphic region (5-HTTLPR), results in two common functional variants. The variant with the short allele leads to less efficient transcription and therefore reduced availability of the serotonin transporter, whereas the long allele is associated with increased transcriptional

efficiency. There are also two variants of the long allele, one of which appears to behave similarly to the short allele (Hu et al., 2006). Therefore, we will use the terms *low-expressing* allele to refer to the variants that result in decreased serotonin transporter expression and *high-expressing* allele to refer to the variant associated with increased serotonin transporter expression. Although we focus on the 5-HTTLPR in our review, other genes implicated in serotonin signaling, such as genes regulating serotonin receptor levels, have also been implicated in the development of anxiety disorders.

Some research has linked the low-expressing alleles of the 5-HTTLPR to increased risk for being high on anxiety-related personality traits such as neuroticism (Lesch et al., 1996), although this link is not always consistent (Munafo et al., 2009). A meta-analysis also revealed a moderate effect size for the low-expressing allele on attention bias for threat, which is a cognitive pattern frequently associated with anxiety disorders (Pergamin-Hight, Bakermans-Kranenburg, van Ijzendoorn, & Bar-Haim, 2012).

There has also been support for the involvement of the 5-HTTLPR in gene × environment interactions on the development of anxiety disorders or anxiety-related traits including the interaction between 5-HTTLPR and low social support on the development of PTSD after a hurricane (Kilpatrick et al., 2007), low family social support on behavioral inhibition in middle childhood (a temperamental pattern associated with anxiety disorders) (Fox et al., 2005), and child maltreatment on anxiety sensitivity (Stein, Schork, & Gelernter, 2008). In all of these cases, the risk allele of the genotype (the low-expressing allele) is only associated with the development of psychopathology or personality traits associated with risk for psychopathology under conditions of environmental risk. In contrast, proponents of a differential susceptibility theory have suggested that the low-expressing allele of the 5-HTTLPR and other "risk-related" gene variants are better conceptualized as conveying increased susceptibility to environmental context, so that susceptible children raised in risky environments are at heightened risk for developing

psychopathology but susceptible children raised in positively enriched environments benefit more from these environments than less susceptible children (Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2011). Understanding the neural mediators of gene × environment interactions will help to clarify the mechanisms through which genes such as the 5-HTTLPR confer increased risk or susceptibility to environmental context.

It should be noted that, as in main effect analyses of genetic risk factors, gene–environment interaction studies have produced mixed results as well. For example, one study found that the high-expressing allele of the 5-HTTLPR interacted with environmental risk factors to predict depression and anxiety in 19-year-olds (Laucht et al., 2009). Because many of these contrary gene–environment interaction results have been found in adolescent or young adult samples, it has been argued that gene–environment interactions may vary at different stages of development (although methodological issues such as the relevance of stressful life event questionnaires for young participants may also underlie variation in findings; Uher & McGuffin, 2010).

Genes and Gene × Environment Interactions in ASD

Although studies examining the heritability of ASD suggest a strong genetic component, the search for genes associated with ASD has yielded inconsistent results. As with anxiety disorders, serotonin-related genes are important potential candidates because a relatively consistent finding has been that ASD is associated with increased blood platelet serotonin levels, or hyperserotonemia (Veenstra-VanderWeele & Blakely, 2012). Some evidence suggests that increased serotonin blood platelet levels may be associated with faster rates of serotonin reuptake and reduced availability of serotonin in the synapse (Daws & Gould, 2011). However, despite the similarities in altered neural function across anxiety disorders and ASD and the consistent finding of altered serotonin levels in ASD, the relation

between 5-HTTLPR variation and risk for ASD is less clear than for anxiety disorders. A meta-analysis of association studies found no main effect of the low-expressing allele of the 5-HTTLPR on autism status, although there was a relation in studies with mixed ethnicity American populations (versus European or Asian) (Huang & Santengelo, 2008).

One complication that arises in genetic research is that ASD encompasses a heterogeneous set of disorders that vary greatly in terms of severity and type of symptoms (e.g., from little language impairment to severely language impaired) across individuals. Given this level of heterogeneity, it is perhaps not surprising that genetic association studies have been inconsistent. Several investigators have suggested that the low-expressing allele may not in fact be associated with greater risk for ASD, but that variation in the 5-HTTLPR may be associated with specific ASD symptoms (Mundy, Henderson, Inge, & Coman, 2007). For example, the low-expressing allele is associated with greater impairment in the social/communication domain, including nonverbal communication, whereas the high-expressing allele is associated with greater severity of restricted and repetitive behaviors in children with ASD (Brune et al., 2006; Tordjman et al., 2001). The results of these studies suggest that variation in the 5-HTTLPR may influence the severity or type of symptoms in ASD, indicating the need to examine potential neural correlates that may mediate this relation.

Environmental interactions with the 5-HTTLPR may also play a role in the emergence of ASD symptoms. For example, maternal smoking during pregnancy and low birth weight interacted with the 5-HTTLPR to predict ASD symptoms in children with attention-deficit/hyperactivity disorder (Nijmeijer et al., 2010). In this case, the low-expressing allele led to more ASD symptoms with exposure to environmental risk factors.

Although these studies suggest a relation between genetic variation in the 5-HTTLPR, environmental risk factors, and anxiety disorders or ASD, they are subject to some limitations. First, as illustrated through the inconsistent

findings in gene association studies, it can be difficult to find direct links between specific genes and mental disorders (Caspi & Moffitt, 2006; Geschwind, 2011). Second, these studies cannot address the underlying neural processes whereby genes and gene × environment interactions influence the development of psychopathology. FMRI has been useful in addressing both of these limitations of previous research by providing more consistent correlations between 5-HTTLPR variation and neural function and providing a potential neural mechanism linking this gene to anxiety disorder and ASD symptoms.

Imaging Genetics, Imaging Gene × Environment Interactions, and Imaging Epigenetics

Some of the difficulty involved in finding direct associations between genes and mental disorders may be due in part to the complexity that arises from probabilistic epigenesis (Gottlieb, 2007a, 2007b), as it is likely that there is not a one-to-one correspondence between genotype and phenotype due to gene-gene and gene–environment interactions over the course of development. fMRI can help to clarify the role of genes in the development of psychopathology. Because genes are distal from the behavioral phenotypes and symptoms observed for a clinical diagnosis, using fMRI to consider brain function as a more proximal mediating step between genes and psychiatric outcomes may improve our ability to pinpoint important genes involved in the development of psychopathology (Hariri & Weinberger, 2003). This approach of using neural activity as a more proximal phenotype to examine genes' contributions to psychopathology is termed imaging genetics (Hariri & Weinberger, 2003).

Investigators have also proposed methods for examining the neural underpinnings of gene × environment interactions using fMRI. One approach is to examine a mediation model in which neural function mediates the interaction of genes and environment on the development of psychopathology, which has been called imaging gene–environment interactions (Hyde et al., 2011). This approach can be thought of as an extension of imaging genetic research that incorporates both genetic and environmental predictors to examine whether their interaction relates to neural function, which in turn mediates behavioral symptoms or disorders.

Another approach involves incorporating epigenetics into fMRI designs. Consistent with the predictions of probabilistic epigenesis, it has been shown that the environment can alter the way that genes are expressed through processes that fall under the category of epigenetics (Meaney, 2010). Epigenetic regulation encompasses modifications to the structure of DNA without changes to the DNA sequence. Modifications to the structure of the DNA can alter its accessibility to transcription factors, either preventing or increasing the transcription of genes into proteins, which could in turn lead to changes in the structure or function of the brain. This occurs through many different mechanisms. One of the most commonly studied is DNA methylation of promoter regions, which occurs when methyl groups attach to cytosines at cytosine-phosphate-guanosine (CpG) sites on the DNA. This epigenetic modification makes the promoter region less accessible to transcription factors, decreasing the expression of the gene (for more extended reviews on this topic see Bagot & Meaney, 2010; Meaney, 2010; van Ijzendoorn, Bakermans-Kranenburg, & Ebstein, 2011). Importantly, DNA methylation can be altered by environmental influences such as quality of parenting during development (McGowan et al., 2009; Meaney, 2010; Weaver et al., 2004). Thus, methylation represents a potentially important pathway for the influence of the environment on gene expression, neural function, and the development of psychopathology. FMRI can be used to examine the functional consequences of these epigenetic influences in an extension of imaging genetic research termed imaging epigenetics (Wiers, 2012), in which methylation levels of genes of interest are related to neural function.

Imaging Genetics in Anxiety Disorders

The first imaging genetic studies examining the 5-HTTLPR were performed in adults and demonstrated that the low-expressing allele is associated with increased amygdala activation (Hariri et al., 2002; Munafo, Brown, & Hariri, 2008) during processing of emotional stimuli. Additional research suggested that the low-expressing allele predicted decreased connectivity between prefrontal regulatory regions and the amygdala (Pezawas et al., 2005), suggesting that the low-expressing allele may lead to decreased prefrontal regulation, which in turn results in heightened amygdala response. Further research in adults replicated these findings (Surguladze et al., 2012; but see Heinz et al. (2005) and O'Nions, Dolan, and Roiser (2011) for inconsistent results).

In typically developing children and adolescents, the low-expressing allele of the 5-HTTLPR is also related to increased amygdala activation (Battaglia et al., 2012; Furman, Hamilton, Joormann, & Gotlib, 2011; Lau et al., 2009) and increased activation in frontal and parietal regions associated with attention to threat (Thomason et al., 2010). These imaging genetic studies demonstrate the utility of fMRI in producing more consistent links between genes and neural function than can be found between genes and behavioral phenotypes. In addition, they suggest a potential mechanism through which genetic variation may lead to risk for psychopathology: low-expressing alleles of the 5-HTTLPR are associated with reduced coupling between the prefrontal cortex and amygdala; this reduced connectivity may interrupt important feedback and regulatory processes that maintain adaptive levels of amygdala activation. Importantly, this is the same pattern of activation that has already been observed in anxiety disorder patients, as described earlier.

An apparent paradox in the serotonin transporter literature has been noted (Sibille & Lewis, 2006). The low-expressing allele of the 5-HTTLPR may confer risk for anxiety disorders, but an effective treatment for adults is the administration of selective serotonin reuptake inhibitors (SSRIs), which function similarly to the low-expressing allele of the 5-HTTLPR by reducing serotonin transporter availability. Results from animal models suggest that developmental processes may underlie these seemingly contradictory results. In mice, SSRIs administered during early childhood (which reduce serotonin transporter availability, similar to being a carrier of the low-expressing alleles of the 5-HTTLPR) lead to increased anxiety-related behaviors when these mice reach adulthood (Ansorge, Zhou, Lira, Hen, & Gingrich, 2004), whereas administering SSRIs chronically to adult mice has an anxiolytic effect (Troelsen, Nielsen, & Mirza, 2005). One potential explanation for this discrepancy is that serotonin is involved in guiding neural development in addition to its role as a neurotransmitter (Nordquist & Oreland, 2010). Therefore, reduced reuptake of serotonin early in development may affect neurodevelopmental processes and produce different results on brain function than reduced reuptake of serotonin later in development, once neurodevelopmental processes are complete (Daws & Gould, 2011; Sibille & Lewis, 2006).

Furthermore, several fMRI studies have suggested that 5-HTTLPR variation may relate to neural function differently depending on developmental stage. For example, fMRI research with typically developing children and adolescents has demonstrated an age x genotype interaction in which 5-HTTLPR genotype influences the cross-sectional association between age and amygdala activation, as well as functional connectivity (Wiggins et al., 2012, in press). Although these results are cross-sectional, they suggest that the 5-HTTLPR may alter the trajectory of changes in connectivity across childhood and adolescence, such that the relation between 5-HTTLPR and brain function will depend on the developmental stage assessed. Indeed, Lau et al. (2009) found that, contrary to the adult literature, children and adolescents with anxiety disorders with the *high-expressing* allele of the 5-HTTLPR

had increased amygdala activation compared to carriers of the low-expressing allele. This illustrates one of the principles of developmental neuroscience that findings from adults cannot necessarily be extrapolated to pediatric populations, as there may be important differences in the gene-brain interplay across development. Consideration of developmental timing will be critical moving forward in imaging genetic research.

Despite the promise of imaging genetic studies, there are also limitations that should be acknowledged. For example, although neural function is more proximal to genetic influence than behavioral phenotypes, there still exists a complex path from gene expression to protein synthesis to neural function, which may lead to weaker relations between genes and neural function than originally anticipated. Additionally, the psychological context or task chosen for investigation may have a large impact on neural function, such that there will be no straightforward relation between genetic variation and neural function across every condition, requiring more nuanced approaches to task design and careful consideration of psychological context.

Imaging Gene–Environment Interactions and Epigenetics in Anxiety Disorders

Although not testing a mediation model, several studies have approximated an imaging gene–environment interaction approach by demonstrating that 5-HTTLPR genotype interacts with life stress on amygdala responsiveness or amygdala activation at rest (Canli et al., 2006; Lemogne et al., 2011; Williams et al., 2009). This could provide support for Hyde et al.'s (2011) synergistic model suggesting that the low-expressing allele of the 5-HTTLPR may interact with environmental stress in a cumulative manner to lead to increased amygdala activity, which mediates heightened vulnerability for anxiety disorders. An additional potential mechanism that may underlie or interact with the mediation pathway proposed is that environmental stress may lead to epigenetic changes that alter gene expression and neural function.

Preliminary evidence suggests that DNA methylation of CpG sites in the promoter region of the 5-HTT gene may play a role in the previously observed gene × environment interactions in anxiety disorders. A series of publications from the Iowa Adoption Studies have examined the association between 5-HTTLPR genotype, history of child abuse, methylation of the serotonin transporter gene, and risk for developing depression. They found that a history of child abuse is associated with increased methylation in the promoter region of the 5-HTT gene (Beach, Brody, Todorov, Gunter, & Philibert, 2010). In another paper, investigators found that the influence of methylation of a CpG island in the 5-HTT gene on serotonin transporter expression (as measured through serotonin transporter mRNA levels) was only significant when 5-HTTLPR genotype was controlled (Philibert et al., 2007). Follow-up analyses revealed a trend for greater methylation associated with the low-expressing allele compared to the high-expressing allele, suggesting that methylation status may interact with 5-HTTLPR variation, although it should be noted this was marginally significant and not replicated with a larger sample (Philibert et al., 2008). Finally, greater methylation of the serotonin transporter promoter is marginally associated with a lifetime history of depression (Philibert et al., 2008).

Similar results have been reported in research on nonhuman primates. For example, Kinnally et al. (2010) found that the low-expressing allele of the 5-HTTLPR was associated with increased methylation of CpG sites on the 5-HTT gene in macaques, which in turn was associated with decreased levels of serotonin transporter mRNA, suggesting that higher methylation leads to reduced serotonin transporter expression. Additionally, increased methylation interacted with early life stress (separation from mother or unpredictable food availability) to predict higher scores on a behavioral measure of stress reactivity (Kinnally et al., 2010, 2011). This initial work suggests a potential pathway for epigenetic influences on the development of psychopathology: early environmental stress (e.g., child abuse) leads to increased methylation of the serotonin

transporter promoter region, but this is stronger for individuals with a low-expressing allele of the 5-HTTLPR (Beach et al., 2010; Kinnally et al., 2010; Philibert et al., 2007). Increased methylation of the 5-HTT gene leads to reduced transcription of the serotonin transporter (Kinnally et al., 2010), and is associated with increased risk for affective disorders such as major depression (Philibert et al., 2008) or heightened stress reactivity in nonhuman primates (Kinnally et al., 2011). This could be one potential mechanism for a gene × environment interaction in which individuals with the low-expressing allele who are exposed to stressful life events are at increased risk for developing psychopathology.

In contrast to the results reported above, others have found that methylation is protective and associated with decreased likelihood of developing PTSD after trauma (Koenen et al., 2011) or experiencing unresolved loss of an attachment figure (in low-expressing 5-HTTLPR allele carriers; van IJzendoorn, Caspers, Bakermans-Kranenburg, Beach, & Philibert, 2010). Indeed, Koenen et al. (2011) reported an interaction in which high methylation levels predicted higher rates of PTSD when individuals were exposed to a low number of traumatic events whereas when individuals were exposed to a high number of traumatic events, high methylation levels decreased the likelihood of developing PTSD. There are many differences in methodology across these studies that could underlie the differences in results including the methods used to assess DNA methylation levels and the CpG sites on the DNA where significant methylation differences were observed. Nevertheless, the finding that increased methylation levels may be protective in some cases raises this intriguing possibility proposed by Meaney (2010): methylation has an adaptive function of preparing the organism for whatever environment the organism is raised in. However, caution must be taken in interpreting results with cross-sectional designs such as those discussed above. Although we can assume that DNA sequences assessed in adulthood have not changed from early development, the same may not necessarily be true for epigenetic modifications, given that they are subject to environ-

mental influence (Houston et al., 2012). Thus, prospective longitudinal designs assessing DNA methylation levels early in development will be necessary in order to examine methylation levels preceding the development of psychopathology in adulthood.

Although the research reviewed above provides a biologically plausible model for gene–environment interactions, we are still restricted in the conclusions that can be drawn due to several limitations. First, these studies reported on peripheral levels of DNA methylation, which may not be reflective of methylation levels in the brain, as research has shown that methylation levels vary by cell type (Houston et al., 2012). Incorporating fMRI measures of brain activity, although not a substitute for directly measuring DNA methylation in brain tissue, could offer a complementary approach to help determine whether methylation levels measured peripherally alter neural activity in the predicted direction. This will be an important direction for research, as it is not possible to obtain levels of DNA methylation in neural cells from human participants except in postmortem studies. Second, the mechanisms linking increased methylation of the 5-HTT gene to increased risk for psychopathology need to be further delineated. Although studies have shown that methylation of the 5-HTT gene alters mRNA transcription of the serotonin transporter gene, the effect of 5-HTT methylation on brain function needs to be examined. An important candidate for investigation is that 5-HTT methylation levels may influence the development of prefrontal-amygdala circuitry, which in turn could lead to decreased emotion regulatory abilities and vulnerability to psychopathology. In order to test this hypothesis, however, imaging epigenetic studies incorporating fMRI assessments with measures of peripheral DNA methylation will need to be conducted. So far, with the exception reported below, relatively little work has been done in this area.

Although not reporting on the 5-HTTLPR, a recent imaging epigenetic study provides an example of how fMRI can help to elucidate the mechanisms of gene–environment interactions and represents what we believe is an important

direction for future research. This study examined a common functional variant in the gene regulating Catechol-O-methyltransferase (COMT), an enzyme that breaks down dopamine in the prefrontal cortex (Ursini et al., 2011). The COMT gene has two functional variants: the Val allele, which is associated with greater COMT activity and reduced prefrontal efficiency, and the Met allele, which is associated with less COMT expression. This gene may be an important candidate for gene × environment interactions because methylation at the region investigated in this study is possible on the Val allele, where there is a CpG site, but not on the Met allele (Wiers, 2012). In this case, unlike with the 5-HTT gene, methylation of the Val allele is associated with better function, because it reduces expression of COMT; reduced expression of COMT increases available dopamine levels and prefrontal cortex efficiency. Ursini et al. found that environmental stress predicted reduced methylation in Val/Val participants. Moreover, reduced methylation was associated with reduced working memory performance and reduced prefrontal cortex efficiency. Importantly, because methylation can only occur on the Val allele, there was a gene × environment interaction: greater stress and reduced methylation predicted less efficient prefrontal cortex function in Val/Val participants only. In contrast, this effect was not seen for Val/Met or Met/Met allele carriers. The results of this study nicely illustrate a potential gene × environment interaction mechanism similar to what we have proposed for the 5-HTTLPR: because Val allele carriers are the high expressers of COMT, methylation has a buffering influence which leads the COMT gene to function more like that of a Met allele carrier. However, when environmental stress is introduced, methylation is reduced, which leads to increased COMT expression, decreased prefrontal cortex efficiency (theoretically through reduced dopamine levels) and decreased working memory performance. However, we only see this effect when environmental stress and the Val/Val alleles are both present, leading to a gene–environment interaction. Future imaging epigenetic studies such as these will help to clarify the mediating neural mechanisms involved in these interactions.

Imaging Genetics in ASD

One example of how imaging genetic research may shed light on the relation between 5-HTTLPR variation and symptomatology in ASD is the use of proton magnetic resonance spectroscopy (measuring levels of certain brain chemicals) in children and adolescents with ASD. Endo et al. (2010) found that the low-expressing allele of the 5-HTTLPR was associated with altered chemical metabolism in the medial prefrontal cortex, possibly reflecting reduced neuronal development. Because the medial prefrontal cortex plays an important role both in communicating with the amygdala and in coordinating signals from the amygdala to aid in social cognition, this could be a neural pathway through which the low-expressing allele of the 5-HTTLPR leads to greater severity of social/communication symptoms in ASD. Therefore, imaging genetic approaches such as these may help us identify how genetic variation contributes to the development of ASD symptoms and could help disentangle the complications associated with a heterogeneous spectrum of disorders by identifying subtypes that share common developmental pathways.

Further complicating the genetic picture for ASD development, rare genetic mutations such as copy number variants (either deletion or extra copy of a chromosomal region) may have a stronger contribution to the development of ASD than common genetic variation (such as the 5-HTTLPR) observed in the general population; although rare genetic mutations and common genetic variation may interact to influence developmental outcomes (Geschwind, 2011). Given that there appears to be a large amount of rare *de novo* (not seen in the parent, but occurring in the gamete or fertilized egg) mutations that may contribute to the development of ASD (Gilman et al., 2011), Geschwind (2011) and others have argued that it will be necessary to identify common developmental pathways at the neural systems level whereby a wide array of genetic variation may lead to specific symptom and behavioral phenotypes. For example, a key neural feature of ASD may be disruption in

functional connectivity such as the connections between the prefrontal cortex and the amygdala. Imaging genetic studies may therefore help link a range of rare mutations in genes involved in axonal development and synaptic formation with the development of ASD through systems-level neural mechanisms observable with fMRI.

Epigenetics in ASD

There are a few lines of evidence suggesting that epigenetic regulation may be important to consider when examining genetic influences on ASD. Investigators have demonstrated altered epigenetic profiles of neuronal cells in postmortem brains of individuals with ASD (Shulha et al., 2012) and several candidate genes linked to ASD that regulate neuronal development are regulated by DNA methylation or other epigenetic mechanisms (Grafodatskaya, Chung, Szatmari, & Weksberg, 2010). Moreover, environmental risk factors that may be linked to the development of ASD may operate by altering methylation levels (LaSalle, 2011). Indeed, epigenetic influences on the development of ASD could help explain why it has been difficult to identify genes linked to ASD through genetic association approaches.

One example of a potential epigenetic influence on ASD is methylation of the oxytocin receptor gene. Oxytocin is a neuropeptide that increases social behaviors such as trust, empathy, emotion recognition, and eye gaze when administered to healthy controls (particularly men) (Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011). FMRI in adults has demonstrated that the effects of oxytocin on social behaviors may be mediated through a decrease in amygdala response to social stimuli (Kirsch et al., 2005). Recent research examining both peripheral DNA methylation levels and DNA methylation in postmortem human brain tissue has provided evidence of increased methylation of CpG sites on the promoter region of the oxytocin receptor gene in ASD, which is associated with decreased expression of the oxytocin receptor in temporal cortex (Gregory et al., 2009). Coupled with what

we know from fMRI about the influence of oxytocin on amygdala function in healthy adults and abnormalities in amygdala function in ASD, this work is suggestive of a potential pathway for epigenetic influence on ASD development: methylation of the promoter region for the oxytocin receptor gene reduces expression of the oxytocin receptor. This could in turn result in heightened amygdala activation to social stimuli, as has been observed in ASD (Dalton et al., 2005; Monk et al., 2010; Weng et al., 2011). Imaging epigenetic approaches such as those we described above could be used to test this hypothesis, which illustrates the utility of leveraging knowledge of brain function in typically developing and atypical populations in order to understand processes of genetic and epigenetic influences on the development of psychopathology.

The Brain as a Biomarker for Treatment Response in Anxiety Disorders and ASD

In addition to examining pathways through which psychopathology develops, fMRI can be a useful tool for developing novel treatments and understanding their effects on the brain. Neural activation probed through fMRI may be used as a biomarker for examining the effects of pharmacological and behavioral treatments as well as measuring their efficacy (Paulus & Stein, 2007). This could be used, for example, as a preliminary examination of novel potential therapies to test whether they alter neural activity in a predicted direction in a small number of participants before conducting multisite large-scale clinical trials that are costly and time-consuming. In addition, by allowing examination of changes in activation in neural circuitry known to relate to specific disorders, fMRI has the capability to characterize how a particular pharmacological agent has a therapeutic effect, compare the effects of different classes of drugs on neural activity, and potentially predict therapeutic response or select the best pharmacological intervention for a particular individual based on their pretreatment patterns of neural activity (Paulus & Stein, 2007). Thus, the

potential applications of fMRI for developing new treatments and predicting treatment response are promising.

Treatment Studies in Anxiety Disorders

Although there are currently treatments available for anxiety disorders including selective serotonin reuptake inhibitors (SSRIs) and cognitive behavioral therapy, these treatments are not effective for many patients, and SSRIs may have adverse side effects. Therefore, fMRI could play an important role in identifying new potential treatments and in helping to select which treatments are most likely to result in positive treatment response for individual patients.

Using fMRI, investigators have demonstrated that currently available treatments for anxiety disorders alter activity in the same neural regions (prefrontal cortex and amygdala) that have been shown to function abnormally in anxiety disorder patients (Murphy, 2010; Strawn, Wehry, DelBello, Rynn, & Strakowski, 2012). FMRI research in healthy adult participants demonstrated that administration of SSRIs results in decreased amygdala activation to emotional faces (Harmer, Mackay, Reid, Cowen, & Goodwin, 2006). Moreover, treatment of anxiety disorder patients (either pharmacological or with cognitive behavioral therapy) results in decreased amygdala activation (Furmark et al., 2002) and increased activation in the ventrolateral prefrontal cortex (Maslowksy et al., 2010). In depressed patients, SSRIs have also been shown to increase connectivity between the amygdala and prefrontal regions, suggesting that SSRIs may increase communication between the amygdala and prefrontal cortex (Chen et al., 2008). Given the established role of altered ventral prefrontal cortex-amygdala circuit function in anxiety disorder patients, these results suggest that therapeutic effects may occur through some combination of decreasing amygdala activation and increasing prefrontal regulation. It is important to note, however, that when changes in neural activity occur in the context of symptom improvement in

patients, we cannot necessarily attribute a causal role in symptom improvement to changes in neural function; instead, it could be that other changes (e.g., changes in cognitive processing patterns or behavior) cause both changes in symptoms and neural activity (Murphy, 2010).

These results have important implications for the development and testing of new medications by providing a potential biomarker for measuring treatment effectiveness. For example, several recent fMRI studies have suggested that pharmacological agents not currently prescribed for the treatment of anxiety disorders may have similar influences on neural activity as SSRIs. These medications alter the release or reception of neurotransmitters other than serotonin and have been demonstrated to affect prefrontal cortex-amygdala circuitry, for instance, by decreasing amygdala activation or increasing anterior cingulate cortex activation (Aupperle et al., 2011; Furmark et al., 2005). Additional fMRI studies such as these have the potential to help identify new treatments for anxiety disorders that may be prescribed to individuals who are nonresponsive or have adverse side effects to SSRIs. Moreover, these studies show that the influence of medications on brain response can be detected with relatively small samples (less than 40 participants in each case), supporting Paulus and Stein's (2007) argument that preliminary fMRI studies of treatment response will be a more cost-effective and less time-consuming method of identifying promising new treatments before they reach the clinical trial phase.

Furthermore, it may be possible to use pretreatment neural function assessed through fMRI as a tool to choose the best treatment for an individual. For example, greater pretreatment amygdala activation predicted better response to SSRI or cognitive behavioral therapy treatment in pediatric anxiety disorder patients (McClure, Adler, et al., 2007), and greater pretreatment anterior cingulate cortex activation predicted better response to pharmacological treatment in adult generalized anxiety disorder patients (Nitschke et al., 2009). Future studies such as these have the potential to help target treatments for patients by predicting which drugs or therapies they will

respond to best. For instance, two related SSRIs (citalopram and escitalopram) both reduced amygdala activation to emotional faces in healthy controls, but had different effects on activation in the ventromedial prefrontal cortex (Windischberger et al., 2010). Although this type of research is still in its infancy, understanding the differences in effects on neural activation of different types of SSRIs could help in choosing the best one to prescribe based on a patient's neural activation.

Treatment Studies in ASD

Unlike anxiety disorders, there is currently no pharmacological treatment available for the core symptoms of ASD. Based on the neuroimaging data pointing to the influence of oxytocin on amygdala function and social behavior, investigators have proposed a potential translational application of oxytocin as a treatment for the social symptoms of ASD (Meyer-Lindenberg et al., 2011). Indeed, intranasal administration of oxytocin improved emotion recognition in children and adolescents with ASD (Guastella et al., 2010), suggesting a promising potential for the treatment of social symptoms. An important question for investigation with fMRI is whether the effect of oxytocin on improvement in ASD symptoms is mediated through decreased amygdala response to social stimuli and whether the effect of oxytocin on amygdala activity varies in strength at different stages of development. FMRI could also play an important role in helping determine which individuals will respond to oxytocin and in identifying other pharmacological agents that have similar effects on neural activation.

Future Directions for fMRI Research in Developmental Psychopathology

Throughout this review we have highlighted areas in need of further investigation through imaging genetics, imaging epigenetics, and imaging treatment approaches. In the final section, we discuss methodological considerations for this research.

External Validity of fMRI Tasks

FMRI requires close attention to task design in order to ensure that the cognitive processes of interest are isolated as much as possible and that the same cognitive processes are being elicited in each participant during scanning. Along these lines, further attention to the external validity of fMRI tasks will also improve our ability to examine neural activation in the context of cognitive and emotional processes that are more likely to represent what occurs in day-to-day life and importantly during the experience of symptoms. For example, Guyer et al. (2008) used a chat room task in which adolescents were asked to rate their desire to have an Internet chat with other peers and in which they were informed that other peers would be rating their desire to chat with the participant. While undergoing fMRI scanning, participants were asked to rate how interested they thought other peers would be in chatting with them. Due to the greater external validity of this task, the cognitive processes elicited by this task may more closely approximate the social anxiety symptoms related to peer evaluation that adolescents experience in everyday life. Future research that can better model the complex social contexts and relationships characteristic of the adolescent period may thus improve the strength of relations between fMRI measures and behavioral or self-report measures of symptoms that are influenced by these social contexts.

Longitudinal Designs in fMRI and the Use of Younger Samples

Structural MRI studies have plotted longitudinal changes in gray and white matter volumes over development. Similar longitudinal work is needed with fMRI in order to examine functional changes across development. One potential concern with longitudinal research in fMRI is that it is difficult to find a task that can be performed equally well and elicits the same cognitive strategies at all age levels. A second related concern is that infants and very young children generally cannot perform task-based fMRI. Resting-state

or task-free fMRI (in which participants simply lie or sleep in the scanner while imaging data is acquired) has the potential to address both of these limitations. Because it requires no task, it removes the concern that participants of different ages may be performing a cognitive task differently, and it allows for participation of very young children who cannot perform tasks.

Analysis of resting-state fMRI usually involves a functional connectivity approach that examines the correlation of low-frequency spontaneous fluctuations in BOLD signal across different neural regions, which is sometimes referred to as intrinsic connectivity (Fox & Raichle, 2007). Importantly, regions that demonstrate intrinsic connectivity at rest also tend to demonstrate functional connectivity while participants perform a task (Smith et al., 2009), suggesting that intrinsic connectivity can provide similar information regarding the strength of integration across neural regions or networks related to specific cognitive or emotional processes. The ability to collect longitudinal data starting with infants or potentially even prenatally is especially important in light of the research mentioned earlier suggesting that genetic and epigenetic influences on psychopathology may occur very early in development. Thus, the ability to examine neural function at these earlier developmental stages with resting-state fMRI could be used as a complementary approach to task-based fMRI in order to gain a more complete picture of the developmental trajectories of neural networks and to examine this development prospectively before symptoms of psychopathology may be apparent.

Large-Scale fMRI Studies

Recognition of the complexity of gene–environment interactions indicates the requirement of large samples to yield the statistical power necessary to examine these effects in imaging gene–environment interaction designs (Hyde et al., 2011). Resting-state fMRI data could be useful in this regard because it allows for the combination of data sets across different research groups without the requirement that participants all performed the same task (Biswal et al., 2010). Another example of a large-scale fMRI approach is the IMAGEN group's multisite collaborative prospective longitudinal study designed to have sufficient power to examine imaging gene–environment interactions (Schumann et al., 2010). By collecting genotype and fMRI data on an estimated 2,000 participants, this study will have increased power to detect gene–gene and gene–environment interactions and their relation to neural function compared to previous studies with smaller sample sizes.

Conclusion

Current fMRI research in developmental psychopathology has helped establish patterns of altered neural function in pediatric psychopathology and linked dysfunction in these regions with cognitive and emotional processes related to the symptoms and behavioral profiles of specific disorders. These studies have highlighted the role of prefrontal cortex-amygdala circuitry in both anxiety disorders and ASD. Imaging genetic studies have linked variation in genes regulating serotonin levels to altered functioning of this circuit, indicating a potential developmental pathway for the influence of genetic variation on neural function and laying the foundation for examination of epigenetic influences on this circuitry. Treatment studies have suggested that currently available treatments and potential novel treatments for anxiety disorders and ASD alter activity in this same neural circuitry, either by increasing prefrontal regulation or dampening amygdala responsiveness. These studies have paved the way for future imaging genetic and imaging epigenetic studies to examine how prefrontal-amygdala cortex circuitry (and, through extension of these methods, other neural circuitry and networks implicated in these disorders) is involved in the development of psychopathology and is influenced through genetic and epigenetic factors. This will help establish critical knowledge necessary to develop novel preventions and treatments, one of the major goals of the field of developmental psychopathology.

References

Adolphs, R. (2010). What does the amygdala contribute to social cognition? *Annals of the New York Academy of Sciences, 1191*, 42–61.

Ansorge, M. S., Zhou, M., Lira, A., Hen, R., & Gingrich, J. A. (2004). Early-life blockade of the 5-HT transporter alters emotional behavior in adult mice. *Science, 306*, 879–881.

Ashwin, C., Baron-Cohen, S., Wheelwright, S., O'Riordan, M., & Bullmore, E. T. (2007). Differential activation of the amygdala and the 'social brain' during fearful face-processing in Asperger Syndrome. *Neuropsychologia, 45*(1), 2–14.

Aupperle, R. L., Ravindran, L., Tankersley, D., Flagan, T., Stein, N. R., Simmons, A. N., et al. (2011). Pregabalin influences insula and amygdala activation during anticipation of emotional images. *Neuropsychopharmacology, 36*(7), 1466–1477.

Bagot, R. C., & Meaney, M. J. (2010). Epigenetics and the biological basis of gene x environment interactions. *Journal of the American Academy of Child & Adolescent Psychiatry, 49*(8), 752–771.

Baron-Cohen, S., Ring, H. A., Wheelwright, S., Bullmore, E. T., Brammer, M. J., Simmons, A., et al. (1999). Social intelligence in the normal and autistic brain: An fMRI study. *European Journal of Neuroscience, 11*, 1891–1898.

Battaglia, M., Zanoni, A., Taddei, M., Giorda, R., Bertoletti, E., Lampis, V., et al. (2012). Cerebral responses to emotional expressions and the development of social anxiety disorder: A preliminary longitudinal study. *Depression and Anxiety, 29*(1), 54–61.

Beach, S. R., Brody, G. H., Todorov, A. A., Gunter, T. D., & Philibert, R. A. (2010). Methylation at SLC6A4 is linked to family history of child abuse: An examination of the Iowa Adoptee sample. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 153B*(2), 710–713.

Biswal, B., Mennes, M., Zuo, X., Gohel, S., Kelly, C., Smith, S. M., et al. (2010). Toward discovery science of human brain function. *Proceedings of the National Academy of Sciences of the United States of America, 107*(10), 4734–4739.

Britton, J. C., Lissek, S., Grillon, C., Norcross, M. A., & Pine, D. S. (2011). Development of anxiety: The role of threat appraisal and fear learning. *Depression and Anxiety, 28*(1), 5–17.

Brune, C. W., Kim, S., Salt, J., Levanthal, B. L., Lord, C., & Cook, E. H., Jr. (2006). 5-HTTLPR genotype-specific phenotype in children and adolescents with autism. *The American Journal of Psychiatry, 163*(12), 2148–2156.

Canli, T., Qiu, M., Omura, K., Congdon, E., Haas, B. W., Amin, Z., et al. (2006). Neural correlates of epigenesis. *Proceedings of the National Academy of Sciences of the United States of America, 103*(43), 16033–16038.

Carmody, D. P., & Lewis, M. (2010). Regional white matter development in children with autism spectrum disorders. *Developmental Psychobiology, 52*(8), 755–763.

Casey, B. J., Jones, R. M., & Hare, T. A. (2008). The adolescent brain. *Annals of the New York Academy of Sciences, 1124*, 111–126.

Caspi, A., & Moffitt, T. E. (2006). Gene-environment interactions in psychiatry: Joining forces with neuroscience. *Nature Reviews. Neuroscience, 7*, 583–590.

Chen, C. H., Suckling, J., Ooi, C., Fu, C. H., Williams, S. C., Walsh, N. D., et al. (2008). Functional coupling of the amygdala in depressed patients treated with antidepressant medication. *Neuropsychopharmacology, 33*(8), 1909–1918.

Cicchetti, D., & Dawson, G. (2002). Multiple levels of analysis. *Development and Psychopathology, 14*, 417–420.

Courchesne, E., Pierce, K., Schumann, C. M., Redcay, E., Buckwalter, J. A., Kennedy, D. P., et al. (2007). Mapping early brain development in autism. *Neuron, 56*, 399–413.

Daleiden, E. L., & Vasey, M. W. (1997). An information-processing perspective on childhood anxiety. *Clinical Psychology Review, 17*(4), 407–429.

Dalton, K. M., Nacewicz, B. M., Johnstone, T., Schaefer, H. S., Gernsbacher, M. A., Goldsmith, H. H., et al. (2005). Gaze fixation and the neural circuitry of face processing in autism. *Nature Neuroscience, 8*(4), 519–526.

Daws, L. C., & Gould, G. G. (2011). Ontogeny and regulation of the serotonin transporter: Providing insights into human disorders. *Pharmacology & Therapeutics, 131*(1), 61–79.

Dawson, G., Webb, S. J., Wijsman, E., Schellenberg, G., Estes, A., Munson, J., et al. (2005). Neurocognitive and electrophysiological evidence of altered face processing in parents of children with autism: Implications for a model of abnormal development of social brain circuitry in autism. *Development and Psychopathology, 17*, 679–697.

Ellis, B. J., Boyce, W. T., Belsky, J., Bakermans-Kranenburg, M. J., & van Ijzendoorn, M. H. (2011). Differential susceptibility to the environment: An evolutionary-neurodevelopmental theory. *Development and Psychopathology, 23*, 7–28.

Endo, T., Kitamura, H., Tamura, R., Egawa, J., Sugai, T., Fukui, N., et al. (2010). 5-HTTLPR polymorphism influences prefrontal neurochemical metabolites in autism spectrum disorder. *Psychiatry Research, 183*(2), 170–173.

Etkin, A., Prater, K. E., Hoeft, F., Menon, V., & Schatzberg, A. F. (2010). Failure of anterior cingulate activation and connectivity with the amygdala during implicit regulation of emotional processing in generalized anxiety disorder. *The American Journal of Psychiatry, 167*, 545–554.

Etkin, A., & Wager, T. D. (2007). Functional neuroimaging of anxiety: A meta-analysis of emotional process-

ing in PTSD, social anxiety disorder, and specific phobia. *The American Journal of Psychiatry, 164*, 1476–1488.

Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews. Neuroscience, 8*, 700–711.

Fox, N. A., Nichols, K. E., Henderson, H. A., Rubin, K., Schmidt, L., Hamer, D., et al. (2005). Evidence for a gene-environment interaction in predicting behavioral inhibition in middle childhood. *Psychological Science, 16*(12), 921–926.

Furman, D. J., Hamilton, J. P., Joormann, J., & Gotlib, I. H. (2011). Altered timing of amygdala activation during sad mood elaboration as a function of 5-HTTLPR. *Social Cognitive and Affective Neuroscience, 6*(3), 270–276.

Furmark, T., Appel, L., Michelgard, A., Wahlstedt, K., Ahs, F., Zancan, S., et al. (2005). Cerebral blood flow changes after treatment of social phobia with the neurokinin-1 antagonist GR205171, citalopram, or placebo. *Biological Psychiatry, 58*(2), 132–142.

Furmark, T., Tillfors, M., Marteinsdottir, I., Fischer, H., Pissiota, A., Langstrom, B., et al. (2002). Common changes in cerebral blood flow in patients with social phobia treated with citalopram or cognitive-behavioral therapy. *Archives of General Psychiatry, 59*, 425–433.

Geschwind, D. H. (2011). Genetics of autism spectrum disorders. *Trends in Cognitive Sciences, 15*(9), 409–416.

Ghashghaei, H. T., Hilgetag, C. C., & Barbas, H. (2007). Sequence of information processing for emotions based on the anatomic dialogue between prefrontal cortex and amygdala. *NeuroImage, 34*(3), 905–923.

Giedd, J. N., & Rapoport, J. L. (2010). Structural MRI of pediatric brain development: What have we learned and where are we going? *Neuron, 67*, 728–734.

Gilman, S. R., Iossifov, I., Levy, D., Ronemus, M., Wigler, M., & Vitkup, D. (2011). Rare de novo variants associated with autism implicate a large functional network of genes involved in formation and function of synapses. *Neuron, 70*(5), 898–907.

Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C., et al. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences of the United States of America, 101*(21), 8174–8179.

Gottlieb, G. (2007a). Developmental neurobehavioral genetics: Development as explanation. In B.C. Jones & P. Mormede (Eds.), *Neurobehavioral Genetics* (2nd ed., pp. 17–27). Boca Raton, FL: CRC Taylor & Francis.

Gottlieb, G. (2007b). Probabilistic epigenesis. *Developmental Science, 10*(1), 1–11.

Grafodatskaya, D., Chung, B., Szatmari, P., & Weksberg, R. (2010). Autism spectrum disorders and epigenetics. *Journal of the American Academy of Child & Adolescent Psychiatry, 49*(8), 794–809.

Gregory, S. G., Connelly, J. J., Towers, A. J., Johnson, J., Biscocho, D., Markunas, C. A., et al. (2009). Genomic and epigenetic evidence for oxytocin receptor deficiency in autism. *BMC Medicine, 7*, 62.

Guastella, A. J., Einfeld, S. L., Gray, K. M., Rinehart, N. J., Tonge, B. J., Lambert, T. J., et al. (2010). Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders. *Biological Psychiatry, 67*(7), 692–694.

Guyer, A. E., Lau, J. Y. F., McClure-Tone, E. B., Parrish, J. M., Shiffrin, N. D., Reynolds, R. C., et al. (2008). Amygdala and ventrolateral prefrontal cortex function during anticipated peer evaluation in pediatric social anxiety. *Archives of General Psychiatry, 65*(11), 1303–1312.

Hare, T. A., Tottenham, N., Galvan, A., Voss, H. U., Glover, G. H., & Casey, B. J. (2008). Biological substrates of emotional reactivity and regulation in adolescence during an emotional go-nogo task. *Biological Psychiatry, 63*, 927–934.

Hariri, A. R., Mattay, V. S., Tessitore, A., Kolachana, B., Fera, F., Goldman, D., et al. (2002). Serotonin transporter genetic variation and the response of the human amygdala. *Science, 297*, 400–403.

Hariri, A. R., & Weinberger, D. R. (2003). Functional neuroimaging of genetic variation in serotonergic neurotransmission. *Genes, Brain, and Behavior, 2*, 341–349.

Harmer, C. J., Mackay, C. E., Reid, C. B., Cowen, P. J., & Goodwin, G. M. (2006). Antidepressant drug treatment modifies the neural processing of nonconscious threat cues. *Biological Psychiatry, 59*(9), 816–820.

Heinz, A., Braus, D. F., Smolka, M. N., Wrase, J., Puls, I., Hermann, D., et al. (2005). Amygdala-prefrontal coupling depends on a genetic variation of the serotonin transporter. *Nature Neuroscience, 8*(1), 20–21.

Houston, I., Peter, C. J., Mitchell, A., Straubhaar, J., Rogaev, E., & Akbarian, S. (2012). Epigenetics in the human brain. *Neuropsychopharmacology, 37*, 1–15.

Hu, X. Z., Lipsky, R. H., Zhu, G., Akhtar, L. A., Taubman, J., Greenberg, B. D., et al. (2006). Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. *American Journal of Human Genetics, 78*(5), 815–826.

Huang, C. H., & Santengelo, S. L. (2008). Autism and serotonin transporter gene polymorphisms: A systematic review and meta-analysis. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 147B*, 903–913.

Hyde, L. W., Bogdan, R., & Hariri, A. R. (2011). Understanding risk for psychopathology through imaging gene-environment interactions. *Trends in Cognitive Sciences, 15*(9), 417–427.

Johnson, M. H., Halit, H., Grice, S. J., & Karmiloff-Smith, A. (2002). Neuroimaging of typical and atypical development: A perspective from multiple levels of analysis. *Development and Psychopathology, 14*, 521–536.

Joseph, R. M., Ehrman, K., McNally, R., & Keehn, B. (2008). Affective response to eye contact and face

recognition ability in children with ASD. *Journal of the International Neuropsychological Society, 14*, 947–955.

Kilpatrick, D., Koenen, K., Ruggiero, K., Acierno, R., Galea, S., & Resnick, H. (2007). The serotonin transporter genotype and social support and moderation of posttraumatic stress disorder and depression in hurricane-exposed adults. *American Journal of Psychiatry, 164*(11), 1693–1699.

Kinnally, E. L., Capitanio, J. P., Leibel, R., Deng, L., LeDuc, C., Haghighi, F., et al. (2010). Epigenetic regulation of serotonin transporter expression and behavior in infant rhesus macaques. *Genes, Brain, and Behavior, 9*(6), 575–582.

Kinnally, E. L., Feinberg, C., Kim, D., Ferguson, K., Leibel, R., Coplan, J. D., et al. (2011). DNA methylation as a risk factor in the effects of early life stress. *Brain, Behavior, and Immunity, 25*(8), 1548–1553.

Kirsch, P., Esslinger, C., Chen, Q., Mier, D., Lis, S., Siddhanti, S., et al. (2005). Oxytocin modulates neural circuitry for social cognition and fear in humans. *The Journal of Neuroscience, 25*(49), 11489–11493.

Kleinhans, N. M., Johnson, L. C., Richards, T., Mahurin, R., Greenson, J., Dawson, G., et al. (2009). Reduced neural habituation in the amygdala and social impairments in autism spectrum disorders. *The American Journal of Psychiatry, 166*, 467–475.

Kliemann, D., Dziobek, I., Hatri, A., Steimke, R., & Heekeren, H. R. (2010). Atypical reflexive gaze patterns on emotional faces in autism spectrum disorders. *The Journal of Neuroscience, 30*(37), 12281–12287.

Kliemann, D., Dziobek, I., Hatri, A., Baudwig, J., & Heekeren, H. R. (2012). The role of the amygdala in atypical gaze on emotional faces in autism spectrum disorders. *The Journal of Neuroscience, 32*(28), 9469–9476.

Klin, A., Jones, W., Schultz, R., Volkmar, F., & Cohen, D. (2002). Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. *Archives of General Psychiatry, 59*, 809–816.

Koenen, K. C., Uddin, M., Chang, S. C., Aiello, A. E., Wildman, D. E., Goldmann, E., et al. (2011). SLC6A4 methylation modifies the effect of the number of traumatic events on risk for posttraumatic stress disorder. *Depression and Anxiety, 28*(8), 639–647.

LaSalle, J. M. (2011). A genomic point-of-view on environmental factors influencing the human brain methylome. *Epigenetics, 6*, 862–869.

Lau, J. Y. F., Goldman, D., Buzas, B., Fromm, S. J., Guyer, A. E., Hodgkinson, C., et al. (2009). Amygdala function and 5-HTT gene variants in adolescent anxiety and major depressive disorder. *Biological Psychiatry, 65*(4), 349–355.

Laucht, M., Treutlein, J., Blomeyer, D., Buchmann, A. F., Schmid, B., Becker, K., et al. (2009). Interaction between the 5-HTTLPR serotonin transporter polymorphism and environmental adversity for mood and anxiety psychopathology: Evidence from a high-risk community sample of young adults.

International Journal of Neuropsychopharmacology, 12, 737–747.

Lemogne, C., Gorwood, P., Boni, C., Pessiglione, M., Lehericy, S., & Fossati, P. (2011). Cognitive appraisal and life stress moderate the effects of the 5-HTTLPR polymorphism on amygdala reactivity. *Human Brain Mapping, 32*(11), 1856–1867.

Lesch, K. P., Bengel, D., Heils, A., Sabol, S. Z., Greenberg, B. D., Petri, S., et al. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science, 274*, 1527–1531.

Lewis, M., & Carmody, D. P. (2008). Self-representation and brain development. *Developmental Psychology, 44*(5), 1329–1334.

Maslowksy, J., Mogg, K., Bradley, B. P., McClure-Tone, E. B., Ernst, M., Pine, D. S., et al. (2010). A preliminary investigation of neural correlates of treatment in adolescents with generalized anxiety disorder. *Journal of Child and Adolescent Psychopharmacology, 20*(2), 105–111.

McClure, E. B., Adler, A., Monk, C. S., Cameron, J., Smith, S., Nelson, E. E., et al. (2007). fMRI predictors of treatment outcome in pediatric anxiety disorders. *Psychopharmacology, 191*(1), 97–105.

McClure, E. B., Monk, C. S., Nelson, E. E., Parrish, J. M., Adler, A., Blair, J. R., et al. (2007). Abnormal attention modulation of fear circuit function in pediatric generalized anxiety disorder. *Archives of General Psychiatry, 64*, 97–106.

McGowan, P. O., Sasaki, A., D'Alessio, A. C., Dymov, S., Labonte, B., Szyf, M., et al. (2009). Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nature Neuroscience, 12*(3), 342–348.

Meaney, M. J. (2010). Epigenetics and the biological definition of gene x environment interactions. *Child Development, 81*(1), 41–79.

Meyer-Lindenberg, A., Domes, G., Kirsch, P., & Heinrichs, M. (2011). Oxytocin and vasopressin in the human brain: Social neuropeptides for translational medicine. *Nature Reviews. Neuroscience, 12*, 524–538.

Monk, C. S. (2008). The development of emotion-related neural circuitry in health and psychopathology. *Development and Psychopathology, 20*(4), 1231–1250.

Monk, C. S., McClure, E. B., Nelson, E. E., Zarahn, E., Bilder, R. M., Leibenluft, E., et al. (2003). Adolescent immaturity in attention-related brain engagement to emotional facial expressions. *NeuroImage, 20*, 420–428.

Monk, C. S., Nelson, E. E., McClure, E. B., Mogg, K., Bradley, B. P., Leibenluft, E., et al. (2006). Ventrolateral prefrontal cortex activation and attentional bias in response to angry faces in adolescents with generalized anxiety disorder. *The American Journal of Psychiatry, 163*, 1091–1097.

Monk, C. S., Telzer, E. H., Mogg, K., Bradley, B. P., Mai, X., Louro, H. M. C., et al. (2008). Amygdala and

ventrolateral prefrontal cortex activation to masked angry faces in children and adolescents with generalized anxiety disorder. *Archives of General Psychiatry, 65*(5), 568–576.

Monk, C. S., Weng, S. J., Wiggins, J. L., Kurapati, N., Louro, H. M. C., Carrasco, M., et al. (2010). Neural circuitry of emotional face processing in autism spectrum disorders. *Journal of Psychiatry and Neuroscience, 35*(2), 105–114.

Munafo, M. R., Brown, S. M., & Hariri, A. R. (2008). Serotonin transporter (5-HTTLPR) genotype and amygdala activation: A meta-analysis. *Biological Psychiatry, 63*(9), 852–857.

Munafo, M. R., Freimer, N. B., Ng, W., Ophoff, R., Veijola, J., Miettunen, J., et al. (2009). 5-HTTLPR genotype and anxiety-related personality traits: A meta-analysis and new data. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 150B*(2), 271–281.

Mundy, P. C., Henderson, H. A., Inge, A. P., & Coman, D. C. (2007). The modifier model of autism and social development in higher functioning children. *Research & Practice for Persons with Severe Disabilities, 32*(2), 124–139.

Murphy, S. E. (2010). Using functional neuroimaging to investigate the mechanism of action of selective serotonin reuptake inhibitors (SSRIs). *Current Pharmaceutical Design, 16*, 1990–1997.

Myers-Schulz, B., & Koenigs, M. (2012). Functional anatomy of ventromedial prefrontal cortex: Implications for mood and anxiety disorders. *Molecular Psychiatry, 17*, 132–141.

Neumann, D., Spezio, M. L., Piven, J., & Adolphs, R. (2006). Looking you in the mouth: Abnormal gaze in autism resulting from impaired top-down modulation of visual attention. *Social Cognitive and Affective Neuroscience, 1*(3), 194–202.

Nijmeijer, J. S., Hartman, C. A., Rommelse, N. N. J., Altink, M. E., Buschgens, C. J. M., Fliers, E. A., & Hoekstra, P. J. (2010). Perinatal risk factors interacting with catechol O-methyltransferase and the serotonin transporter gene predict ASD symptoms in children with ADHD. *Journal of Child Psychology and Psychiatry, 51*(11), 1242–1250.

Nitschke, J. B., Sarinopoulos, I., Oathes, D. J., Johnstone, T., Whalen, P. J., Davidson, R. J., et al. (2009). Anticipatory activation in the amygdala and anterior cingulate in generalized anxiety disorder and prediction of treatment response. *The American Journal of Psychiatry, 166*, 302–310.

Nordquist, N., & Oreland, L. (2010). Serotonin, genetic variability, behaviour, and psychiatric disorders – A review. *Upsala Journal of Medical Sciences, 115*, 2–10.

O'Nions, E. J. P., Dolan, R. J., & Roiser, J. P. (2011). Serotonin transporter genotype modulates subgenual response to fearful faces using an incidental task. *Journal of Cognitive Neuroscience, 23*(11), 3681–3693.

Paulus, M. P., & Stein, M. B. (2007). Role of functional magnetic resonance imaging in drug discovery. *Neuropsychology Review, 17*(2), 179–188.

Pergamin-Hight, L., Bakermans-Kranenburg, M. J., van Ijzendoorn, M. H., & Bar-Haim, Y. (2012). Variations in the promoter region of the serotonin transporter gene and biased attention for emotional information: A meta-analysis. *Biological Psychiatry, 71*(4), 373–379.

Pezawas, L., Meyer-Lindenberg, A., Drabant, E. M., Verchinski, B. A., Munoz, K. E., Kolachana, B., et al. (2005). 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: A genetic susceptibility mechanism for depression. *Nature Neuroscience, 8*(6), 828–834.

Philibert, R., Madan, A., Andersen, A., Cadoret, R., Packer, H., & Sandhu, H. (2007). Serotonin transporter mRNA levels are associated with the methylation of an upstream CpG island. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 144B*(1), 101–105.

Philibert, R., Sandhu, H., Hollenbeck, N., Gunter, T., Adams, W., & Madan, A. (2008). The relationship of 5HTT (SLC6A4) methylation and genotype on mRNA expression and liability to major depression and alcohol dependence in subjects from the Iowa Adoption Studies. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 147B*(5), 543–549.

Philip, R. C., Dauvermann, M. R., Whalley, H. C., Baynham, K., Lawrie, S. M., & Stanfield, A. C. (2012). A systematic review and meta-analysis of the fMRI investigation of autism spectrum disorders. *Neuroscience and Biobehavioral Reviews, 36*(2), 901–942.

Phillips, M. L., Ladouceur, C. D., & Drevets, W. C. (2008). A neural model of voluntary and automatic emotion regulation: Implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. *Molecular Psychiatry, 13*(9), 829, 833–857.

Pine, D. S. (2007). Research review: A neuroscience framework for pediatric anxiety disorders. *Journal of Child Psychology and Psychiatry, 48*(7), 631–648.

Pinto, A. O., & Sesack, S. R. (2003). Prefrontal cortex projections to the rat amygdala: Spatial relationships to dopamine and serotonin afferents. *Annals of the New York Academy of Sciences, 985*, 542–544.

Ray, R. D., & Zald, D. H. (2012). Anatomical insights into the interaction of emotion and cognition in the prefrontal cortex. *Neuroscience and Biobehavioral Reviews, 36*(1), 479–501.

Rubia, K., Overmeyer, S., Taylor, E., Brammer, M., Williams, S. C. R., Simmons, A., et al. (2000). Functional frontalisation with age: Mapping neurodevelopmental trajectories with fMRI. *Neuroscience and Biobehavioral Reviews, 24*, 13–19.

Sameroff, A. (2010). A unified theory of development: A dialectic integration of nature and nurture. *Child Development, 81*(1), 6–22.

Sarter, M., & Markowitsch, H. J. (1984). Collateral inner-vation of the medial and lateral prefrontal cortex by amygdaloid, thalamic, and brain-stem neurons. *The Journal of Comparative Neurology, 224*, 445–460.

Schultz, R. T. (2005). Developmental deficits in social perception in autism: The role of the amygdala and fusiform face area. *International Journal of Developmental Neuroscience, 23*(2–3), 125–141.

Schumann, C. M., Hamstra, J., Goodlin-Jones, B. L., Lotspeich, L. J., Kwon, H., Buonocore, M. H., et al. (2004). The amygdala is enlarged in children but not adolescents with autism; The hippocampus is enlarged at all ages. *The Journal of Neuroscience, 24*(28), 6392–6401.

Schumann, G., Loth, E., Banaschewski, T., Barbot, A., Barker, G., Buchel, C., et al. (2010). The IMAGEN study: Reinforcement-related behaviour in normal brain function and psychopathology. *Molecular Psychiatry, 15*, 1128–1139.

Shulha, H. P., Cheung, I., Whittle, C., Wang, J., Virgil, D., Lin, C. L., et al. (2012). Epigenetic signatures of autism: Trimethylated H3K4 landscapes in prefrontal neurons. *Archives of General Psychiatry, 69*(3), 314–324.

Sibille, E., & Lewis, D. A. (2006). SERT-ainly involved in depression, but when? *The American Journal of Psychiatry, 163*(1), 8–11.

Smith, S. M., Fox, P. T., Miller, K. L., Glahn, D. C., Fox, P. M., Mackay, C. E., et al. (2009). Correspondence of the brain's functional architecture during activation and rest. *Proceedings of the National Academy of Sciences of the United States of America, 106*(31), 13040–13045.

Stein, M. B., Schork, N., & Gelernter, J. (2008). Gene-by-environment (serotonin transporter and childhood maltreatment) interaction for anxiety sensitivity, an intermediate phenotype for anxiety disorders. *Neuropsychopharmacology, 33*(2), 312–319.

Steinberg, L., Dahl, R., Keating, D., Kupfer, D. J., Masten, A. S., & Pine, D. S. (2006). The study of developmental psychopathology in adolescence: Integrating affective neuroscience with the study of context. In D. Cicchetti & D. J. Cohen (Eds.), *Developmental psychopathology, Vol 2: Developmental neuroscience* (2nd ed., pp. 710–741). Hoboken, NJ: Wiley.

Strawn, J. R., Wehry, A. M., DelBello, M. P., Rynn, M. A., & Strakowski, S. (2012). Establishing the neurobiologic basis of treatment in children and adolescents with generalized anxiety disorder. *Depression and Anxiety, 29*(4), 328–339.

Swartz, J. R., Wiggins, J. L., Carrasco, M., Lord, C., & Monk, C. S. (2013). Amygdala habituation and prefrontal functional connectivity in youth with autism spectrum disorders. *Journal of the American Academy of Child & Adolescent Psychiatry, 25*(1), 84–93.

Surguladze, S. A., Radua, J., El-Hage, W., Gohier, B., Sato, J. R., Kronhaus, D. M., et al. (2012). Interaction of catechol O-methyltransferase and serotonin transporter genes modulates effective connectivity in a facial emotion-processing circuitry. *Translational Psychiatry, 2*(1), e70.

Thomas, K. M., Drevets, W. C., Dahl, R. E., Ryan, N. D., Birmaher, B., Eccard, C. H., et al. (2001). Amygdala response to fearful faces in anxious and depressed children. *Archives of General Psychiatry, 58*, 1057–1063.

Thomason, M. E., Henry, M. L., Paul Hamilton, J., Joormann, J., Pine, D. S., Ernst, M., et al. (2010). Neural and behavioral responses to threatening emotion faces in children as a function of the short allele of the serotonin transporter gene. *Biological Psychology, 85*(1), 38–44.

Tordjman, S., Gutknecht, L., Carlier, M., Spitz, E., Antoine, C., Slama, F., et al. (2001). Role of the serotonin transporter gene in the behavioral expression of autism. *Molecular Psychiatry, 6*, 434–439.

Troelsen, K. B., Nielsen, E. O., & Mirza, N. R. (2005). Chronic treatment with duloxetine is necessary for an anxiolytic-like response in the mouse zero maze: The role of the serotonin transporter. *Psychopharmacology, 181*, 741–750.

Uher, R., & McGuffin, P. (2010). The moderation by the serotonin transporter gene of environmental adversity in the etiology of depression: 2009 update. *Molecular Psychiatry, 15*(1), 18–22.

Ursini, G., Bollati, V., Fazio, L., Porcelli, A., Iacovelli, L., Catalani, A., et al. (2011). Stress-related methylation of the catechol-O-methyltransferase Val 158 allele predicts human prefrontal cognition and activity. *The Journal of Neuroscience, 31*(18), 6692–6698.

van Ijzendoorn, M. H., Bakermans-Kranenburg, M. J., & Ebstein, R. P. (2011). Methylation matters in child development: Toward developmental behavioral epigenetics. *Child Development Perspectives, 5*(4), 305–310.

van IJzendoorn, M. H., Caspers, K., Bakermans-Kranenburg, M. J., Beach, S. R., & Philibert, R. (2010). Methylation matters: Interaction between methylation density and serotonin transporter genotype predicts unresolved loss or trauma. *Biological Psychiatry, 68*(5), 405–407.

Veenstra-VanderWeele, J., & Blakely, R. D. (2012). Networking in autism: Leveraging genetic, biomarker and model system findings in the search for new treatments. *Neuropsychopharmacology, 37*(1), 196–212.

Weaver, I. C., Cervoni, N., Champagne, F. A., D'Alessio, A. C., Sharma, S., Seckl, J. R., et al. (2004). Epigenetic programming by maternal behavior. *Nature Neuroscience, 7*(8), 847–854.

Weng, S. J., Carrasco, M., Swartz, J. R., Wiggins, J. L., Kurapati, N., Liberzon, I., et al. (2011). Neural activation to emotional faces in adolescents with autism spectrum disorders. *Journal of Child Psychology and Psychiatry, 52*(3), 296–305.

Wiers, C. E. (2012). Methylation and the human brain: Towards a new discipline of imaging epigenetics. *European Archives of Psychiatry and Clinical Neuroscience, 262*, 271–273.

Wiggins, J. L., Bedoyan, J. K., Peltier, S. J., Ashinoff, S., Carrasco, M., Weng, S., et al. (2012). The impact of serotonin transporter (5-HTTLPR) genotype on the development of resting-state connectivity in children and adolescents: A preliminary report. *NeuroImage, 59*, 2760–2770.

Wiggins, J. L., Bedoyan, J. K., Carrasco, M., Swartz, J. R., Martin, D. M., & Monk, C. S. (in press). Age-related effects of serotonin transporter-linked promoter region (5-HTTLPR) variants on amygdala and prefrontal cortex function in adolescence. *Human Brain Mapping.*

Williams, L. M., Gatt, J. M., Schofield, P. R., Olivieri, G., Peduto, A., & Gordon, E. (2009). 'Negativity bias' in risk for depression and anxiety: Brain-body fear circuitry correlates, 5-HTT-LPR and early life stress. *NeuroImage, 47*(3), 804–814.

Windischberger, C., Lanzenberger, R., Holik, A., Spindelegger, C., Stein, P., Moser, U., et al. (2010). Area-specific modulation of neural activation comparing escitalopram and citalopram revealed by pharmaco-fMRI: A randomized cross-over study. *NeuroImage, 49*(2), 1161–1170.

Yurgelon-Todd, D., & Killgore, W. D. S. (2006). Fear-related activity in the prefrontal cortex increases with age during adolescence: A preliminary fMRI study. *Neuroscience Letters, 406*, 194–199.