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Neural Substrates of Childhood Anxiety Disorders A Review of Neuroimaging Findings

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INTRODUCTION

Anxiety disorders are the most common group of childhood psychiatric disorders, with almost one in three children having suffered from an anxiety disorder at some point during childhood or adolescence.[1] Most anxiety disorders begin early in development, with a median age at onset of 12 years.[1] Although significant advances have been made in identifying the best treatments for anxious children,[2] little is known about the neural underpinnings of anxiety disorders. Identifying the neural basis of childhood anxiety disorders can guide development of prevention programs, a critical step in reducing these early-onset and highly prevalent disorders. This article reviews the available literature to provide a current understanding of the neural basis of childhood anxiety disorders. It reviews the development of normative fear and the development of the brain regions that subserve fear and anxiety. It further provides a comprehensive summary of relevant functional and structural neuroimaging studies, including studies examining children with anxiety disorders and children at-risk for developing anxiety disorders.

NORMATIVE DEVELOPMENT OF FEAR

Development of Fear

Fear is a normal and adaptive response to potential threat. Key components of the fear system mature early in development,[3] and multiple periods of child development are marked by normative fears[4] (see Ref.[3] for a review). For example, most infants experience a period of stranger anxiety around 8 to 12 months of age, marked by wariness or distress around new people.[5–8] Stranger anxiety is often followed by separation anxiety, typically evident

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around 10 to 18 months, and characterized by distress about being separated from the mother or father.[6] Stranger and separation fears are thought to be protective, preventing the child from encountering harm during developmental periods marked by the onset of walking and increased exploration away from caregivers. For most children, these normative fears vanish by 2 to 3 years of age; however, for some, childhood is marked by the persistence of these fears and the development of new fears. Increases in the prevalence of anxiety disorders parallel decreases in normal fear, such that separation anxiety disorder typically arises relatively early in life, shortly after the age-typical diminution in normal separation anxiety. Similarly, social phobia typically arises in adolescence, around the time of age-typical decreases in normal social anxieties.

These normative fears are observed in most children and manifest across cultures,[3] suggesting that fundamental aspects of human brain development sculpt developmental changes in fear. The universality of the development of early fears raises questions about the nature of relationships between brain development and fear. Although we expect that developmental changes in brain function relate to developmental changes in both normal and abnormal fears, the nature of these relationships largely remains unknown.

Fear Neurocircuitry

Research on rodents and nonhuman primates has identified the key components of fear circuitry.[9–14] Using fear conditioning tasks in rodents, researchers have identified that the amygdala—a small subcortical collection of nuclei in the medial temporal lobe—is critical for the production of fear behaviors.[9] In nonhuman primates, amygdala lesions result in significantly reduced fear behaviors,[11,15] providing further support for the amygdala's role in the production of fear behaviors. However, some debate persists concerning the precise role of the amygdala in fear. Findings appear most consistent for stimulus-reinforcement learning, as it relates to fear in classical conditioning, in which the amygdala is necessary for such forms of learning. But the amygdala also supports stimulus-reinforcement learning as it relates to positive stimuli.[16–18] Moreover, animals that suffer amygdala lesions still are capable of manifesting fear. In fact, under some circumstances, amygdala lesions actually can lead to increases in fear.[19] Thus, the amygdala's role in fear may represent one prototypical function of a broader role in emotional processing.

The amygdala has received substantial attention as a core component of fear circuitry; however, other brain regions are also involved in fear and anxiety. For example, the bed nucleus of the stria terminalas (BNST)—a part of the “extended amygdala”—is involved in sustained fear reactions (in contrast to short-term or phasic fear responses) in rodents.[10] These sustained reactions, which are elicited by less specific and less predictable threats, are maintained over time and are considered akin to anxiety in humans.[20]

Another major component of the fear circuit is the prefrontal cortex (PFC), a brain region involved in both the automatic and effortful regulation of emotion. Within the prefrontal cortex, multiple regions are engaged during emotion processing and emotion regulation; however, as with research on the amygdala, debate persists about the nature of specific PFC contributions. Most current theories divide the primate PFC using two axes, one separating the medial from lateral PFC and another separating the dorsal from ventral PFC (**Fig. 1**).

Of the multiple PFC brain regions, the ventromedial PFC (vmPFC) is most strongly implicated in anxiety. The vmPFC plays a critical role in the inhibition of conditioned fear expression[14,21] and extinction of conditioned fear,[22–24] which can be viewed as two instances of emotion regulation.[23,25] Evidence also exists showing that vmPFC activity in some specific locales correlates positively with negative emotions,[26,27] suggesting that at least some particular portions of the vmPFC may drive negative emotions. These multiple

roles may reflect different functions of subregions of the vmPFC. For example, some research suggests that in rodents the prelimbic component of vmPFC supports fear-related behaviors whereas the infralimbic component of vmPFC suppresses fear-related behaviors. However, because the majority of this research has examined rodents, issues of cross-species differences in PFC function preclude firm conclusions in humans.

In humans, other research focuses on lateral and dorsal regions of the PFC. The ventrolateral PFC (vlPFC) has been implicated in emotion regulation,[28,29] which may reflect the role of this region in attention control. The dorsomedial PFC (dmPFC) is engaged during the intentional control of emotional reactions,[23,30–33] which may reflect the broader role of the dmPFC in monitoring. Finally, the dorsolateral PFC (dlPFC) is implicated in intentional emotion regulation,[33–35] which may relate to the dlPFC's role in cognitive control and executive function.

Neuronal tracer studies in nonhuman primates provide evidence of anatomic connections between the amygdala and multiple regions of the PFC (for reviews see Ref.[35–37]). The amygdala has strong, bidirectional connections to medial prefrontal regions along the anterior cingulate cortex surrounding the corpus callosum, extending from ventral regions (subgenual cingulate cortex) to rostral (pregenual cingulate) and dorsal (supragenual cingulate) regions (**Fig. 2**). The amygdala also has dense projections to the vlPFC,[38 – 40] but these connections are more unilateral and are mostly ascending from vlPFC to the amygdala.[38 – 42] In contrast, the amygdala appears to have relatively few connections to frontal regions of the PFC (frontal pole) or dlPFC regions.[38,40–42] Ongoing research continues to refine understandings of these connections, both from anatomic and functional perspectives. Given that the majority of this research has focused on mature organisms and that connections continue to change across development, understandings of these connections remain even less precisely specified in immature organisms. For example, although it is clear that children and adolescents are capable of utilizing all portions of the PFC to perform at least some of the functions for which adults utilize the PFC, the precise timing when specific PFC functions and associated connections mature in humans remains unclear.

PFC connections to the amygdala synapse in multiple regions. However, interest focuses primarily on γ-aminobutyric acid-ergic (GABAergic) neurons, emphasizing an inhibitory role for the PFC over amygdala function.[41,43,44] At least in some contexts, neuroimaging studies in humans show an inverse relationship between the amygdala and multiple PFC regions including vmPFC,[45,46] vlPFC,[32,47,48] dmPFC,[23,34,49–54] and dlPFC.[25,34] Particularly for the vlPFC and vmPFC, in which PFC–amygdala connections have been mapped, these findings suggest inhibitory input; however, such findings remain indirect.

In summary, the amygdala and PFC are key components of human fear neurocircuitry. The amygdala and PFC are interconnected with the PFC modulating amygdala responses. To date, the majority of our knowledge about the neural bases of anxiety comes from functional neuroimaging studies in adults (for a meta-analysis see Ref.[55]). Results from these studies suggest that adult anxiety disorders may be characterized by brain dysfunction resulting in “too much gas and not enough brakes”; that is, the fear production system is too strong and the fear regulation system is too weak.

Development of Fear Circuitry

The developmental trajectories of both the amygdala and PFC are consistent with this idea of an imbalance between the fear production and fear regulation systems. The amygdala is functional early in development,[56] shortly after birth in humans.[57] Studies of amygdala lesions occurring early versus late in development provide critical information about the

development of amygdala function. In rhesus monkeys, early lesions (2 weeks) result in a decreased fear to threatening objects during multiple stages of development,[19,58,59] demonstrating that early damage to the amygdala has an early and sustained impact on nonsocial fear processing. In contrast, amygdala lesions in neonatal rhesus monkeys result in increased fear during nonthreatening social interactions at both 6 to 8 months of age[19] and 12 months of age,[60] suggesting a different early role for the amgydala in social processing. In adult rhesus monkeys, amygdala lesions produce decreased fear to threatening objects[11] and decreased fear during both nonthreatening and threatening social interactions.[11,15] Thus, the amygdala's role in nonsocial fear is consistent across development, with both early and late amygdala lesions similarly decreasing fear to threatening objects. However, the role of the amygdala in the development of social fear is more complex, pointing to possible developmental differences in the contribution of the amygdala to social behaviors.

Evidence from human studies of amygdala lesions also indicates developmental effects; for example, individuals with early amygdala lesions fail to show the normal emotional enhancement of memory and understanding of others' emotional states.[61,62] Developmental functional magnetic resonance imaging (fMRI) studies of amygdala responses to human expressions of fear ("fear faces") may provide clues about amygdala development (see Ref.[63] for a review). When viewing fear faces, adult humans show an increase in amygdala activation relative to amygdala activation during a baseline condition, such as viewing a fixation cross or blank screen.[16–18] Increased amygdala activation likely represents the salience of the stimulus[64 – 66] because the amygdala responds robustly to negative and positive stimuli,[16] as well as novel[67] stimuli. Preliminary studies in children and adolescents suggest that amygdala activation to fear faces in children is similar to adults, but intriguingly is heightened in adolescents[45,68,69] (although not all studies find this developmental effect[70]). This heightened fear response in adolescence is consistent with heightened emotion recognition accuracy during this period.[70] Together, findings from lesion and neuroimaging studies demonstrate that the amygdala is critical for the normal development of the fear system.

Both the ventral and dorsal regions of the PFC are among the last brain regions to mature, undergoing significant structural and functional changes during development.[71–76] fMRI studies comparing different age groups provide evidence of differences across between children, adolescents, and adults in activation in the vlPFC,[69,77] vmPFC,[78,79] dmPFC,[70,79–81] and dlPFC.[72,79,82,83] These findings are consistent with behavioral data showing increasing skill with age for both emotional tasks[45,84] and cognitive tasks.[84 – 87] PFC development is relatively linear with age, and the development of the PFC provides a mechanism for dampening amygdala hyper-responsivity through increased emotion regulation abilities. Casey and colleagues[88,89] provide an integrative developmental theory that postulates that the increased emotionality common during adolescence results from the imbalance between patterns of amygdala and PFC development (**Fig. 3**). According to this model, during adolescence amygdala function is enhanced relative to PFC function, resulting in an overcontribution of the amygdala to adolescent emotions and behavior. As PFC development catches up during early adulthood, emotions and behavior are stabilized. This amygdala–PFC imbalance may contribute to the increased prevalence of anxiety disorders during early adolescence.

Attentional Modulation of the Amygdala

Attention contributes to fear processing and the amygdala's response to stimuli is modulated by attention. Multiple studies have demonstrated that amygdala activity varies as a function of task demands.[34,68,90–93] Neuroimaging studies using a passive viewing task—in which attention is not specifically constrained by the task—show greater amygdala activation than

studies that use a specific task, such as gender discrimination or emotion rating.[16,17] Reduced amygdala activation during tasks likely reflects the effects of emotion regulation brain regions that are engaged during the tasks.[34,90–93] However, it should also be noted that attention is not required in all circumstances for amygdala response to emotional stimuli—for example, amygdala activation to fearful faces can occur in the absence of attention, potentially when the fearful faces are masked and not consciously detected[94]—although debate remains surrounding this point.[95]

The modulating role of attention is especially important for understanding anxiety disorders, given that attentional processes are altered in children and adults with anxiety disorders.[96,97] In anxiety disorders, a commonly studied attentional process is attentional bias. Attentional bias is often measured using the "dot probe task." In that task, individuals fixate on a central point on the screen and are then shown a threatening and a neutral image on opposite sides of the screen. After the brief stimulus presentation, a dot is presented on one side of the screen and individuals must press a button as soon as they detect the dot. A shorter latency to detect the dot that appears in the same position as the threatening stimulus is evidence of attentional vigilance to threat. Anxious individuals are more likely to show attentional bias to threat, such as aversive images, fear faces, or angry faces (see Refs.[96,98] for reviews).

In fMRI studies of anxiety, a limitation of passive viewing studies (studies that do not require the subject to perform a task) is that observed amygdala differences may be a consequence of differences in attention. Controlling for attentional differences using a task can help to dissect differences in amygdala activation caused by anxiety from those caused by attention. Thus, neuroimaging findings need to be considered within the context of the attention requirements of various study designs.

NEUROIMAGING STUDIES OF FEAR-BASED ANXIETY DISORDERS: GENERALIZED ANXIETY DISORDER, SOCIAL PHOBIA, SEPARATION ANXIETY DISORDER

Although we assume that differences in brain function underlie childhood anxiety, little research has focused on identifying the underlying neural causes. Studies of adult anxiety have provided critical information about possible brain dysfunction in childhood anxiety disorders; however, we do not know whether the differences found in adults reflect the underlying causes of anxiety or are the consequence of anxiety. Thus, studies in children with anxiety or at high-risk for developing anxiety are critical for uncovering the neural causes of anxiety.

Findings from fMRI studies of adults with anxiety disorders[55] provide the initial candidate brain regions for studies of childhood anxiety—the amygdala and PFC. Most neuroimaging studies of child anxiety have used the same experimental tasks previously used to study anxious adults. However, several groups are developing new tasks that are especially valid for studying children and adolescents, such as the "chat room" task (see section on Social Phobia). While this is an exciting time in the evolution of our understanding of the neural bases of childhood anxiety disorders, we still have much to discover.

Studies of children with anxiety disorders provide a direct approach to identifying the neural bases of anxiety disorders. An equally important approach is to study traits that are associated with high-risk for developing anxiety.[99] Advances in neuroscience methods, such as neuroimaging and genetics, provide new opportunities to link neurobiological measures to dimensional traits in individuals with and without anxiety disorders. Among various high-risk traits, a commonly studied trait is behavioral inhibition— or inhibited temperament—a trait characterized by wary or avoidant responses to novel people, places, or things.[100] Behavioral inhibition emerges in infancy,[101,102] is heritable,[103] and is associated with a distinct physiologic profile.[104–107] Inhibited children have a four-fold increase in risk for

developing any anxiety disorder, with specific risk for social phobia.[108–110] Studies of young adults who were inhibited as children provide evidence for amygdala dysfunction[111–114] which is best characterized as a failure of the amygdala to habituate normally to repeated presentations of faces,[114,115] resulting in a sustained amygdala response.[112] Recent studies provide initial evidence for both structural[116] and functional differences in the PFC.[117] Thus, studying traits associated with anxiety provide a promising approach to identifying the structural and functional correlates of anxiety.

This section reviews and integrates functional and structural neuroimaging findings in generalized anxiety disorder, social phobia, and separation anxiety disorder, as well as the associated high-risk traits.

Generalized Anxiety Disorder

Functional MRI—Childhood generalized anxiety disorder (GAD) is characterized by excessive anxiety and worry about a variety of events and situations, difficulty controlling the anxiety, and presence of one or more physical symptoms.[118] To date, the majority of studies in GAD have focused on the amygdala. The most consistent finding in childhood GAD is increased amygdala activation during viewing of negative emotional expressions. Increased amygdala activation has been reported across multiple study designs including passive viewing of fear faces,[119] subjective ratings of fear,[120,121] viewing masked angry faces during a dot-probe task,[122] and viewing both subsequently remembered and forgotten faces during a face memory task.[123] In one of the studies, amygdala activation to fear faces also correlated with anxiety severity,[119] suggesting a direct link between amygdala response and anxiety. It should be noted that one study failed to find differences in amygdala activation when viewing masked angry faces during the dot-probe task.[124]

Multiple studies also report differences in PFC activation to negative emotions in GAD. For example, anxious children had increased activation during subjective ratings of fear, relative to healthy controls, in the vlPFC[120,121] and dmPFC.[120] In another study, adolescents with GAD showed increased activation in the vlPFC relative to healthy controls when viewing masked angry faces in a dot-probe task; but, within the GAD adolescents, degree of vlPFC activation correlated negatively with anxiety severity, suggesting a regulatory role.[124] However, not all studies report PFC differences.[122]

Children with GAD also show differences in functional connectivity between the amygdala and other brain regions. For example, when making subjective ratings of fear faces, anxious children showed increased functional connectivity between the amygdala and insula, relative to healthy controls,[120] and the degree of connectivity correlated positively with anxiety symptoms. In another study, healthy controls showed an inverse functional connectivity between the amygdala and vlPFC that was diminished in the children with GAD.[122]

Several studies have examined the neural correlates of treatment effects in childhood GAD. A preliminary study examined the association between pretreatment differences in brain function with symptom improvement following treatment with medication or cognitive behavior therapy in adolescents with GAD.[125] Pretreatment amygdala activation was associated with less clinical improvement after treatment. A second study examined the neural correlates of treatment response in adolescents with GAD.[126] Successful treatment with either cognitive behavioral therapy (CBT) or fluoxetine was associated with increased activation to angry faces in the right vlPFC, a region associated with emotion regulation.

In summary, children with GAD consistently show increased amygdala activation across a variety of tasks. Although several studies reported PFC differences, the direction of the effect was not consistent. It is important to note that task differences likely impact the

direction of the PFC effect (increase vs decrease) when comparing individuals with anxiety relative to healthy controls. For example, because healthy controls do not typically show an attentional bias, it is unlikely that they will engage attentional or regulatory regions. In this case, PFC activation should be higher in the anxious group because they have an attentional bias, but increased activation should not be interpreted as "better" function. To understand how PFC dysfunction relates to anxiety, it is critical to examine the association between PFC activation and anxiety severity or symptom improvement. Relatively lower vlPFC activation was associated with higher anxiety severity and lower symptom improvement with treatment, suggesting dysfunction in vlPFC regulation of the amygdala contributes to GAD anxiety symptoms.

Structural MRI—Findings of structural differences in the amygdala are less consistent. A study of adolescents with GAD showed larger right amygdala volume relative to controls[127]; however, another study of adolescents with anxiety disorders (predominantly GAD) found smaller left amygdala volume.[128] Sample sizes in both studies were relatively small; moreover, methods in the two studies also were quite different. Therefore, larger samples studied comprehensively will be useful in resolving the conflicting amygdala results. To date, only one study has examined PFC volume and found no differences in adolescents with GAD compared to controls in PFC gray matter volume or white matter volume.[129] Thus, support for structural differences in childhood GAD remains weak.

At-risk children—Trait anxiety reflects a temperamental trait characterized by persistent anxiety and worry and is therefore very similar to GAD. Generally, higher trait anxiety is associated with increased risk for GAD; however, a child can have high trait anxiety but not meet diagnostic criteria for GAD. Telzer and colleagues[130] demonstrated that trait anxiety in healthy children and adolescents corresponded to both a behavioral attentional bias toward angry faces and increased activation in the right dlPFC. When viewing all faces (regardless of emotion), higher trait anxiety was associated with increased vlPFC activation.

Krain and colleagues[131] examined intolerance of uncertainty—the tendency to react negatively to situations that are uncertain—a major symptom of GAD.[132,133] In healthy adolescents and anxious adolescents (GAD, social phobia, or both), higher intolerance of uncertainty was associated with increased activation in the amygdala, vmPFC and dmPFC during decision making in the context of absolute uncertainty (50/50 chance of being right). Within only the anxious adolescents, there was substantial variability in both intolerance of uncertainty and brain function. Anxious adolescents with high intolerance of uncertainty had increased amygdala and orbitofrontal cortex activation, whereas anxious adolescents with low intolerance of uncertainty had decreased activation in these same brain regions. These findings point to the importance of examining specific traits or symptoms of anxiety even within individuals with an anxiety diagnosis.

Social Phobia

Functional MRI—Among the anxiety disorders, social phobia (SP) is very common, second in prevalence only to specific phobias.[1] Blair and colleagues[134] explored brain function differences in adolescents with SP relative to healthy controls during an emotional face processing task. Adolescents with SP had increased activation in the amygdala and vmPFC when viewing fear faces. In addition, social anxiety severity correlated with vmPFC activation to both angry and fearful faces in the anxious group. The findings in adolescents were similar to results in adults with SP compared to controls, suggesting that the neural substrates of adult SP are already present in adolescence.

The emotion processing tasks commonly used to study brain function in anxiety disorders use both human faces and negative emotional expressions—both of which are particularly salient for SP—however, emotion processing tasks may not tap into other key factors that elicit SP, such as social-evaluative processes. Recently, several groups have begun to develop ecologically valid experimental tasks. Guyer and colleagues[135] have developed a "chat room" task to engage concerns about peer evaluation. In this task, adolescents rate pictures of other adolescents based on their desire to chat with them in a future encounter. During a second visit, adolescents rate how much they think the other adolescents want to chat with them. Anxious adolescents showed increased activation in the amygdala and vmPFC when rating how much the other adolescents would want to chat with them; interestingly, activation was increased only when viewing the adolescents that the subjects had previously rated as low desirability. Anxious adolescents, but not healthy controls, showed functional connectivity between the amygdala and vlPFC, with higher anxiety associated with stronger functional connectivity.

At-risk children—Several studies in children and adolescents have examined traits relevant to SP, such as behavioral inhibition. Inhibited children and adolescents are typically shy, cautious, and reserved and are at significantly increased risk for developing social phobia.[108,110,136] Behavioral inhibition is observable across development and can be measured using a variety of methods including direct observation, parent report, current self-report, and retrospective self-report. The most commonly used method for identifying behavioral inhibition in children is direct observation of behavior and using measured with laboratory assessments consisting of unfamiliar objects, unfamiliar peers, and unfamiliar adults.[100,101,106,137] Laboratory assessments are considered by many to be the gold standard because they provide objective assessments of behavior; but, behavioral assessments are time-consuming, expensive, and may not reflect real-world behaviors. Parent-report and self-report questionnaires provide efficient and economical assessments of behavior across a wide variety of situations; but, questionnaires are subject to a variety of reporter biases, including over-reporting and under-reporting. Although there is evidence for moderate convergence across the two methods,[138] it is important to consider methodologic issues when interpreting study results.

Studies of young adults who were inhibited as children demonstrate that behavioral inhibition is associated with amygdala hyperactivity[111–114,117] and dmPFC hypoactivity[117]; however, only a handful of studies have examined brain function in inhibited children and adolescents. Perez-Edgar and colleagues[139] compared neural responses during emotion processing in adolescents who were either characterized as inhibited or noninhibited as young children. The emotion processing task included a passive viewing (no task) condition and several attention conditions in which subjects subjectively rated emotional or nonemotional characteristics of the faces. In the inhibited adolescents, amygdala activation to fear faces was increased, relative to the noninhibited adolescents, when attention was focused on rating the emotion but decreased when the fear faces were passively viewed. These results suggest that inhibited adolescents have different neural responses to emotional faces and that the neural responses are modulated by attention and emotional state.

An important contribution of high-risk trait studies is the discovery that behaviorally inhibited adolescents are not only sensitive to threatening stimuli, but are also sensitive to reward. In an initial behavioral study, shy (inhibited) adolescents had faster reaction times during reward conditions in the Monetary Incentive Delay (MID) task, suggesting increased reward sensitivity.[140] Using fMRI, Guyer and colleagues[141] compared neural responses in the striatum (including the nucleus accumbens, caudate, and putamen) during the MID task in inhibited, relative to noninhibited, adolescents. Inhibited adolescents showed significantly greater striatal activation to increasing amounts of incentives (gain or loss) relative to the

noninhibited adolescents. In a subsequent fMRI study, Bar-Haim and colleagues[142] tested the effects of reward while controlling for possible effects due to performance evaluation by including a noncontingent motor task. Inhibited adolescents showed increased activation in the nucleus accumbens when reward outcome was contingent on their response but did not show differences in the noncontingent condition. These studies demonstrate that behaviorally inhibited adolescents have increased sensitivity during performance-dependent rewarding tasks, in addition to increased sensitivity to threat. This pattern of increased sensitivity to both threatening and rewarding stimuli is remarkably similar to increases seen normally during adolescence, consistent with an imbalance between development of the amygdala and PFC.

In summary, studies of children with SP or children at-risk for developing SP demonstrate increased amygdala activation to anxiogenic stimuli and demonstrate increased striatal activation to rewarding stimuli, suggesting a general heightened reactivity. In the PFC, childhood SP was associated with increased vmPFC activation. Although more studies of PFC function are needed, increased the observed vmPFC activation may result from specific regions of the vmPFC that drive amygdala activation and negative emotions.

Separation Anxiety Disorder

Separation anxiety disorder (SAD) is characterized by anxiety caused by separation from the child's home or caretakers that causes impairment because it leads to avoidance of separation. School refusal and difficulty sleeping alone are common symptoms of SAD. Although no study to date has used neuroimaging methods to probe brain structure or function in SAD, one study included a continuous measure of separation anxiety. In that study, amygdala activation to fear faces was examined in healthy children.[143] Continuous measures of anxiety symptoms were assessed using the Multidimensional Anxiety Scale for Children (MASC[144]). Higher separation anxiety symptoms were associated with increased amygdala activation to fear faces, providing preliminary evidence for the amygdala as one neural basis of separation anxiety disorder.

Summary

In summary, children and adolescents with GAD, SP, SAD, or high-risk traits show dysfunction in the amygdala and multiple PFC brain regions during experimental tasks probing fear neurocircuitry (**Fig. 4**). These findings are consistent with the results of a recent meta-analysis that reports that childhood anxiety (GAD, OCD, PTSD) is associated with alterations in the amygdala, vlPFC, and dmPFC.[145] Across the studies, amygdala activation was increased in anxious children and adolescents, consistent with findings in anxious adults. Increased amygdala activation was also demonstrated in high-risk individuals, suggesting that amygdala hyper-reactivity is a heritable trait that confers risk for developing anxiety. In the PFC, the most common finding was increased activation, not a lack of PFC activation as predicted by developmental evidence for increasing emotion regulation and PFC activation with age. These preliminary findings are intriguing and suggest several possibilities. Group differences in PFC activation may reflect differential effects of the tasks on the two groups; examination of the relationship between anxiety severity and PFC function is important for understanding the role of the PFC. Also, increased PFC activation in anxious children may reflect differences in the duration of amygdala–PFC processing. Whereas both anxious and nonanxious children may initially engage the PFC during emotional tasks, the PFC may effectively inhibit amygdala activation quickly in nonanxious children, but not in the anxious children. Thus, anxious children may continue to engage the PFC in an attempt to inhibit amygdala response, with the effect of greater activation over the task. Alternatively, increased PFC activation could be driving increased amygdala activation, as suggested by some findings of coactivation of these regions in adults.[26]

Functional differences may be caused by underlying structural differences, but to date there are too few structural studies to draw any conclusions. Thus, although the foundation has been laid, much research is needed to understand the precise nature of the brain dysfunction that gives raise to childhood anxiety.

NEUROIMAGING STUDIES OF OBSESSIVE–COMPULSIVE DISORDER

Childhood-onset obsessive– compulsive disorder (OCD) can be considered to be distinct from the other childhood anxiety disorders.[146] Instead of having fear at its core, childhood OCD is defined by recurrent obsessions and compulsions that are time consuming or cause marked distress or significant impairments in daily function.[118] Childhood-onset OCD, relative to adult-onset OCD, is characterized more by motor and vocal tics and the presence of comorbid diagnoses such as Tourette syndrome and attention-deficit/hyperactivity disorder.[147,148] In addition, the prevalence of OCD is substantially lower than for the other anxiety disorders (see the article by Franklin and colleagues elsewhere in this issue for further exploration of this topic).[149]

Although fear is not a defining feature of OCD, some early theories about the neural substrates of OCD posited amygdala deficits[150,151] with the amygdala having a role in maintaining compulsive behaviors. Like the other anxiety disorders, OCD has been conceptualized as an imbalance between a subcortical hyper-responsivity and cortical hyporesponsivity. In the case of OCD, the hyper-responsivity has been hypothesized to arise from the basal ganglia, with hyporesponsivity in multiple PFC regions, including the orbitofrontal cortex (OFC) and the anterior cingulate cortex (ACC). Deficits in these regions support the notion of OCD as a disorder of overmonitoring and difficulty inhibiting responses. Neuroimaging findings to date suggest that dysfunction in cortico–striato–thalamic circuit may underlie OCD.[152,153]

Relative to the other childhood anxiety disorders, OCD has received significantly more neuroimaging research attention. A relatively large and growing number of neuroimaging studies have examined both functional and structural correlates of childhood OCD. In light of this volume and the broad focus of the current review, only general conclusions can be provided. Despite the many challenges of studying childhood OCD—including small sample sizes, different experimental tasks, and medication status—some common trends are emerging (for extensive review please see Refs.[154–158]).

Functional MRI

Early neuroimaging research in childhood OCD has not shown evidence of increased amygdala activation in response to either contamination or symmetry provocations.[159] A common probe of amygdala function used to study other anxiety disorders is the presentation of pictures of human emotional expressions. As reviewed earlier, anxious children often show increased amygdala activation when viewing fear faces; however, in children with OCD, amygdala activation is decreased, relative to healthy controls.[160] This result is in contrast to other studies in the other childhood anxiety disorders, providing further evidence for a distinction between OCD and the other disorders.

To examine cortico–striato–thalamic dysfunction Woolley and colleagues[161] tested response inhibition. During successful response inhibition, OCD was associated with decreased activation in the OFC, thalamus, and basal ganglia (caudate head, putamen, globus pallidus). During unsuccessful response inhibition OCD was associated with decreased medial PFC activation. To isolate the contributions of cognitive flexibility deficits to OCD, Britton and colleagues[162] tested cognitive inflexibility while controlling for motor behavior. Children with OCD, relative to controls, had decreased OFC activation during set shifting, but there

were no differences in the striatum, dmPFC, or dlPFC. Caudate activation was positively correlated with a behavioral measure cognitive flexibility in healthy controls, but negatively correlated in OCD. Findings from these studies are consistent with a meta-analysis of functional brain differences found that childhood OCD was associated with functional differences in the frontal and parietal cortices, striatum, and thalamus.[145] Together, these fMRI studies provide preliminary evidence that children with OCD have dysfunction in the OFC, thalamus, and basal ganglia.

The first neuroimaging studies to examine the effect of treatment on brain function in children with OCD used regional cerebral blood flow (rCBF) measures. Diler and colleagues[163] compared rCBF at baseline and after 12 weeks of treatment with paroxetine. At baseline, children with OCD had increased blood flow in the caudate, dlPFC, and ACC; blood flow in these regions was reduced following treatment. A subsequent study failed to find changes in rCBF using clomipramine.[164] Using fMRI, Lazaro and colleagues[165] examined the effect of treatment on brain activation during a serial reaction time task in treatment-naïve children with OCD. At baseline, the serial reaction time task produced increased activation in the caudate, middle frontal gyrus, and inferior parietal lobe; total OCD scores correlated with activation in the nucleus accumbens and superior parietal lobe and obsession scores correlated with activation in the ACC. After 6 months of fluoxetine treatment and significant clinical improvement, activation in the insula and putamen were decreased during performance of the serial reaction time task.

Structural MRI

Investigations of differences in amygdala volume have been inconsistent. An initial study found no amygdala volume differences in medication-naïve children with OCD[152]; however, a later study reported an initial amygdala asymmetry in OCD (left larger than right) relative to controls.[151]

Several structural studies have found evidence that children with OCD have larger volumes in the putamen[166–168]; however, two studies reported either smaller volumes or no differences in the putamen[169,170] and another study reported smaller volume in the globus pallidus.[170] Other structural differences include larger volume in the thalamus,[171] caudate,[168] and cerebellum.[172] In the PFC, the most consistent structural finding to date is that childhood OCD is associated with larger gray-matter volume in the ACC, a finding that has been replicated in multiple samples using both manual tracing[152,166,170] and voxel-based morphometry[162] methods. However, one study reported areas of smaller gray matter volume in the ACC.[167] Larger gray-matter volume has also been reported in the OFC[162,166] and larger gray matter volume correlated with higher symptom severity.[166] Other PFC areas that show differences in OCD include the medial frontal gyrus[162,167] and inferior frontal gyrus.[162]

Several studies have examined treatment effects on brain structure. For the amygdala, one study reported that an initial amygdala asymmetry was normalized with selective serotonin reuptake inhibitor (SSRI) treatment.[151] In another study, thalamic volume normalized with treatment and decreased volume with treatment was associated with reduced OCD symptom severity.[171] However, in another study no changes in thalamic volume were seen with CBT, even though symptom severity reduced with treatment.[173]

IMPLICATIONS FOR RESEARCH AND CLINICAL PRACTICE

Using functional and structural neuroimaging methods to isolate the neural underpinnings of childhood anxiety disorders is still in its infancy, with the first childhood anxiety fMRI study conducted a little over a decade ago. Given this relatively short period of time, significant

progress has been made in identifying possible sources of brain dysfunction contributing to childhood anxiety. In the fear-based anxiety disorders (GAD, SP, SAD), neuroimaging studies have reported brain dysfunction in both the amygdala and multiple regions of the PFC. In OCD, the basal ganglia, orbitofrontal cortex, and anterior cingulate cortex are emerging as key regions of structural and functional deficits.

Studies of children and adolescents at high-risk for developing an anxiety disorder have contributed substantially to our current knowledge of possible neural substrates of anxiety disorders. Given the National Institute of Mental Health's new emphasis on dimensional traits—the Research Domain Criteria (RDoC)—we expect that more neuroimaging studies will begin to study high-risk traits, such as behavioral inhibition. The use of dimensional approaches may be especially useful for childhood anxiety disorders given that many children have subsyndromal symptoms or symptoms across multiple anxiety disorders.[174]

Although progress has been made, many important questions remain. Some important future areas for research include:

1. Measure individual differences in developmental brain trajectories to identify the neural underpinnings of trajectories that result in childhood anxiety.
2. Study the developmental brain trajectories of children with anxiety disorders, because not all anxious children become anxious adults. Identifying the brain and behavioral trajectories associated with reduction in anxiety may inform novel targets for treatment.
3. Increase focus on isolating the neural bases of dimensional traits associated with risk for developing anxiety, such as behavioral inhibition, trait anxiety, and intolerance of uncertainty.
4. Collect measures of behavior and arousal, in addition to functional neuroimaging measures, to provide greater clarity about the meaning of differences in brain activation in anxious children.
5. Develop new functional tasks to examine the relative contributions of the amygdala and the PFC to anxiety and to identify the sequelae of individual differences in the amygdala–PFC imbalance.
6. Test the effects of pharmacologic and nonpharmacologic treatments on the developing brain. Research is greatly needed to identify whether treatment success is associated with changes in brain function and/or development.

The current findings from the functional and structural neuroimaging studies reviewed in this article suggest that anxious children and adolescents have dysfunction in amygdala–PFC neurocircuitry. While it is likely that common treatments for childhood anxiety—such as CBT and selective serotonin reuptake inhibitors (SSRIs)—act on this circuit, empirical evidence is still needed. Importantly, identification of dysfunction in the amygdala–PFC neurocircuitry may suggest new avenues for the development of novel therapies. For example, evidence of dysfunction in PFC-dependent attentional processes has led to the development and testing of attention retraining therapies.[97,175] In addition, new pharmacotherapies or behavioral therapies can capitalize on neuroscience findings by targeting emotion regulation abilities in anxious children.

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KEY POINTS

- Development of fear is a normative process; normal development of the fear system goes awry in children who develop anxiety disorders and dysfunction in the amygdala-prefrontal cortex fear circuitry is likely.
- In the fear-based anxiety disorders, neuroimaging studies have reported brain dysfunction in both the amygdala and multiple regions of the PFC.
- In OCD, neuroimaging studies have reported functional and/or structural anomalies in the basal ganglia, orbitofrontal cortex and anterior cingulate cortex.
- Functional and structural neuroimaging studies have contributed to the significant progress made in identifying possible neural substrates of childhood anxiety disorders.

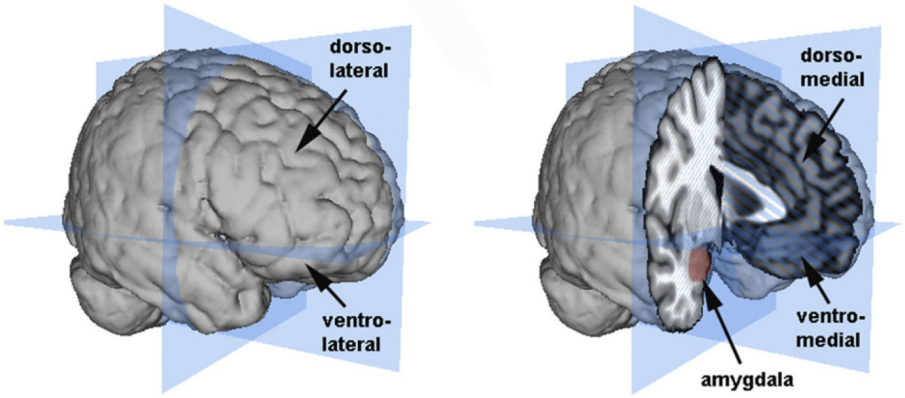

Fig. 1.

Illustration of the amygdala and the major divisions of the PFC. The planes (*in blue*) show the major dorsal/ventral and anterior/posterior divisions of the brain. The lateral PFC is shown on the left and the medial PFC and amygdala are shown on the right. Brain images and surface constructions were created using Mango (Research Imaging Center, UTHSCSA; http://ric.uthscsa.edu/mango/mango.html) and a Montreal Neurological Institute standard brain.

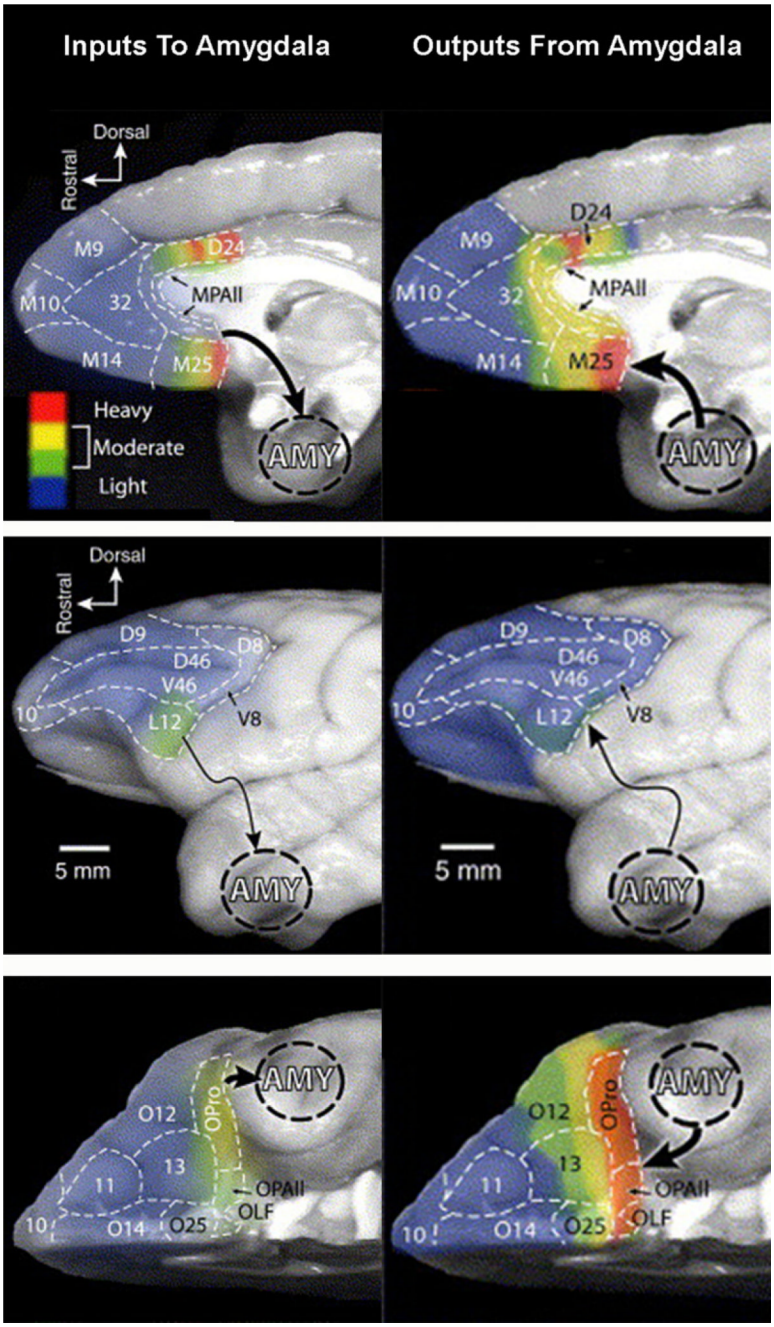

Fig. 2.

Degree of labeling intensity in PFC neurons for both inputs to the amygdala (*left column*) and outputs from the amygdala (*right column*). Rows show different surface views: medial surface (*top*), lateral surface (*middle*), and ventral surface (*bottom*). (*Adapted from* Ghashghaei H, Hilgetag CC, Barbas H. Sequence of information processing for emotions based on the anatomic dialogue between prefrontal cortex and amygdala. NeuroImage 2007;34:905–23; with permission.)

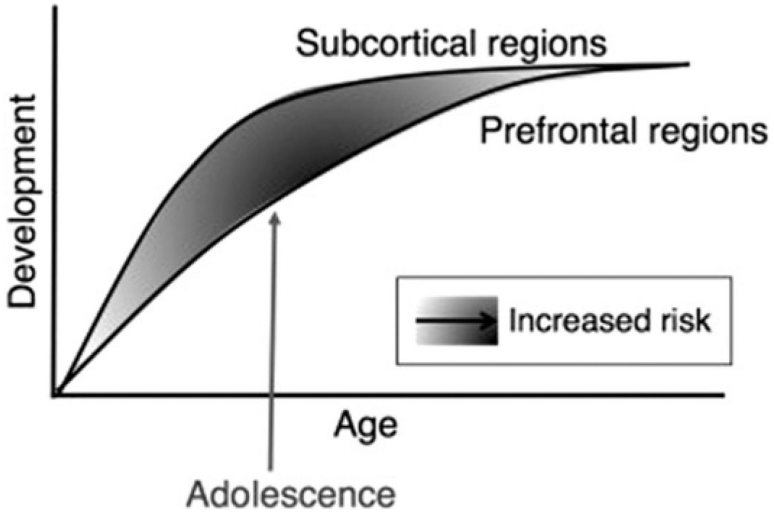

Fig. 3.

Model illustrating the imbalance between the early maturation of subcortical regions, such as the amygdala, and late maturation of PFC regions during adolescence. The shaded areas indicate degree of amygdala–PFC imbalance. (*From* Somerville LH, Jones RM, Casey B. A time of change: behavioral and neural correlates of adolescent sensitivity to appetitive and aversive environmental cues. Brain Cogn 2010;72:124–33; with permission.)

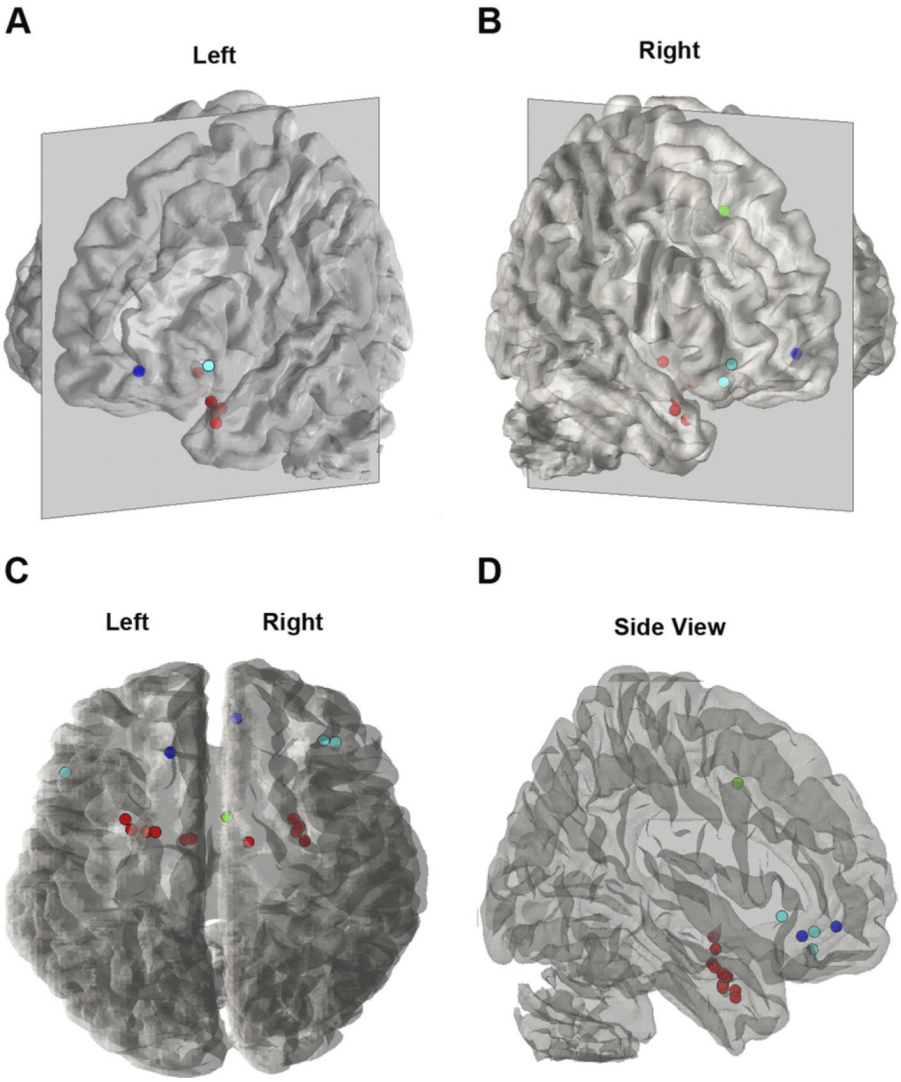

Fig. 4.

Peak activations from studies of children and adolescents with GAD, SP, or SAD (relative to healthy controls). Seventeen peaks from nine studies are illustrated on a 3-D transparent brain. Four perspectives are shown: (*A*) left lateral view, (*B*) right lateral view, (*C*) top view, and (*D*) side view. Dot colors represent different brain regions: red = amygdala (n = 11); dark blue = vmPFC (n = 2); light blue = vlPFC (n = 3); green = dmPFC (n = 1). Images were created using the plot_points_on_suface Matlab script included in the Multilevel Kernel Density Analysis toolbox (Tor Wager; http://wagerlab.colorado.edu/tools/).