The development of emotion-related neural circuitry in health and psychopathology

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Abstract
Disturbances in the detection of, response to, and interpretation of emotion are common in many forms of psychopathology. The amygdala, striatum, and structures within the prefrontal cortex are highly involved in mediating these stages of emotion processing, and evidence indicates that these regions show structural and functional alterations in different types of psychopathology, including anxiety, depression, and autism spectrum disorders. However, we do not know how genes and the environment interact to alter development of these brain regions in ways that give rise to emotion-related psychopathology. This review discusses the current understanding of brain regions that are involved in emotional functioning, how they develop, and how they are altered in three forms of psychopathology: anxiety, depression, and autism. For the present review, there are two goals. The first goal is to describe current knowledge of the brain processes that relate to the development of emotional functioning in health and in the emergence and course of three forms of psychopathology: anxiety, depression, and autism. The second goal is to propose a framework that may facilitate the integration of research on genetic variation and brain function with symptom and diagnostic measures. Such a framework could be used to gain a multilevel understanding of psychopathology within a developmental context.

Abnormalities in the detection of, response to, and interpretation of emotion are fundamental to many forms of psychopathology. Subcortical structures, including the amygdala and striatum, interact with the prefrontal cortex to mediate these stages of emotion processing. In psychopathology, the neural circuitry that subserves emotion is altered in adults and youth. What is unknown is how genetic and environmental forces interact to alter the development of these neural structures that give rise to emotion-related psychopathology. For the present review, there are two goals. The first goal is to describe current knowledge of the brain processes that relate to the development of emotional functioning in health and in the emergence and course of three forms of psychopathology: anxiety, depression, and autism. The second goal is to propose a framework that may facilitate the integration of research on genetic variation and brain function with symptom and diagnostic measures. Such a framework could be used to gain a multilevel understanding of psychopathology within a developmental context.

With the completion of sequencing the human genome, a major effort is underway to decipher the genetic variants that combine with experience to confer risk for disease. Within the field of developmental psychopathology, there is enormous potential to use this information to increase our understanding of the etiology, trajectories, and possible treatments for mental disorders. However, relating gene variants to psychopathology will not tell us how disorders arise. Psychopathology often emerges through the continuous interplay of genes and environment (the relative influence of each depends on the condition and individual case) during development. Through
alterations in the molecules, neurons, glia, and circuits, the brain is the physical manifestation of the gene and environmental interactions. These brain alterations subsequently influence how the child interacts with the environment, which in turn leads to further alterations of the brain. Thus, to understand the mechanisms that mediate genetic risk and environmental effects, it is necessary to examine brain development.

Neuroimaging techniques are being used to help decipher the complex relationships among brain function, emotion processing, and the development of psychopathology. Moreover, the introduction of molecular genetics has allowed studies to explore how genetic polymorphisms interact with the environment to influence developmental trajectories related to emotion-based disturbances (Caspi et al., 2003; Fox et al., 2005; Kaufman et al., 2004). In order to understand how these levels all interrelate in development, more work is required, work focusing on one major deficiency. This deficiency concerns the limited understandings of complex cascades that extend from genes to behavior. Specifically, it remains unclear how genetic variation interacts with the environment to alter protein expression at specific points in development, which in turn, alters brain development and function in structures such as the amygdala, striatum, and prefrontal cortex.

This review postulates that development of anxiety, depression, and autism spectrum disorders (ASDs) relates to disturbances of emotion processing. Therefore, in order to understand the neural circuitry that relates to these disorders, it is important to examine brain areas that are involved in emotion processing and document how disturbed processing develops in these three conditions. Key neural regions involved in emotion are the amygdala, the ventral striatum, including the nucleus accumbens, and structures of the ventral prefrontal cortex, including the ventrolateral region, the orbitofrontal cortex, and the anterior cingulate. The amygdala is involved in the detection of stimuli that may impact (positively or negatively) the well-being of the organism (Phan et al., 2004). The most widely used stimuli for examining amygdala activation are emotional faces. Structures of the ventral striatum within the basal ganglia are highly responsive to rewarding stimuli, such as positive social stimuli, food, and money (Reynolds & Berridge, 2002; Schultz, 2004). As for the ventral prefrontal cortex, structures within this area are involved in modulating and amplifying emotion-related signals from the subcortical structures (Kalin, Shelton, & Davidson, 2007). Thus, tasks that tap attention, inhibitory control, and decision making functions in the context of emotional situations are thought to engage the ventral prefrontal cortex.

The review is divided into five sections. The first four sections review the state of the field. Specifically, normal neural and affective development is reviewed in the first section. The second, third, and fourth sections comprise a discussion of how neural and affective development goes awry in three disorders: anxiety, depression, and ASD, respectively. Although the emphasis in these sections is on youth and the development of these forms of psychopathology, findings from adult literature are often included to provide a fuller picture of the brain correlates of these conditions. Finally, in the fifth section, a framework is offered that may facilitate the simultaneous consideration of multiple levels of analysis related to developmental psychopathology (genetics, molecular neurobiology, brain function, cognitive-affective performance, symptoms, and disorders) in order to more fully integrate these levels and devise more integrative translational research within a developmental context.

Healthy Development

Structural

In anatomical investigations, the brain is typically segmented into gray and white matter. Measures of gray matter capture the glial cells, neural cell bodies, dendrites, and unmyelinated axons. White matter includes myelinated axons. There are few studies that have examined amygdala development in humans. In one study, it was found that the amygdala increased in overall size between 4 and 18 years in boys, but not girls (Giedd et al., 1996). Similarly, another study reported that the amygdala increases 40% in size between ages 8 and 18 (Schumann et al., 2004). In the prefrontal cortex, a longitudinal study revealed that gray matter peaks in volume during early adolescence and then declines between the ages of 4 and 21 (Gogtay et al., 2004).
In contrast, white matter increases in volume through the adolescent years (Barnea-Goraly et al., 2005). These findings indicating that the prefrontal cortex follows a protracted developmental time course have generated considerable interest in identifying associations between this trajectory and behaviors that are slow to mature and that are mediated by the prefrontal cortex, such as inhibitory control, planning, and decision making. To more fully understand the development of the prefrontal cortex and how this aspect of development impacts the amygdala, future research may wish to examine the reciprocal connections between the amygdala, ventral striatum, and prefrontal cortex using diffusion tensor imaging (DTI), which provides a measure of myelinated tracts (Cascio, Gerig, & Piven, 2007). Of note, one study using DTI with participants of a broad age range (7–31 years) found that anisotropic diffusion (the DTI measure that indexes the degree to which the fibers are myelinated) was positively correlated with cognitive control independent of age (Liston et al., 2006). Further work with these methods would help elucidate how the development of neural connections between structures relates to the emergence of controlled behavior.

Functional

Before reviewing the functional magnetic resonance imaging (fMRI) findings, it is important to first discuss the methodological issue of susceptibility. In fMRI research, brain tissue that is adjacent to open spaces, such as nasal cavities, is susceptible to artifacts and loss of signal, which both translate into missing data regarding brain activity. Because structures that are particularly involved in emotion processing, specifically the amygdala and ventral prefrontal cortex, are susceptible to such signal drop out, we must be cautious in the interpretation of these findings. For instance, a greater number of subjects in Group A relative to Group B may have signal drop out in a region of interest. Analyses of these data could lead to spurious results. Specifically, because of group differences in signal drop out, Group B would show greater activation than Group A. Two possible approaches are suggested to guard against this possibility. In the first approach, a particular voxel (a small three-dimensional space that is imaged) is only included in a group analysis if each subject shows a minimal level of activation. Thus, if one or more subjects have no signal from a particular voxel, it is not considered in the group analysis. A second possible approach is to manually examine results where group differences are found and to ensure that each subject contributes activation in the activated voxels. Either approach effectively reduces the likelihood of reporting findings in which group differences are driven by susceptibility.

Since the first fMRI study with youth was published well over a decade ago (Casey et al., 1995), three neurodevelopmental patterns have emerged: (a) a transition from broad activation to more focal activation in the dorsolateral and ventrolateral prefrontal cortex, (b) a shift from greater subcortical processing to greater processing within regions of the prefrontal cortex (“frontalization”), and (c) greater interaction between subcortical and cortical structures. Each of these is discussed below.

Based on evidence from a study involving cross-sectional and longitudinal components with young subjects (average 11 and 12 years of age), Durston and colleagues (2006) found that activation decreased with age in the dorsolateral prefrontal cortex and activation became more focal in the ventral prefrontal cortex during a cognitive control task. The authors suggest that the increased focal activation may relate to the experience-dependent pruning of excess neural connections that permits more efficient processing (Huttenlocher, 1979, 1990; Zecevic & Rakic, 2001). Similarly, using a novel task that involved the presentation of sad video clips, girls relative to women showed more extensive activation in the multiple structures of the prefrontal cortex, including the orbitofrontal cortex, anterior cingulate, and ventrolateral prefrontal cortex, in a task that involved self-regulation of sadness (Levesque et al., 2003, 2004).

Turning to the shift from subcortical to cortical processing, particular interest has focused on the functional changes of the amygdala in development. In part, this interest is driven by many years of work from animal models establishing that the amygdala is involved in anxiety-like behaviors (Davis, 1999; Davis & Whalen, 2001; LeDoux, 1996, 2000). Understanding the healthy
development of the amygdala would help us to eventually determine how amygdala development deviates in youth with anxiety and other disorders.

Following the first study that established that the amygdala in healthy youth is responsive to threatening stimuli (fearful faces; Baird et al., 1999), Thomas, Drevets, Whalen, et al. (2001) examined differences in amygdala activation to threat in children relative to adults. In a comparison of activation to fearful faces relative to a fixation cue, both children and adults showed left amygdala activation. However, developmental differences emerged when activation to fearful and neutral faces was compared. Specifically, whereas adults showed greater activation to fearful faces, children showed greater activation to neutral faces.

In another study, a range of emotional (happy, fearful and angry) and neutral faces was presented to healthy youth and adults (Monk et al., 2003). In contrast to Thomas, Drevets, Whalen, and colleagues (2001), we found that youth showed greater right amygdala activation when viewing fearful relative to neutral faces. We recently replicated this finding in a larger sample of youth (n = 31) and adults (n = 30; Guyer et al., 2008). Differences in task paradigm between the former and latter two studies may, at least in part, explain the discrepant results. In particular, Thomas, Drevets, Whalen, et al. (2001) used a block design and we used an event-related design. In block designs, trials for a given condition are grouped together over relatively long periods of time (e.g., 30 s). Thomas, Drevets, Whalen, et al. (2001) presented 42-s long blocks of fearful faces; each face appeared for 200 ms, with an 800 ms interstimulus interval. In the Monk et al. (2003) and Guyer et al. (2008) studies, in contrast, we used a hybrid block/event-related design, in which trials of different types are presented in random order. Thus, we presented different faces for 4 s each, randomly varying the emotional expression displayed from trial to trial within blocks that instructed participants to passively view the faces or directed their attention to different aspects of the faces. Thus, even though both studies included a passive viewing procedure, the participants’ experience differed dramatically between these studies, and these differing experiences may account for the discrepant results.

In particular, these two paradigms may differentially affect psychological mechanisms, such as habituation and attention. The repeated presentation of different faces displaying the same emotion in Thomas, Drevets, Whalen, et al. (2001) affords the opportunity for the amygdala to habituate to a class of emotional cues (Fischer et al., 2003). Similarly, in our work, faces were presented for relatively long durations (4 s), which also could allow for habituation to specific individuals displaying emotional expressions. Thus, differences in habituation to facial expressions in these two tasks (i.e., habituation to the category of fearful faces in Thomas, Drevets, Whalen, et al., 2001, compared to habituation to a specific fearful face in Monk et al., 2003) could account for the discrepant findings.

Moreover, variations in these paradigms could have led to developmental differences in attention to facial expressions. Because group differences in attention to faces can influence amygdala activation (Dalton et al., 2005), the discrepant findings may be related to an interaction of the procedures between studies and development. Future studies examining development and brain function may wish to include measures of habituation and attention. For example, psychophysiological measures such as pupil dilation effectively capture attention to emotional stimuli (Siegle, Granholm, Ingram, & Matt, 2001). In addition, eye gaze recording and procedures that provide an index of attention bias offer measures of attention to and away from emotional stimuli during fMRI acquisition (Dalton et al., 2005; Monk et al., 2006). Group differences in such measures could be considered in the fMRI analysis. Through the incorporation of such measures in fMRI studies, it may be possible to develop a more complete understanding of brain function and development.

In a study that represents the third pattern (development of interactive function between the amygdala and prefrontal cortex), Yurgen-lun-Todd and Killgore (2006) presented fearful and happy faces in blocks to children and adolescents (8–15 years of age) as they passively viewed the stimuli. Fearful faces activated the amygdala across ages, but multiple structures within the dorsal and ventral prefrontal cortex showed increasing activation with age. Based on evidence that the prefrontal cortex, particularly the ventral region, has many reciprocal
connections with the amygdala in adult organisms (Carmichael & Price, 1995; Ongur & Price, 2000; Sarter & Markowitsch, 1984) and the prefrontal cortex matures more slowly than structures in other areas (Gogtay et al., 2004), the authors predicted that increased activation in the prefrontal cortex with age would correspond to decreased amygdala activation. Instead, the authors found that the frontal cortex showed increased engagement in response to negatively valenced stimuli with age, and this developmental change was independent of the amygdala activation. As the authors note, perhaps the inclusion of older adolescents or young adults would yield evidence of changes in amygdala engagement.

In the study discussed above that included both youth and adults, we used an event-related design and found that youth activated the amygdala and the ventral prefrontal cortex to fearful faces to a greater degree than adults (Monk et al., 2003). Thus, whereas some work suggests that increased prefrontal cortex activation can more effectively inhibit subcortical structures such as the amygdala, our findings suggest that the reverse may also occur: activation in one of these emotion-related regions may be associated with amplification activation in another. With age, amplification may diminish.

Recently, intense interest has focused on the development of the neural circuitry, primarily the nucleus accumbens and prefrontal cortex, as it relates to processing reward-related stimuli (Bjork et al., 2004; Ernst et al., 2005; Galvan et al., 2006; Guyer et al., 2006; May et al., 2004). This interest is driven, in part, by the suggestion that neural responsivity to reward in adolescence may relate to increased risk-taking behavior in this developmental stage (Ernst, Pine, & Hardin, 2006; Steinberg, 2005). Moreover, as will be discussed below, depression is associated with reduced pleasure from rewarding events (Forbes & Dahl, 2005). Indeed, one approach to exploring why adolescence is a period of marked increases in depression has been to focus on the neural correlates of reward response during this developmental stage.

Presently, the results of studies targeting reward responsiveness in the adolescent nucleus accumbens are inconsistent. Several studies found that adolescents showed greater nucleus accumbens activation to monetary rewards (Ernst et al., 2005; Galvan et al., 2006). These findings suggest that adolescents may be more sensitive than adults to reward and, therefore, more willing to take greater risks in order to achieve immediate rewards (Galvan et al., 2006). However, in another study, adolescents demonstrated reduced nucleus accumbens activation in anticipation of a reward and no developmental differences in nucleus accumbens activation in response to gain outcomes (Bjork et al., 2004). These findings indicate that, at least in anticipation of rewards, adolescent reward circuitry may be underactivated. In an effort to compensate for the reduced activation, adolescents may seek higher levels of reward (with corresponding greater risks). Recently, Galvan, Hare, Voss, Glover, and Casey (2007) reported that nucleus accumbens activation was positively associated with likelihood of engaging in risk-taking behavior across ages in a sample of children, adolescents, and adults. Therefore, the inconsistent findings between ages described above may be because nucleus accumbens activation relates more closely to individual differences in risk taking behaviors than to age alone. Further work is necessary to better understand the relations among nucleus accumbens activity, age, and risk-taking behaviors.

For studies that evaluated the development of prefrontal cortex activation in relation to the nucleus accumbens engagement, the results are more consistent. Galvan and colleagues (2006) found that the increased nucleus accumbens activation was associated with lower activation of the orbital frontal cortex. Similarly, in another study, youth relative to adults demonstrated less activation in the orbital frontal and ventral prefrontal cortices in a reward-based task (Eshel, Nelson, Blair, Pine, & Ernst, 2007). Moreover, lower activation in these frontal regions was associated with greater risk-taking behavior in the task in youth alone and in both groups together. These findings suggest that late maturation of the prefrontal cortex may relate to altered nucleus accumbens activation, biasing youth toward riskier choices.

To date, there are no published studies that have examined the normative development of interactions among the amygdala, striatum, and prefrontal cortex using functional connectivity, an analytic approach that examines positive and
negative correlations in activation over the course of an fMRI task. This approach makes it possible to see whether structures show activation in concert with one another. Although this is a correlational procedure, results from this method suggest whether the structures might be influencing one another positively (amplifying) or negatively (inhibiting). Using connectivity analyses in a developmental sample would suggest how interstructure interactions and, possibly neural circuits, change with age.

**Anxiety**

This section focuses on three related and prevalent disorders in youth: generalized anxiety disorder, social phobia, and separation anxiety disorder. Although the *Diagnostic and Statistical Manual for Mental Disorders—Fourth Edition* (American Psychiatric Association, 1994) treats these conditions as distinct, epidemiological investigations provide mixed support for current classification schemes (Brown & Barlow, 1992; Pine, Cohen, Gurley, Brook, & Ma, 1998). In particular, during development, children’s diagnoses with specific anxiety disorders often change. Of more importance, meeting diagnostic criteria for more than one anxiety disorder is the rule rather than the exception. Thus, findings described below regarding specific anxiety conditions may or may not apply to other forms of anxiety. Neuroimaging studies directly comparing one anxiety to another would help to shed light on the specificity of the findings.

Animal models of fear processing offer one framework within which to understand these anxiety disorders (Pine, 2007). In particular, research on animals has yielded a detailed model of the neural circuitry underlying fear and anxiety-like behavior (Emery et al., 2001; Gewirtz, McNish, & Davis, 1998; Hitchcock & Davis, 1986, 1987; Kalin, Shelton, Davidson, & Kelley, 2001; LeDoux, Cicchetti, Xagoraris, & Romanski, 1990; Lee & Davis, 1997). Central to this circuitry are the amygdala and the ventral prefrontal cortex. The amygdala is fundamentally involved in registering salient stimuli, including fear provoking stimuli, in the environment (Davis & Whalen, 2001; LeDoux, 1990; Whalen, 1998). Lesions to the central nucleus of the amygdala of the rat prevent the fear-potentiated startle response, an index of fear (Campeau & Davis, 1995; Hitchcock & Davis, 1986, 1987). In nonhuman primates, amygdala lesions lead to decreases in anxiety-related behaviors (Emery et al., 2001) and diminished fear response to threat stimuli such as snakes (Kalin et al., 2001). Turning to the ventral prefrontal cortex, this region contains reciprocal connections with the amygdala (Carmichael & Price, 1995; Sar et Markowitsch, 1984) and the ventral prefrontal cortex modulates amygdala activity (Timms, 1977). Furthermore, lesions to the orbitofrontal cortex, a region within the ventral prefrontal cortex, prolong extinction in fear conditioning (Morgan & LeDoux, 1995). This structure is also essential to the processing of information that conveys emotional significance (Baxter, Parker, Lindner, Izquierdo, & Murray, 2000; Butter, Mishkin, & Rosvold, 1963; Gallagher, McMahan, & Schoenbaum, 1999). Clinical research on anxiety disorders is testing this animal-based model by focusing on the amygdala and ventral prefrontal cortex.

**Anatomical**

Relative to work on anxious children and adults using functional imaging methods, there is surprisingly little work examining the brains of people with anxiety disorders using structural approaches. Two studies that have examined amygdala volume in youth with anxiety focused on generalized anxiety disorder (De Bellis et al., 2000; Milham et al., 2005). Despite the fact that the two studies had participants of similar ages (mean age = 12–13) and a similar proportion of subjects with comorbid depression, the studies yielded opposite results. Specifically, whereas De Bellis and colleagues (2000) found that generalized anxiety was associated with greater amygdala volume, Milham et al. (2005) reported that anxious patients had reduced amygdala volume. In light of the work described above showing that the amygdala dramatically increases in size around the age range studied in these two reports, it is important to consider developmental change in structural work with anxious youth. For example, as illustrated in the structural work on ASD (see below), it is unlikely that psychopathology is simply linked to static abnormalities in brain.
morphology; rather the disorder may impact developmental trajectories of neural growth. Thus, characterizing the sample in terms of developmental characteristics (e.g., pubertal stage) and precisely considering the effects of age may help us to understand how amygdala development among those with anxiety disorders is atypical.

**Functional**

Based on the animal model work described above, a compelling framework is emerging to help us to understand the functional neural circuitry of anxiety.

This framework has led to one of the more reliable findings in clinical neuroscience: the amygdala is reliably activated to a greater extent in individuals with anxiety relative to controls when procedures are used that involve symptom provocation. For instance, adults with social phobia relative to controls showed increased amygdala activation in response to angry and contemptuous faces (Stein, Goldin, Sareen, Zorrilla, & Brown, 2002). Using another procedure that involved positron emission tomography, adults with social phobia relative to comparisons exhibited greater amygdala activation during a public speaking task (Tillfors et al., 2001). Nevertheless, there are some findings that do not neatly fit into the model that the amygdala is active to anxiety symptom provocation. Notably, two studies found that anxious subjects relative to controls showed greater amygdala activation to neutral faces (Birbaumer et al., 1998; Cooney, Atlas, Joormann, Eugene, & Gotlib, 2006) and another study reported a positive correlation between amygdala activation to neutral faces and state anxiety (Somerville, Kim, Johnstone, Alexander, & Whalen, 2004). These findings are somewhat surprising because neutral faces are not thought to induce anxiety symptoms. However, neutral faces may be better characterized as affectively ambiguous (Cooney et al., 2006). Thus, more anxious subjects may infer greater threat from the ambiguous expression.

Turning to children and adolescents, Thomas, Drevets, Dahl, and colleagues (2001) found that youth with an anxiety disorder (predominantly generalized anxiety) relative to controls showed greater amygdala activation while viewing fearful relative to neutral faces. More recently, using a task in which participants shifted their attention between emotional and nonemotional features of facial expressions, youth with generalized anxiety disorder compared to controls manifested greater amygdala activation when they viewed fearful relative to happy faces while attending to their subjective emotional state (McClure et al., 2007). What is particularly intriguing about this study is that group differences in activation fundamentally depended on the behavioral task. There was no compulsory activation to fearful faces. Instead, to a large extent, the behavioral task dictated the activation. Thus, these findings (along with other ones discussed below) suggest that if we are to understand the brain basis of psychopathology, it is crucial that we build a theory that includes brain–behavioral relationships. By alternating among different behavioral conditions (e.g., subjective fear, facial expression identification, and passive viewing) during a functional neuroimaging task, specific cognitive functions can be more tightly coupled to brain function. Moreover, by including tasks that tap relevant symptoms (e.g., sensitivity to threat in anxiety), we will better understand the neural basis of these symptoms that constitute the disorder (Monk & Pine, 2004).

From these findings regarding amygdala activation in anxiety, the question arises: what roles do other regions, particularly the ventral prefrontal cortex, play in this heightened amygdala response? In a study that used an attention cueing paradigm with faces, youth with generalized anxiety disorder showed greater amygdala activation relative to controls in response to angry faces presented under conditions of restricted awareness (faces were presented for 17 ms and masked; Monk et al., 2008). In addition, amygdala activation positively correlated with anxiety severity. However, in another study, when angry faces were presented for 500 ms, youth with generalized anxiety disorder relative to controls showed greater ventrolateral prefrontal cortex activation to angry faces (Monk et al., 2006). In contrast to several studies in anxious adults that examined amygdala activation to angry faces when awareness was not restricted (Phan, Fitzgerald, Nathan, & Tancer, 2006; Stein, Goldin, Sareen, Zorrilla, & Brown, 2002; Stein, Simmons, Feinstein, &
Paulus, 2007), we found no group differences in amygdala activation. Indeed, the amygdala was not particularly responsive. Moreover, ventrolateral prefrontal cortex activation in the patients was negatively associated with anxiety symptom severity. That is, patients with the worst symptoms showed less ventrolateral prefrontal cortex activation and patients who were functioning better, although they still had generalized anxiety disorder, showed greater activation in this region. These findings suggest that the ventrolateral prefrontal cortex activation may not directly relate to the symptoms of anxiety; instead, this activation is perhaps modulating activity in another structure, possibly the amygdala, which is more directly involved in the anxiety symptoms.

Taken together, these studies provide a possible model for how anxiety-provoking information is processed differently in youth with generalized anxiety disorder. Specifically, when threatening stimuli, such as angry faces, are briefly displayed under conditions of restricted awareness, anxious youth show amygdala hyperactivation. It is of interest that controls do not show increased amygdala activation to angry relative to neutral faces. Thus, anxiety disorders may relate to a lower threshold in the amygdala for detecting potential threats in the environment. However, when angry faces are displayed for a longer period and further processing is possible, the ventrolateral prefrontal cortex is engaged, possibly to reduce the amygdala activation. Further work is necessary to understand how altered activation of specific structures in time gives rise to anxiety.

Depression

Throughout the life span, anxiety and depression are highly comorbid (Angold, Costello, & Erkanli, 1999; Costello, Mustillo, Erkanli, Keeler, & Angold, 2003). Moreover, during development, anxiety may precede or follow depression within individuals (Pine et al., 1998). Among offspring of depressed parents, rates of major depression peak between midadolescence and young adulthood (15–20 years of age), and this increase is primarily evident in females (Weissman et al., 2006; Weissman, Warner, Wickramaratne, Moreau, & Olfson, 1997). Although it remains unclear precisely how developmental changes in brain function relate to the onset of depression, the following discussion summarizes current knowledge on this topic. Knowledge appears somewhat strong on the neural abnormalities of adult major depression, a condition linked to pediatric major depression in family and longitudinal studies. Therefore, the current summary also reviews findings on adults to help clarify the manner in which brain function is altered in depression across the life span.

Structural

MRI findings suggest that adult patients with major depressive disorder (MDD) have smaller amygdalae than healthy comparison subjects (Sheline, Gado, & Price, 1998; Siegle, Konecky, Thase, & Carter, 2003). However, these findings are not entirely consistent across studies (Bremner et al., 2000). In support of the MRI studies indicating that MDD is associated with reduced amygdala volume, a postmortem study found that glia cells were reduced in MDD cases relative to controls (Bowley, Drevets, Ongur, & Price, 2002). Moreover, Frodl and colleagues (2003) found that amygdala volumes were increased in patients during first episode MDD, but patients with recurring MDD had smaller amygdalae. Thus, inconsistencies in the data may relate to stage of the disorder. In the striatum, MRI and postmortem studies showed volumetric reductions in the caudate and the ventral region of the striatum in individuals with depression (Baumann et al., 1999; Krishnan et al., 1992, 1993), but other studies have found no differences (Lacerda et al., 2003; Lenze & Sheline, 1999; Pillay et al., 1998). Turning to the ventral prefrontal cortex, anatomical MRI studies consistently show that multiple structures, including the subgenual prefrontal cortex and the orbitofrontal cortex, are reduced in size in adult patients with MDD. Again, evidence from postmortem data support this finding, and suggest that fewer glia cells may contribute to the overall reduced size of the region (Ongur, Drevets, & Price, 1998). In summary, the anatomical data suggest that adult MDD is associated with altered amygdala volume and reduced ventral prefrontal cortex volume relative to controls.
Studying the structural development of the amygdala, striatum, and ventral prefrontal cortex in youth with depression or at risk for depression would shed light on whether these structural differences are causally related to the disorder or if they are by-products of the condition. Unfortunately, to date, there is little work in this area. In the one structural study to date that examined youth with MDD, it was found that those who met diagnosis for depression had smaller amygdalae (Rosso et al., 2005), as in most of the adult studies. In addition, in a large, albeit subclinical, sample, the rostral anterior cingulate (including the subgenual prefrontal cortex) was reduced in males with greater depressive symptoms (Boes, McCormick, Coryell, & Nopoulos, 2008). Because the relationship between clinical and subclinical depression is unclear at the neurobiological level, it will be important to extend these findings to the youth with MDD. Nevertheless, these two anatomical studies of youth indicate that depression manifests at least somewhat consistently across ages in the amygdala and ventral prefrontal cortex.

**Functional**

In functional studies that use emotion-based tasks, such as the presentation of facial expressions or valenced words, adults with MDD reliably show greater amygdala activation relative to comparisons. In response to briefly presented masked emotional faces (fearful and happy), depressed adults showed greater amygdala activation than controls (Sheline et al., 2001). The group differences were particularly strong to fearful faces. Similarly, depressed adults also evidenced greater amygdala activation to sad faces relative to controls (Surguladze et al., 2005). In response to negatively valenced words, depressed adults showed greater amygdala activation relative to controls (Siegle, Steinhauser, Thase, Stenger, & Carter, 2002; Siegle, Thompson, Carter, Steinhauser, & Thase, 2007). In addition, the hyperactivation to emotional faces normalized with antidepressant medication (Sheline et al., 2001). Moreover, in an effort to integrate the structural and functional relationship of the amygdala, Siegle and colleagues found that greater amygdala activity was associated with reduced structural volume in depressed adults.

In the striatum, MDD is associated with less activation to happy faces in the right putamen and greater activation to sad faces in the left putamen (Surguladze et al., 2005). Moreover, a hallmark symptom of depression, anhedonia, the loss of pleasure in response to formerly rewarding stimuli, was negatively related to ventral striatal activation in depression when viewing happy faces (Keedwell, Andrew, Williams, Brammer, & Phillips, 2005). That is, the more severe the anhedonia, the less ventral striatal activation there was in response to happy faces. However, it was recently found that depressed adults showed comparable levels of activation in the nucleus accumbens (a structure within the ventral striatum) relative to healthy controls in response to a monetary reward task (Knutson, Bhanji, Cooney, Atlas, & Gotlib, 2008). Thus, the association between reward, the striatum and depression requires further investigation.

In general, adults with MDD also show increased activation in various structures of the ventral prefrontal cortex, particularly medial/subgenual regions, in response to a range of tasks. For example, in a study using PET, depressed subjects showed greater subgenual prefrontal cortex activation in a paradigm involving induction of sadness (Mayberg et al., 1999). In an fMRI study, Kumari and colleagues (2003) found that patients with treatment-resistant depression showed greater subgenual prefrontal cortex activation relative to controls in a task with positively valenced picture-caption pairs. In contrast, some studies reported relative decreased activation in the subgenual prefrontal cortex in MDD patients (Buchsbaum et al., 1986; Drevets et al., 1997). However, when the group differences in the anatomical volume were considered in the analysis, MDD patients showed greater activation in the subgenual region relative to controls (Drevets, 1999).

The subgenual prefrontal cortex results in depression have been extended to treatment studies. Specifically, it was found that successful treatment with an antidepressant (fluoxetine) attenuates subgenual prefrontal cortex activation (Mayberg et al., 2000). This provides further support to the suggestion that this structure is involved in the core symptoms of depression. Moreover, this line of research has led to what may become the first application...
of a neuroscience hypothesis to treat a mental health condition. Specifically, treatment-resistant depressed patients had a deep brain stimulator implanted to modulate activation of the subgenual prefrontal cortex (Mayberg et al., 2005). Four of the six patients responded to treatment, and responsivity was associated with reduced activation of the subgenual prefrontal cortex.

Functional neuroimaging findings from depressed children are less consistent. In the first study to examine depressed youth, it was found that fearful relative to neutral faces elicited less amygdala activation in those with MDD than in healthy controls (Thomas, Drevets, Dahl, et al., 2001). However, because there were only five depressed participants (all females), these findings are considered preliminary. More recent studies found that depression in youth was associated with increased amygdala activation across a range of tasks. Specifically, in a decision-making task involving money, MDD youth relative to controls showed greater amygdala activation during events when they found out whether they won or lost money (Forbes et al., 2006). In addition, in a memory task with emotional faces, depressed youth relative to healthy and anxious controls showed greater amygdala activation in the contrast of remembered versus forgotten faces (Roberson-Nay et al., 2006). Finally, using another task with emotional faces, youth at high risk for depression based on family history exhibited greater activation in the amygdala in response to fearful faces relative to low-risk controls (Monk et al., 2008). Thus, these studies suggest that like adults, youth with depression or who are at risk for depression show hyperactivation of the amygdala.

Moreover, in the same study of youth at risk for depression, it was found that the high-risk group showed greater activation in the nucleus accumbens to fearful faces and less activation to happy faces in a passive viewing condition (Monk et al., 2008). Of note, when participants performed tasks (rate nose width on face; rate subjective fear while viewing face) during the face viewing, there were no group differences in activation in the nucleus accumbens or the amygdala. Furthermore, during the tasks, the high-risk relative to the low-risk group showed greater medial prefrontal cortex activation. These findings suggest that attention-based tasks, possibly via engagement of the medial prefrontal cortex, may normalize aberrant subcortical activation in the high-risk group. Moreover, like the work by McClure et al. (2007) discussed above, these findings highlight the need to consider the relevance of behavior when developing brain-based models of psychopathology.

Other than this study of youth at risk for depression, there are two relevant studies that examined how the ventral prefrontal cortex functions in depressed youth. One study described above, which used a decision-making task with money, found that MDD youth showed less activation during task events in the anterior cingulate and orbitofrontal cortex (Forbes et al., 2006). However, a study with a nonclinical sample found the opposite: subclinical depression scores correlated with greater ventromedial prefrontal cortex and anterior cingulate gyrus activation when viewing fearful faces (Killgore & Yurgelun-Todd, 2006). Differences between the former and latter studies may relate to depression status (clinical vs. subclinical), aspects of the tasks (decision making vs. emotional face viewing), specific regions of ventral prefrontal cortex activation, or possibly another variable. Further work in this area is crucial if we are to better understand how the development of the prefrontal cortex in adolescence and the rise of depression rates in the same developmental stage relate to one another.

ASD

The three core features of ASD are social impairment, language and communication problems, and repetitive behaviors/rigidity (American Psychiatric Association, 1994). The majority of neuroimaging studies have examined three forms of ASD: autism, Asperger syndrome, and pervasive developmental disorder not otherwise specified. Those conditions are the focus here. Because impairments in social functioning are such a prominent feature of ASD, many neuroimaging investigations have concentrated on understanding neural correlates of this symptom. However, emotion is fundamentally involved in social functioning in healthy individuals as well as those with ASD (Bachevalier & Loveland, 2006; Meyer, Mundy, Van Hecke, & Durocher, 2006). Indeed, the same neural structures that are
implicated in ASD are also involved in emotion processing. Thus, ASD studies are reviewed that show altered structure and functioning of emotion-related regions. However, further work must be done to clarify whether these disturbances relate to social functioning, emotion processing, or both in ASD.

**Structural**

The amygdala is a region of considerable interest in ASD research. This may be partly because the amygdala is implicated in emotional face processing, and subjects with ASD are often impaired in this domain (Davies, Bishop, Manstead, & Tantam, 1994; Joseph & Tanaka, 2003; Klin, Jones, Schultz, Volkmar, & Cohen, 2002; Langdell, 1978; Volkmar, Sparrow, Rende, & Cohen, 1989). The literature has been inconsistent about whether ASD is associated with larger, smaller, or no differences in amygdala volume (Aylward et al., 1999; Sparks et al., 2002). Recently, however, consensus is emerging that these inconsistent results are related to developmental changes. Specifically, young children (3–4 years of age in one study and 7.5–12.5 in another) with ASD have greater amygdala volume (Schumann et al., 2004; Sparks et al., 2002), whereas with age, amygdala size decreases compared to controls (Aylward et al., 1999; Nacewicz et al., 2006; Schumann et al., 2004). These effects may be partly driven by increases in amygdala volume in normative development (Nacewicz et al., 2006). That is, whereas typically developing individuals show marked increases in amygdala size with age (Giedd et al., 1996; Nacewicz et al., 2006; Schumann et al., 2004), those with autism do not. Moreover, developmental changes in amygdala volume occur in the context of volume changes in the rest of the brain with age and diagnosis (Courchesne, Carper, & Akshoomoff, 2003; Courchesne et al., 2007; Redcay & Courchesne, 2005). Specifically, although three of the studies described above found that group differences in amygdala volume were independent of cerebral volume (Aylward et al., 1999; Nacewicz et al., 2006; Schumann et al., 2004), one study found that differences in amygdala volume were not independent of cerebral volume (Sparks et al., 2002). As discussed more fully in the final section, these findings highlight the need to consider developmental factors in psychopathology (interactions of age and the disorder, the duration of the disorder, and possible compensatory mechanisms that emerge with maturation) in trying to understand more specifically the role that a lack of increased amygdala volume in development plays in autism. Furthermore, ASD sets a child on a path that involves very different experiences from those that healthy children encounter. These experiences, such as fewer positive social interactions, certainly impact brain development and contribute to group differences.

There are few studies that have explored anatomical volume within the ventral prefrontal cortex in ASD. However, recently, a study reported findings that complement the developmental work on the amygdala. Hardan and colleagues (2006) found that children and adolescents with ASD have reduced volume in the right orbitofrontal cortex. Moreover, in the same study, adults with ASD show increased orbitofrontal cortex volume. Therefore, ASD is associated with decreasing amygdala volume and increasing orbitofrontal cortex volume relative to controls during the course of development. Many studies from rodents, monkeys, and humans reported dense interconnections between these structures. Further research must be done to understand how these developmental changes relate to the disorder.

**Functional**

Just as there has been an increasing focus on understanding amygdala structure in ASD, there is intense interest in examining amygdala activity. Similar to the structural studies, research in this area has yielded inconsistent findings. As in healthy development, anxiety, and depression, many studies have used faces and facial expressions to elicit amygdala activation. Using neutral and emotional faces, multiple studies found that individuals with ASD show less amygdala activation relative to comparison subjects (Ashwin, Baron-Cohen, Wheelwright, O’Riordan, & Bullmore, 2007; Critchley et al., 2000; Dapretto et al., 2006; Grelotti et al., 2005; Hadjikhani, Joseph, Snyder, & Tager-Flusberg, 2006). However, another study found no group differences in amygdala activation (Pierce, Haist, Sedaghat, & Courchesne, 2004) and one
study found that ASD subjects showed increased amygdala activation relative to controls (Dalton et al., 2005). As discussed above, fMRI results are highly dependent on the behavioral task. Therefore, relative to the structural studies, considering results across fMRI findings is difficult. As a result, it is not possible to determine whether development might account for the inconsistency in the results.

One study did suggest that attention to the faces may influence amygdala activation and account for the reduced engagement in those with ASD (Dalton et al., 2005). During the fMRI scanning, subjects’ eyes were monitored, and it was found that the extent that subjects gazed at the stimuli eyes positively correlated with amygdala activation in the ASD group. Because studies that examined amygdala function in ASD typically presented faces for 2–4 s, subjects had the opportunity to gaze away from the face during the presentation. Thus, group differences in gaze direction and, possibly attention, may have influenced amygdala activation. This work highlights the importance of effectively monitoring group differences in attention either with a behavioral task or through eye tracking.

Despite the view that the striatum is involved in social interaction (Delgado, Frank, & Phelps, 2005; Rilling et al., 2002), and ASD is, in part, a disorder of social interaction, little work has examined the functioning of this region in ASD. One study that reported effects in the striatum was done by Dapretto and colleagues (2006). In this work, subjects viewed emotional faces and were asked to imitate the expressions during scanning. In this task, subjects with ASD showed less activation in the caudate and putamen relative to controls. Similarly, another study using facial stimuli found hypoactivation of the putamen in ASD relative to controls (Ogai et al., 2003). Although not directly addressed in the studies, these findings are consistent with the suggestion by Dawson and colleagues (2005) that social interaction impairment in ASD is related to a developmentally early deficit in assigning rewarding value to social stimuli. However, because structures within the striatum are heavily involved in motor function and autism is also associated with impairments in motor abilities (Jansiewicz et al., 2006; Mostofsky, Burgess, & Gidley Larson, 2007), the findings described above may be due to motor differences between groups. More work is needed to directly examine the role of the striatum in autism and how it relates to social interaction in ways that are distinct from motor function.

In the ventral prefrontal cortex, two recent studies reported group differences in activation between youth with ASD and controls (Dalton et al., 2005; Dapretto et al., 2006). However, once again, the results were inconsistent. Dapretto and colleagues (2006), using their procedures described above, found that controls showed greater activation in the anterior cingulate and inferior frontal gyrus relative to those with ASD. In contrast, another study described above found that subjects with ASD showed greater orbitofrontal cortex activation to emotional faces (Dalton et al., 2005). More work is needed to understand the variables that contribute to these discrepant findings. As described above, one possible factor is differences between the tasks. In addition, different parts of the ventral prefrontal cortex subserve different cognitive processes. Further work is needed to understand the specific functions of the various structures within the ventral prefrontal cortex and how they are altered in ASD. Finally, differences between ASD samples across studies may help to account for differences. For example, as discussed above, age clearly plays a major role in group differences in brain structure. In addition, the specific form of ASD, co-occurring conditions such as anxiety and depression, and overall functioning and IQ level may all impact the results and lead to inconsistent findings across studies.

Translational Research

The field of developmental psychopathology is inherently interdisciplinary (Cicchetti, 1984, 1990) and emphasizes the importance of integrating across many domains to better understand how psychopathology emerges in development (Cicchetti & Blender, 2004; Cicchetti & Dawson, 2002). Moreover, as proposed by others (Cicchetti & Blender, 2004; Cicchetti & Dawson, 2002; Masten, 2007), integration has also come to include considering multiple levels of analysis to better understand the etiology and trajectories of psychopathology. Building on these prior
proposals, a three-part framework is offered to further facilitate the integration of these levels within the context of development. First, to be able to more effectively consider the emergence of psychopathology in the context of brain development, genetic variation and Gene × Environment interactions, it is important to acquire and simultaneously consider more than two levels in investigations. Second, further integration of developmental considerations, including timing of environmental events, adaptations (or maladaptations), and trajectories that guide some children toward atypical experiences, is crucial for gaining a fuller understanding of the emergence and course of these disorders. Third, because current technologies do not allow us to understand how genetic polymorphisms influence molecular changes in human development, greater cross-talk is needed between human and animal investigators.

**Integrative research of psychopathology**

Currently, most gene-based studies of developmental psychopathology consider only two levels of analysis, such as prevalence of a particular disorder in individuals with a specific genetic polymorphism. However, genes do not directly cause symptoms and disorders; instead, genes exert their effects during development by guiding the maturation of neurons and circuits that underlie cognitive, affective, and social function. Through gene- and environment-guided brain development, symptoms and psychopathology emerge. Therefore, to gain a more precise understanding of how genes relate to psychopathology and how environmental events interact with genetic effects, it is crucial to integrate these multiple levels of analysis. For example, a polymorphism of the serotonin transporter gene relates to increased social impairment in individuals with ASD (Brune et al., 2006). However, presently, it is unknown what neural events occur to mediate the association between the genetic variant and the symptom of social impairment. Children with ASD could be identified based on this genetic variation and a symptom-relevant fMRI task that taps social functioning could be used to understand how brain activation in these children might relate to the symptom of impaired social function. Such a study would permit the simultaneous measurement of genetic variation, brain activation, social processing, symptom severity, and mental disorder classification. One major goal of this line of research would be to take an identified neural perturbation that is associated with social deficits and design effective treatments that would ameliorate the dysfunction.

**Integration of development into a model of psychopathology**

With the integration of these levels, it is important to continue to consider the role of development. For example, incorporating longitudinal research into an integrative framework would allow for a greater understanding of how the timing of environmental events impacts the organism differently across developmental periods. Genes program development to unfold over a protracted time course. Clearly, environmental events would have profoundly different effects on brain development depending on the developmental period in which they take place. In turn, the effects on brain development would impact cognitive, affective, and social functioning, as well as symptoms, and influence risk for psychopathology. Given that the developmental timing of environmental influences is vitally important, it may be more useful to highlight the relevance of developmental timing when discussing gene by environment interactions (Leonardo & Hen, 2008).

In addition, psychopathology guides individuals toward some experiences and away from other experiences. Moreover, the emergence of psychopathology likely induces adaptations (or maladaptations) that are manifested at the neural level. By the time brain imaging is conducted, children and adolescents have accumulated many years of experiences as well as effective and ineffective adaptations that are the result of their pathology. Youth who go on to develop anxiety disorders, for example, were more likely to have been inhibited in early development (Biederman et al., 1993; Schwartz, Snidman, & Kagan, 1999) and to have had parents with anxiety disorders (Rosenbaum et al., 1988, 1991). For youth who develop ASD, their condition sets a course that deprives them of many normative experiences and increases the occurrence of other nonnormative experiences. Developmentally appropriate use of language and the formation
of close friendships with peers are two areas where youth with ASD are likely to have limited or no experience. Thus, research on brain imaging would benefit from considering the developmental impact of these disorder-related experiences.

**Interaction between animal and human investigations**

Despite advancements in technologies that help us to uncover the biological correlates of developmental psychopathology, we are still relatively limited in the questions that we can answer using only humans as research participants. For example, it will be nearly impossible in human-only research to obtain a high level of precision in understanding the issue of timing of environmental events and their impact of development, because it is obviously unethical to experimentally manipulate children’s environments in ways that risk their well being. In addition, presently, it is ethically impermissible to evaluate many aspects of neurobiology, such as neurotransmitter receptor distributions in individuals below 18. At the same time, exciting neurobiological techniques have been developed that have helped to show the importance of timing in the gene–environment interactions (Gross & Hen, 2004; Meaney & Szyf, 2005). For example, building on work showing that a mutation of a serotonin receptor (5-HT1A) led to increased anxiety-like behaviors in mice (Heisler et al., 1998; Parks, Robinson, Sibille, Shenk, & Toth, 1998; Ramboz et al., 1998), Gross, Hen, and colleagues used a conditional knockout strategy and showed that suppressing 5-HT1A expression in adulthood does not affect anxiety-like behaviors. However, suppressing expression up to 4 weeks of age yields adult mice who behave more “anxiously” (Gross et al., 2002). By altering 5-HT1A expression at specific points in development, this work illustrates how developmental timing can determine the phenotypic outcome.

Through interdisciplinary collaborations that target specific mental disorders, these neurobiological studies of animals can be combined with human work to yield a more precise and mechanistic understanding of developmental psychopathology. In particular, there are at least five ways in which human work may inform the development of more precise animal models. First, genetic association studies detect markers for alleles that are common to specific disorders. Such information can then be integrated with animal model approaches to constrain the number of genes that are considered to relate to a phenotype. Second, neuroimaging methods on developing humans will continue to identify regions that show disturbed functioning in particular disorders. Investigations of animal models could then more precisely target these regions and identify possible neurobiological mechanisms that would give rise to the disturbed functioning and phenotype. Third, because mental disorders have only been defined in humans, a fuller understanding of the phenotype must necessarily come from human work and be extended to animals. Fourth, longitudinal investigations could provide animal research approximate developmental windows when environmental events may have a differential impact. Fifth, human work offers sophisticated analyses of the environmental contexts that may affect the emergence of psychopathology.

In turn, animal models can provide the following to construct an integrative understanding of developmental psychopathology. First, because an array of powerful neuroimaging and tracing techniques are available for animal investigations, animal models of specific disorders may be used to evaluate the role of specific mechanisms (e.g., receptors, neurotransmitters, neuropeptides) that may contribute to the phenotype. These mechanisms could then be used to constrain hypothesis in human clinical work. Second, studies of animal models could take the findings about developmental timing in humans described above and then specify timing with greater precision. Such work could then be used to inform prevention studies with humans. Third, experimental interventions could be developed to ameliorate symptoms in the phenotype in animals. Once shown to be safe and effective, these interventions could then be tested in humans.

**Conclusion**

This review describes the development of emotion-related brain structures, including the amygdala, striatum, and prefrontal cortex in healthy
individuals as well as those with anxiety, depression, and ASD. In the final section, a framework is described that would take these findings on brain development and psychopathology and integrate them with research on genetic variation and environmental effects. Such a framework may not only provide a deeper understanding of the mechanisms that give rise to psychopathology in development, but may also eventually lead to hypothesis-driven treatment and prevention approaches that will reduce the burden of these conditions.

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