Neurobiology of Pediatric Anxiety Disorders

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Abstract Anxiety during childhood and adolescence is a highly prevalent problem that contributes to long-term dysfunction in adulthood. This chapter highlights research on the neurobiology of pediatric anxiety disorders aimed at understanding how anxiety takes hold in the brain and the mechanisms that fuel its developmental course. We present an overview of anatomical and functional brain-based differences in children and adolescents with and without anxiety disorders. With regard to work focused on brain function in pediatric anxiety, we discuss four key psychological processes that are highly relevant to clinical characteristics in anxiety: attention orienting, threat learning, social–emotional information processing, and reward processing. We also review recent work that delineates connections between and within neural regions that appear to be distinctly modulated by anxiety both in response to specific tasks and while at rest. We close the chapter with a summary of emerging work on neurobiological response to treatments for anxiety in children and adolescents, followed by conclusions and future directions for this course of work.

Keywords Anxiety • Adolescence • Childhood • Neuroimaging • Brain structure • Brain function • Neural connectivity

Introduction

Anxiety disorders are highly prevalent and exert adverse effects on children and adolescents in both the short and long term [1, 2]. Despite their high prevalence and major impact on functioning over time, pediatric anxiety disorders have been largely understudied, particularly from a neuroscience perspective [3, 4]. Relative to less common conditions that arise in childhood, such as attention deficit hyperactivity disorder and autism, far fewer studies examine the pathophysiology of pediatric anxiety [5].

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This chapter presents four sections that review research on the neurobiology of pediatric anxiety disorders with an emphasis on neuroimaging studies. First, we briefly introduce the primary brain regions involved in fear responses. Next, we highlight the development of these regions during childhood and adolescence. In the third section, we review neuroimaging findings in pediatric anxiety with a focus on research directed at mapping relationships among brain function, psychological processes, and clinical characteristics. In particular, we review four constructs reflecting key cognitive and emotional processes associated with differentiated behavioral and neural responses in anxious and non-anxious individuals: (1) attention orienting, (2) threat learning, (3) social–emotional information processing, and (4) reward processing. In the fourth section, we present recent work focused on understanding the connections between and within neural regions that appear to be distinctly modulated by anxiety both in response to specific tasks and while at rest. Finally, we discuss emerging work on neurobiological responses to treatment for anxiety in children and adolescents.

Discussions throughout this chapter primarily review studies of pediatric samples with one of three anxiety disorders: generalized anxiety disorder (GAD), social phobia (SoPh), or separation anxiety disorder (SAD), as they are highly prevalent among children and adolescents [2]. These three disorders also are frequently comorbid and exhibit similarities in many features, such as course and treatment response. As a result, questions remain concerning the degree to which they represent unique conditions or alternative manifestations of the same underlying syndrome. This chapter reviews data both on their similarities and differences, although very little research documents clear differences among these disorders from a neurophysiological perspective. Thus, in the following discussion, we refer to these disorders together as "pediatric anxiety."

While other anxiety disorders occur in children, they are not the focus of this chapter. Obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) are not a main focus here given their unique pathophysiological profiles. Similarly, panic disorder is rare before late adolescence and accordingly is only minimally discussed. Finally, specific phobia is not discussed as it has been the focus of very little neurobiological research with children. For in-depth discussion about these disorders, readers are referred to Chaps. 9 and 10 in this volume. In addition, given our focus on neuroimaging and pediatric anxiety, the research reviewed herein primarily focuses on studies of individuals in late childhood through late adolescence given greater availability of research published in this age range relative to younger ages.

Brain Regions Implicated in Fear Processing

Considerable work has delineated the engagement of a neural fear circuitry that processes and guides responses to threat in one's surroundings [6–8]. In this basic science work, the term "threat" refers to collections of cues that signal the presence of danger to the organism. When such threats are proximal, immediately present, and extremely dangerous, they are thought to evoke a state of "fear" in the organism; when they are more distal, less immediate, and more ambiguous in terms of their dangerousness, they evoke a state of "anxiety." Such work provides useful cross-species models for understanding the neurobiology of threat processing, fear, and anxiety responses in humans across various stages of development [3, 9]. Drawing on research in both animals and humans, the neural circuitry implicated in threat processing and fear-related behaviors centers on the amygdala, located in the medial temporal lobe, as well as the ventral prefrontal cortex (vPFC). The amygdala aids in processing information about salient stimuli either positive or negative in valence and in mediating emotional responses [10–12]. The vPFC encompasses at least two subregions [13]. One of these subregions encompasses the lateral PFC and is involved in attention control along with other related processes. The other subregion encompasses the medial PFC, which has been implicated in fear extinction.

Lesion studies have confirmed hypotheses about the amygdala's role in processing stimuli that signify threat and translating reactions to fear-induced behaviors. For example, the application of lesions to the amygdala in nonhuman primates results in decreases in anxious behavior and blunted fear responses [6, 14, 15]. Similarly, a series of studies in humans show that adults with amygdala lesions cannot recognize fearful facial expressions, despite the ability to identify other facial expressions of emotion [7, 16, 17].

Facets of Brain Development Relevant to Pediatric Anxiety

Adolescence is a period of heightened emotionality and cognitive-regulatory changes driven in part by maturation of brain structures and their functions [18]. Subcortical brain structures that support basic functions such as detecting danger and safety in the environment (e.g., the amygdala) and forming memories that guide future behavior (e.g., the hippocampus) follow a relatively early maturational trajectory given their role in human survival [19]. Cortical brain structures such as the prefrontal cortex (PFC) show a more prolonged and continued maturation pattern across adolescence and into early adulthood. During this time, the PFC shows a decline in gray matter volume reflecting the pruning of unused and unnecessary neural circuits [20] and an increase in white matter as signal transmission becomes faster and more efficient [21]. Such a prolonged maturational period suggests that frontal brain areas do not reach full functional status until late adolescence or early adulthood [22]. Thus, adolescents may be vulnerable to the onset of mental illnesses such as anxiety and depression due to immaturity of PFC-based cognitive-regulatory functions [23]. Indeed, adolescents in the middle-late stages of puberty relative to those in early stages of puberty show altered patterns of amygdala and ventrolateral PFC responses that vary based on the emotional and social nature of stimuli and that relate to negative affect and mood [24].

Because the amygdala and associated projections are implicated in the detection and evaluation of potentially threatening stimuli [6, 25], developmental changes in structural characteristics of the amygdala should be considered with regard to understanding the emergence of pediatric anxiety. For example, the rate of amygdala growth in the nonhuman primate is most accelerated within the early postnatal period after which amygdala growth begins to decelerate and flatten [26]. The timing of damage to the amygdala also shows unique effects on fear responses as a function of development. For example, amygdala lesions applied to monkeys in adulthood result in reduced social fears, whereas such lesions applied in childhood lead to increased social fears [27]. In humans, structural changes in the amygdala generally extend from one year of age into late childhood [19]. Sex differences have also been noted in amygdala development, whereby females show adult volumes by age 4 and males show continued amygdala volume growth from ages 4 to 18 [28–30]. Finally, as amygdalo-cortical fibers thicken in adolescence, better regulatory control with respect to harm avoidant behaviors may be coming online [31].

Brain Function in Pediatric Anxiety

Before beginning discussion of studies of brain function, it is important to review the two published studies of brain morphology in pediatric anxiety. These studies, which include early adolescent samples, have reported discrepant results. Specifically, compared to samples of typically developing children, youth with GAD exhibited greater amygdala volumes [32], whereas reduced amygdala volume was identified in adolescents with GAD, SAD, or SoPh [33]. Morphometry of other regions has also differentiated healthy youth from those with anxiety. Notable patterns in children with anxiety

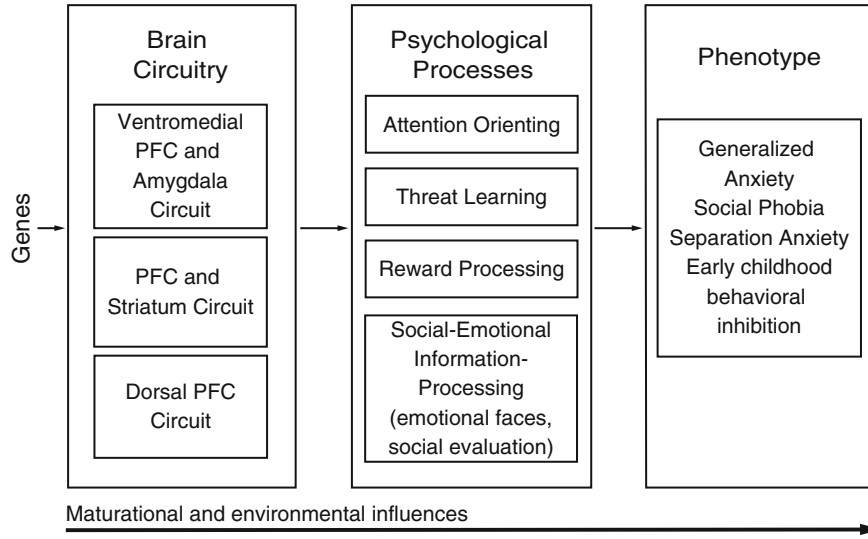

Fig. 1 A schematic framework of the mechanisms underlying associations among brain circuitry, psychological processes, and phenotypes, accounting for the influences of genes, environments, and maturation. *PFC* prefrontal cortex

compared to healthy comparisons show larger superior temporal gyrus [34] and decreased volume of the ventrolateral PFC and precuneus [33]. While these studies provide preliminary evidence of structural differences associated with pediatric anxiety, more work is clearly needed to elucidate characteristic structural perturbations of these disorders.

Relative to the number of structural neuroimaging studies in pediatric anxiety, functional neuroimaging studies are a burgeoning area. A goal of this work is to link neural function with psychological processes that are characteristic of specific anxiety phenotypes and symptoms, while also accounting for genetic, maturational, and environmental influences (see Fig. 1) [4]. In pediatric anxiety, it has been hypothesized that both fear and reward circuits are involved. Thus, much of the functional neuroimaging work in children and adolescents has examined amygdala function in response to threatening stimuli such as fearful or angry faces. However, intriguing findings are now emerging in pediatric anxiety regarding the role of the striatum and vPFC, which support reward processing and regulatory processes that may provide new avenues of research on, and treatment approaches for, pediatric anxiety.

In this section, we highlight evidence gathered from a growing body of work that uses functional magnetic resonance imaging (fMRI) to examine the neural substrates of different psychological processes relevant to the symptoms of anxiety in children and adolescents. FMRI has proven to be a useful technique to pursue these investigations because of its excellent temporal and spatial resolution. In addition, fMRI procedures are safe, noninvasive, and tolerable for use with young populations. Below we focus on pediatric fMRI studies that assess the neural correlates of core anxiety-related cognitive and affective processes including attention orienting, threat learning, social–emotional information processing, and reward processing (refer to Table 1 [35–52] for study details). Many of these studies use faces depicting emotional states as stimuli as well as other emotionally evocative (but not extremely frightening) stimuli. These stimulus types are generally used with pediatric populations in order to (1) adhere to ethical research designs due to potential harm from exposure to extremely threatening or frightening stimuli; (2) remove confounds introduced by word-based stimuli that may be associated with age-related differences in emotional and linguistic processing abilities; (3) consistently and reliably capture attention; and (4) represent stimuli encountered regularly by children in their daily lives.

Table 1 Functional neuroimaging studies including children and adolescents with anxiety diagnoses, anxiety symptoms, or risk for anxiety

Study	Sample demographics	Anxiety status	Task
Attention orienting			
Monk et al. [35]	Age range: 9–17 years Patient group: $n=18$, 8 females Healthy group: $n=15$, 8 females	Generalized anxiety disorder	Attention to angry faces using a dot-probe task
Monk et al. [36]	Age range: 11–16 years Patient group: $n=17$, 6 females Healthy group: $n=12$, 6 females	Generalized anxiety disorder	Attention to masked angry faces using a dot-probe task
Telzer et al. [37]	Age range: 11–18 years Healthy group: $n=16$, 8 females	Trait anxiety	Attention to angry faces using a dot-probe task
Social–emotional information processing			
Face emotion processing			
Thomas et al. [38]	Age range: 8–16 years Patient group: $n=12$, 5 females Healthy group: $n=12$, 5 females	Generalized anxiety disorder and/or panic disorder Anxiety symptom severity	Fearful face processing using a passive viewing face emotion task
Killgore and Yurgelun-Todd [39]	Age range: 8–15 years Healthy group: $n=16$, 7 females	Anxiety symptom severity	Fearful face processing using a passive viewing face emotion task
McClure et al. [40]	Age range: 10–14 years Patient group: n = 17, 7 females Healthy group: $n=20$, 11 females	Generalized anxiety disorder	Attention to subjective fear of fearful faces using an attention–emotion face task
Perez-Edgar et al. [41]	Age Range: 10–15 years Behaviorally inhibited group: $n=10$, 8 females Non-Inhibited group: $n=17$, 9 females	Risk for anxiety	Attention to subjective fear of fearful faces using an attention–emotion face task
Beesdo et al. [42]	Age range: 11–16 years Anxiety no MDD: $n=16$, 5 females MDD no anxiety: $n=12$, 7 females MDD with or without anxiety: $n=26$, 15 females Healthy controls: $n=45$, 24 females	Generalized anxiety disorder, social phobia, separation anxiety disorder, and/or major depressive disorder	Attention to subjective fear of fearful faces using an attention–emotion face task
Lau et al. [43]	Age range: 10–16 years Patient group: $n=31$, 18 females Healthy controls: $n=33$, 18 females	Generalized anxiety disorder, social phobia, separation anxiety disorder, and/or major depressive disorder	Attention to subjective fear of fearful faces using an attention–emotion face task
Blair et al. [44]	Age range: 9–41 years Patient group: $n=39$, 14 adolescents, 22 females Healthy group: $n=39$, 16 adolescents, 17 females	Social phobia	Gender judgment of faces using a morphed facial emotion task
Social evaluation processing			
Guyer et al. [45]	Age range: 9–15 years Patient group: $n=14$, 10 females Healthy group: $n=14$, 10 females	Social phobia, generalized anxiety disorder + social concerns, and/or separation anxiety disorder + social concerns	Anticipation of peer evaluation using the chat room task

(continued)

Table 1 (continued)

Study	Sample demographics	Anxiety status	Task
Lau et al. [46]	Age range: 9–14 years Patient group: $n = 12$, 8 females Healthy group: $n = 12$, 8 females	Social phobia, generalized anxiety disorder + social concerns, and/or separation anxiety disorder + social concerns	Receipt of peer evaluation using the chat room task
McClure-Tone et al. [47]	Age range: 10–15 years Patient group: n = 12, 7 females Healthy group: $n = 17$, 8 females	Generalized anxiety disorder, social phobia, and/or separation anxiety disorder	Betrayal and cooperation using a Prisoner's Dilemma task
Reward processing			
Guyer et al. [48]	Age range: 10–15 years Behaviorally Inhibited Group: $n = 13$, 8 females Non-inhibited group: $n = 19$, 10 females	Risk for anxiety	Response to anticipated incentives using the monetary incentive delay task
Krain et al. [49]	Age range: 13–17 years Patient group: $n = 16$, 7 females Control group: $n = 13$, 8 females	Generalized anxiety disorder and/or social phobia	Intolerance to uncertainty using the Hi/Lo decision-making task
Bar-Haim et al. [50]	Age range: 14–18 years 15 females Behaviorally inhibited group: $n = 16$, 5 females Non-inhibited group: $n = 16$, 10 females	Risk for anxiety	Response to anticipated incentives using a reward contingency task
Helfinstein et al. [51]	Age range: 14–18 years Behaviorally inhibited group: $n = 16$, 5 females Non-Inhibited group: $n = 16$, 10 females	Risk for anxiety	Response to incentive outcomes using a reward contingency task
Guyer et al. [52]	Age range: 10–16 years GAD group: $n = 18$, 10 females Social phobia group: $n = 14$, 9 females Healthy group: $n = 26$, 11 females	Generalized anxiety disorder and/or social phobia	Response to anticipated incentives using the monetary incentive delay task

Attention Orienting

Attention orienting is a process that involves focusing one's attention on salient stimuli. A central feature of anxiety and fear-related behavior is atypical modulation of attention that manifests as hypervigilance and enhanced attention to threatening stimuli, referred to as attentional bias [53–55]. The specific role of this attention bias in the etiology and/or maintenance of pediatric anxiety disorders is unknown. However, recent randomized controlled trials have demonstrated that training anxious children to modify their attentional threat biases can facilitate disengagement of attention to threat, which in turn can reduce anxiety symptoms [56, 57]. These findings imply a direct link between attention bias towards threat and anxiety symptoms. Further, they suggest that attention biases might emerge over time through reinforcement or as a means to reconcile ambiguous situations [58].

Several paradigms (e.g., dot-probe tasks, emotional Stroop tasks) have been used to manipulate attention orienting and measure how anxious individuals orient their attention to threat stimuli, such

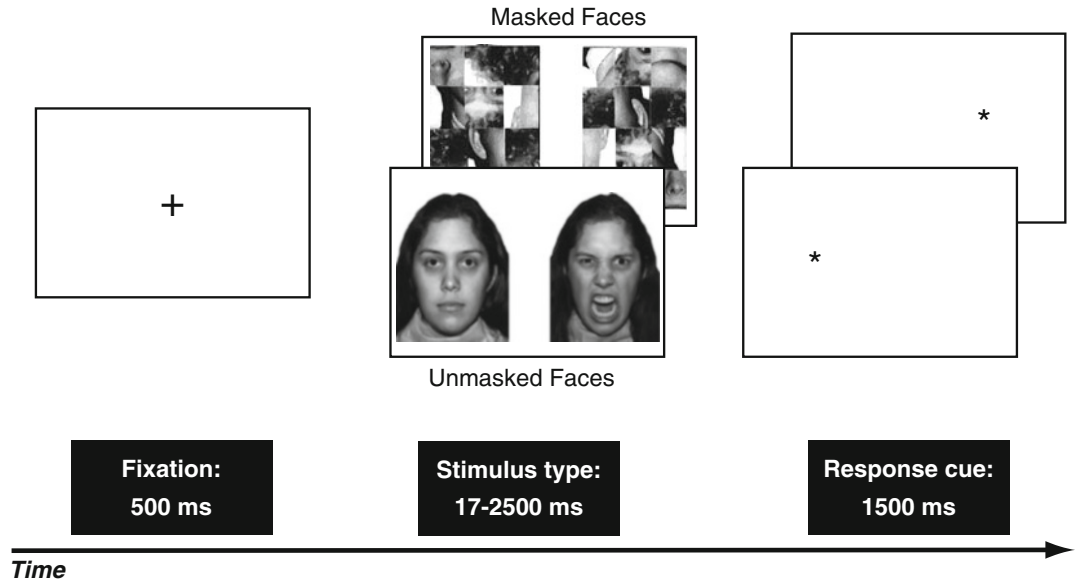

Fig. 2 An example of a trial in the dot-probe paradigm used to measure the influence of threats on attention orienting. A fixation cue is presented first. Then, pairs of stimuli depicting threat or nonthreat cues are presented. Stimulus pairs may be presented for varying time durations (e.g., 17–2,500 ms). Finally, a dot-probe cue appears to which participants respond via a button press. Attention bias to threat can be assessed through the time it takes to respond to the dot-probe cue as well as associated changes in neural response to the cue

as pictures of angry faces or words connoting threat [4, 53, 54]. Variants of the dot-probe task (see Fig. 2) have been the most widely used approaches to assess attention biases, particularly in studies of pediatric anxiety and health [35, 36, 56, 59, 60]. The dot-probe task displays two stimuli side-by-side, one depicting threat and one that is neutral. After the stimuli are removed, a target probe such as an asterisk (e.g., "*") appears in the same location as either the previously presented threat or neutral stimulus. Participants are then asked to indicate the location of the target (e.g., left or right side of the screen). Attention bias to threat is considered to be present if it takes an individual more time to draw their attention away from the location of the threat than from the neutral stimulus in order to locate the target. Anxious relative to non-anxious individuals (adults and children) tend to focus their attention toward threat stimuli to a greater extent and thus take longer to disengage from the location of the threat stimulus when turning their attention to the target [53, 60]. Some work suggests that younger versus older anxious individuals are more distracted by threat stimuli when other information demands their attention [61]. Further, adolescents who were behaviorally inhibited in early childhood have also shown heightened attention bias to threat, a bias further linked with social withdrawal [62]. However, in some situations, extremely high levels of threat can lead the anxious individual to avoid rather than linger their attentional focus on threat cues. Such patterns have been found both in adults exposed to extreme life-stress and danger [63, 64] and in youth with anxiety disorders [35]. Such tendencies to avoid acute threat appear to be transient in individuals studied in lower threat states [63, 65].

Neuroimaging techniques have been used to identify the neural substrates involved in attention orienting and to examine differences in neural responses during attention orienting to threat between youth with anxiety disorders and youth who are psychiatrically healthy. Key regions that have emerged from these investigations include the amygdala and ventrolateral regions of the PFC. For example, in one fMRI dot-probe study that used a relatively long period of exposure to threat stimuli (500 ms), greater ventrolateral prefrontal cortex (vlPFC) activation was elicited in response to angry faces in anxious relative to healthy adolescents; however, amygdala activation did not differ between the two

groups [35]. This pattern of vlPFC activity also correlated negatively with the severity of anxiety symptoms, such that more vlPFC activity was associated with less severe anxiety.

Rodent studies suggest that activation of the amygdala is particularly relevant during the rapid processing of threatening stimuli [15]. Thus, individual differences in the function of the amygdala for anxious adolescents may be predicted specifically during brief stimulus presentations. To test this hypothesis, a second fMRI study was conducted with the same dot-probe paradigm as described above but with shorter (17 ms), masked exposures to threat [36]. In this second study, greater amygdala activation occurred in response to angry faces in anxious than in healthy adolescents, and this pattern of activation correlated positively with greater attention bias, as indexed by response time to the target, and the severity of anxiety symptoms. Together, the results from these two neuroimaging studies with the dot-probe suggest that the duration of threat exposure modulates activation in different key neural regions in anxious youth.

A third fMRI study used the dot-probe face emotion task to examine whether trait anxiety in a sample of healthy children and adolescents would be associated with attention bias towards threat [37]. As expected, trait anxiety was positively associated with an attention bias towards angry but not happy faces. With regard to neural function, trait anxiety was positively related to right dorsolateral PFC activation only to angry faces. In addition, trait anxiety was associated with greater vlPFC activation regardless of the valence of the face stimulus. Finally, with regard to genetic influences, research has focused on a variant of the serotonin transporter (5-HTT) gene given its implications in anxiety [66, 67]. Although patterns of anxiety and 5-HTT variations are somewhat mixed, lower levels of 5-HTT are found among carriers of the short allele (S/S and/or S/L) relative to individuals with two long alleles (L/L). Relative to L-allele carriers, healthy adolescents who are S-allele carriers exhibit greater attentional bias to subliminally shown fear faces and greater response to fearful and angry faces in the brain's association cortex, an area implicated in attention control [68].

In sum, neural response patterns associated with attention orienting to threat show heightened amygdala response in youth with anxiety relative to those without anxiety, particularly when rapid processing of threat is required. Furthermore, greater amygdala responsivity also relates to more severe anxiety symptoms, again in the context of processing threat cues in a brief amount of time. When the time during which threat processing is lengthened, a different pattern emerges. Specifically, youth with anxiety disorders relative to healthy youth show greater vlPFC response to threat with no amygdala differences observed. Interestingly, among pediatric anxiety patients, those with the most severe anxiety symptoms had lower vlPFC activity whereas patients with less severe impairment had greater vlPFC activity. These patterns suggest that vlPFC response is not necessarily tied directly to anxiety symptoms but might modulate activity in other regions, such as the amygdala, which is closely linked to anxiety symptoms. Thus, the vlPFC could play a compensatory role by regulating and reducing perturbed function in the amygdala, particularly if it comes online further along in the sequence of reacting to threat to regulate emotions and behaviors to allow for more strategic allocation of attention [9]. This role would be consistent with higher vlPFC activity among anxiety patients with less severe functioning. Overall, vlPFC input may be recruited during longer exposures to threats to facilitate deeper, more comprehensive processing whereas the amygdala serves as a rapid threat detector that is overly responsive to immediate, even subconscious perceptions of threat, in anxious youth. As such, the vlPFC may be recruited at different time points to help modulate emotional responses related to anxiety through cognitive functions in order to inhibit behaviors or thoughts or to update rules or goals.

Threat Learning

The excessive fear responses to threat cues seen both behaviorally and physiologically in anxiety may also arise from difficulties in learning to discriminate threat cues from safety cues, also known as

threat learning [69–71]. Threat learning involves correctly determining what cues and in which situations indicate potential danger or safety. Fear conditioning paradigms have been used to assess threat learning processes relevant to anxiety. In fear conditioning experiments, a neutral stimulus is set to acquire a value signifying threat via repeated pairings with an aversive unconditioned stimulus (UCS). Over time the UCS becomes a reinforced conditioned stimulus (CS+) (see Chap. 1 for further discussion of fear learning). Perturbations in threat learning are seen in adults with high levels of anxiety who show greater fear toward a CS+ than do adults with low levels of anxiety [72]. Anxious adults also show greater fear toward non-reinforced conditioned stimuli (CS−) which are nonthreatening cues that are not followed by the UCS [72]. This latter finding represents stimulus generalization whereby the more similar a CS+ and a CS− are perceptually (e.g., hair color), which can be achieved by morphing two different faces together incrementally until they overlap, the more anxious individuals respond to both stimulus classes with excessive fear [73, 74].

Research on threat learning in adults has set the stage for both behavioral and neuroimaging studies of threat learning in pediatric anxiety. Behavioral studies have found that, relative to healthy children, children with anxiety disorders show difficulty discriminating between CS+ and CS− cues and greater arousal via skin conductance during fear conditioning, and stronger orienting and anticipatory sensitivity to emotional valence during extinction [75, 76]. Evidence also suggests that children with anxiety disorders experience a CS+ stimulus as more unpleasant than healthy children or children at familial risk for anxiety disorders [75]. Other work has shown that even when both anxious and healthy children similarly experience discriminative conditioning, children with anxiety relative to healthy children show greater arousal (via larger skin conductance responses) to CS+ and CS− cues during acquisition, report that the CS+ relative to the CS− cue is more arousing, and exhibit more resistance to extinction as measured by skin conductance responses but not as measured by arousal ratings to the CS+ versus the CS− cues [77]. Together, these studies indicate that anxious children have greater difficulty discriminating between threat and safety cues and modulating their emotional arousal and orientation to such cues and, subsequently, do not easily dissociate during extinction the previously established connections between threat and neutral cues. These patterns suggest that pediatric anxiety, as adult anxiety, is clearly associated with perturbations in the ability to make flexible and adaptive associations between emotionally valenced cues and outcomes.

While behavior-based threat learning difficulties have been documented in anxious children [75–77], less work has focused on assessing the neural correlates of threat learning difficulties in pediatric anxiety. An experimental task has been developed recently using a UCS that maintains its aversive meaning but remains appropriate for use with pediatric populations and lends itself to use within a neuroimaging context. This task paradigm presents a fearful female face that is accompanied by an extremely loud scream [70], two cues that imbue high biological and social salience. Presentations of the aversive UCS (fearful female face + scream) are paired with a neutral face to probe conditioning and extinction to a neutral cue that becomes a threat cue (CS+). A second stimulus, novel neutral face, is used as a safety cue since it is not presented with the UCS in order to assess generalization from threat to safety cues (CS−). This fear conditioning paradigm has been tested in an fMRI study of healthy adolescents and adults to ascertain typical neurodevelopmental correlates of threat learning and to generate a baseline in healthy development against which the atypical pediatric anxious pattern may be compared in the future [78]. Three key results emerged from this study. First, behavioral data indicated weaker discrimination between threat and safety cues in adolescents than adults. Second, adolescents relative to adults showed greater amygdala and hippocampus activation to CS+ versus CS− conditions, indicating enhanced sensitivity of these early-maturing subcortical regions in younger individuals when distinguishing between threat and safety cues [78]. Finally, adults relative to adolescents showed a positive association between dorsolateral PFC (DLPFC) recruitment and fear ratings when discriminating between threat and safety. Because prefrontal areas such as the DLPFC follow a more protracted developmental course [79], enhanced engagement of the DLPFC in adults suggests that it helps support making distinctions between relatively similar-looking cues to inform correct

categorization of stimuli. Overall, these neural data suggest age differences in the degree to which subcortical and prefrontal regions are engaged during threat learning.

To date, the fear conditioning paradigm described above has only been studied behaviorally in adolescents with anxiety disorders [70]. In this initial study, conditioning was established based on higher ratings to the CS+ versus the CS−, but it did not vary as a function of anxiety diagnosis; thus, all adolescents were more afraid of the threat than the safety cue. Pediatric anxiety was associated with high levels of reported fear after conditioning, but the levels of fear were not associated with greater discrimination between the classes of conditioning cues, rather they were associated with both the CS− and the CS+ neutral faces. Future work will need to establish whether distinct neural correlates are associated with these patterns of behavior in youth with anxiety disorders.

Taken together, the available work on the developmental course of threat learning and anxiety suggest that the neurodevelopmental differences in subcortical and prefrontal brain responses during the discrimination between threat and safety cues may play a role in the emergence of anxiety in childhood or adolescence and its maintenance into adulthood. In cases of immature prefrontal development, flexibility in adapting to increased ambiguity may be compromised and lead to difficulties in threat learning and a greater generalized fear response to threat and safety cues encountered in day-to-day life. Future work should include longitudinal studies of large groups of similarly aged individuals at this developmental transition and follow them well into adulthood as well as compare them to anxiety-disordered age mates.

Social–Emotional Information Processing

Moving beyond cognitive functions such as attention orienting and fear conditioning, the processing of affect displayed by social cues and within different social contexts is another key, symptom-relevant construct well represented in fMRI studies of pediatric anxiety. By targeting how the brain responds to social–emotional information such as emotions displayed on faces, specific neural patterns have emerged in relation to type of emotion, attentional focus, and stimulus class. For example, during very specific instances of potential social evaluation, socially anxious adolescents react with an exaggerated fear response even to positive smiling faces [45]. Moreover, as noted above, lesion work in monkeys suggests that neural correlates of social–emotional information processing exhibit unique developmental changes [27]. As such, it is particularly important to chart the neural correlates of social threat processing in adolescents and adults. In the sections that follow, we review results from neuroimaging studies of pediatric anxiety that involve either processing emotional faces or responding to conditions of social evaluation or judgments.

Face Emotion Processing

Initial studies used facial expressions of emotions to probe whether patient groups with impaired emotion processing and regulation would show aberrant neural responses to different facial emotions. Fearful facial expressions have been particularly useful because of their ability to increase amygdala activity, a region highly relevant to anxiety, even if an individual does not necessarily report feeling fearful of such a face [80]. One reason for this threat-related response to fearful relative to angry faces may be due to the ambiguity conveyed by a fearful face about the location of potential threat. Furthermore, fearful faces are not encountered frequently in one's environment, but when they are present, they signal that there is a threat and the source of potential threat needs to be determined to remain safe.

In the first functional neuroimaging study of children and adolescents (8–16 years old) with anxiety disorders, higher levels of amygdala activity were found in response to simply viewing fearful faces as compared to youth with no psychiatric disorders [38]. An additional comparison showed a blunted amygdala response in a small group of depressed youth relative to anxious youth, suggesting that increased amygdala response during fear processing is specific to anxiety disorders. Similarly, in other work, greater amygdala response to fearful faces was associated with greater severity of daily anxiety symptoms [38] as well as severity of social anxiety symptoms [39].

A series of neuroimaging studies in adolescents with anxiety disorders have also reported enhanced amygdala response to fearful faces, particularly when anxious adolescents are asked to contemplate how afraid they felt while looking at the faces [40, 42, 43]. In contrast, when asked to just view fearful faces without monitoring emotional responses, both anxious adolescents [40] and those at temperamental risk for anxiety [41] have shown reduced amygdala response to fearful relative to neutral faces, a pattern that opposes that seen in healthy adolescents [81]. These studies suggest that attentional focus matters in youth with anxiety insofar as it modulates amygdala response. One possibility is that amygdala hyperactivation occurs when attention is drawn to the act of monitoring one's feelings of fear but not when attention is unconstrained. This could occur because anxious youth avert their attention away from the face to avoid a feared stimulus. When required to focus on the feared stimulus, amygdala perturbation could reflect high sensitivity to processing subjectively experienced feelings of fear in the anxious child.

Research on the genetic and developmental variations in amygdala response to fearful faces has also started to emerge. These approaches are important because pediatric anxiety disorders strongly predict adult anxiety disorders [1, 82, 83]. As such, for some individuals, the association between anxiety disorders in early and later life may be shaped by genetic influences on the brain during critical developmental transitions such as from adolescence to adulthood. Thus, brain function may serve as a potential intermediate phenotype worthy of attention for understanding the underpinnings of adult anxiety.

To examine developmental mechanisms underlying associations between genetic influences on brain responses to emotional stimuli and anxiety, Lau et al. [43] examined the effects of the 5-HTT gene variant and diagnoses on amygdala response to emotional faces. While focused on internal feelings of fear, healthy adolescents who were S/L carriers had greater amygdala activation than L/L individuals, whereas L/L adolescents with anxiety or depression diagnoses showed greater amygdala response than their S/L counterparts. While the effect of heightened amygdala response to fearful faces found in healthy adolescents with the S/L allele was consistent with past findings in healthy adults, the opposite effect of increased amygdala response to fearful faces in adolescent patients with the L/L allele was contrary to past reports in adult patients [84]. The former result suggests that the risk conveyed by the short allele 5-HTT gene variant may be conserved across development; however, the latter result is harder to interpret as very few studies have examined gene–brain function relationships in affected individuals (including youth or adults), and more work is needed to reconcile inconsistent results from these studies.

Given its role in affect dysregulation, research has targeted the Val, Met, and Val-Met polymorphisms of the human Brain Derived Neurotrophic Factor (BDNF) gene in adolescents with anxiety and/or depressive disorders [85]. Results from this study found that Met-carriers showed greater amygdala and hippocampal responses to emotional faces than Val/Val homozygotes among adolescent patients relative to controls. Although preliminary, these new data from "imaging genetics" pediatric studies suggest that a continued focus on brain function and genes may reveal vulnerability mechanisms for anxiety across development.

Other work has taken a developmental approach to investigate potential vulnerability mechanisms given the persistence and long-term risk that adolescent anxiety predicts for adult anxiety. In a recent study, neural response to emotional facial expressions was compared between adults and adolescents with social phobia [44]. Results from this study indicated greater activation in the amygdala and

rostral anterior cingulate cortex (rACC) in response to angry and fearful, but not neutral faces in both adolescents and adults with social phobia. In adults but not adolescents, greater severity of social phobia was also associated with greater rACC activation. Although these findings are cross-sectional, the similar neural correlates in adolescent and adult social phobia suggest persistence in the neural mechanisms underlying social phobia.

Social Evaluation Processing

A series of studies have used a type of face viewing task that simulates potential social evaluation, a prominent experience for adolescents overall but also a main fear experienced by individuals with social anxiety [45, 46, 86, 87]. The task used in these studies was designed to create a context for measuring neural response while an adolescent anticipates receiving feedback from an unknown peer and another context to assess their emotional and neural responses to actually receiving either positive or neutral feedback. These constructs were selected specifically to give ecological validity to the neuroimaging task by mimicking adolescents' daily life experiences but also to reflect core symptoms in social anxiety.

With regard to the anticipation of peer feedback, as expected, greater amygdala activity was observed among socially anxious versus healthy adolescents when judging how interested unknown peers would be in chatting with them during a later interaction [45]. This was particularly evident when viewing peers the adolescent had judged as being of low interest to them for an interaction. Additional results from functional connectivity analyses showed that amygdala and vlPFC activations were more strongly correlated in socially anxious adolescents than in healthy adolescents when anticipating social evaluation from the negatively perceived peers. In addition to these findings in socially anxious adolescents, data in typically developing adolescents reveal neural activation within key areas implicated in affective processing (e.g., ventral striatum, hippocampus, insula, and hypothalamus) that varies by age and sex [86]. Specifically, neural activation increased with age in older (14–17 years old) relative to younger females (9–13 years old) but showed no association with age in males. These developmentally based results suggest that vulnerabilities to anxiety problems may be more prominent at certain ages for females. Thus, further work is clearly needed using this paradigm in healthy and anxious children and adolescents of various ages and sexes.

Examination of adolescents' emotional response to the receipt of peer feedback has yielded intriguing findings as well. Both healthy adolescents and those with social anxiety showed activation in the amygdala–hippocampal complex just prior to receiving positive or negative peer feedback relative to baseline [46]. However, after being rejected by peers, anxious relative to healthy adolescents showed persistent amygdala–hippocampal activation, whereas the healthy adolescents showed reductions in amygdala activity once they received negative feedback. This poor neural recovery from a negative emotional experience seen in adolescent anxiety may relate to problems with inhibiting amygdala response or with regulation of amygdala sensitivity [88, 89]. Though not directly examined in this study, these anxiety-related neural perturbations may be associated with greater cognitive distortions about emotional events, which, in turn, may result from the imbalance between cognitive and affective processing during the adolescent period [18, 90].

Finally, another form of social interaction and evaluation that has been examined in conjunction with fMRI involves the Prisoner's Dilemma game in which participants must choose to cooperate or betray a co-player in an attempt to earn as much money as possible. Behaviorally, anxious adolescents were more likely than healthy adolescents to maintain positive interactions when possible through cooperation with co-players, particularly after a co-player chose to betray the participant [47]. FMRI data showed increased activation in the anterior precuneus and right temporal parietal junction among anxious versus healthy adolescents but increased medial PFC and ACC activation in healthy relative to anxious adolescents [47]. These results suggest that anxious youth exhibit a heightened

tendency to engage in increased self-focus and may also tend to ruminate about their behaviors during interpersonal interactions which manifests in altered brain function. Overall, these studies provide important clues to cognitive and emotional processing of social stimuli in health and anxiety [18].

Reward Processing

Across the processes involving attention orienting, threat learning, and social–emotional information processing, the repeated findings of abnormal amygdala function suggest that anxious adolescents are readily influenced by threatening cues; in turn, this set of processes may compromise emotion regulation and perpetuate chronic, extreme anxiety. While the amygdala clearly processes social threat, research on social–emotional development in primates suggests that structures beyond the amygdala are likely to play equally important roles in facilitating response to social threats. For example, findings of enhanced social fear in juvenile primates without a functioning amygdala demonstrate that social fears in juveniles must also be instantiated in neural circuitry that extends beyond the amygdala [91, 92]. Moreover, given that removal of the amygdala heightens social fears, components of the circuitry mediating response to social threats are likely to be involved in feedback loops with the amygdala. Although most work on social fears and anxiety in humans examines amygdala function, these data in nonhuman primates highlight the need to examine other structures early in development.

Beyond the amygdala, another key subcortical structure that has recently been investigated in relation to pediatric anxiety is the striatum. The striatum generally includes the nucleus accumbens, caudate, and putamen and encompasses a ventral and dorsal area, with strong connections to frontal cortical regions, the hippocampus, and the amygdala [93, 94]. The striatum is involved in associating emotionally salient environmental stimuli with anticipated outcomes to guide approach or avoidance behavioral responses [93, 95]. As such, striatal circuitry has been well characterized in research on substance abuse and addiction [96, 97]. Extensions of the addiction literature have focused on striatal function with other classes of motivationally salient stimuli, namely, rewards and punishments.

New discoveries have emerged in our understanding of reward processing in anxiety with the use of monetary incentive cues that highlight how incentives modulate approach and avoidance behaviors [98, 99]. A focus on neural correlates of reward processing in pediatric anxiety grew out of initial work on behavioral inhibition, an early-life temperament style that carries increased risk for later anxiety, especially social anxiety [100, 101]. One of the first neuroimaging studies in this area documented heightened sensitivity in the striatum to anticipated incentives [48]. Specifically, adolescents whose temperament had been characterized in early childhood as behaviorally inhibited showed increased striatal response as the magnitude of the incentive increased; adolescents not characterized as behaviorally inhibited did not show this modulation by incentive value. One possible explanation for this pattern is that striatal dysfunction may reflect anxiety during anticipation of uncertain outcomes or concern over performance when the stakes increase. Indeed, follow-up studies showed increased striatal activation in adolescents characterized by early-childhood behavioral inhibition relative to their non-inhibited counterparts when receipt of anticipated incentives was contingent on one's actions [50] and when anticipated incentives were not actually provided [51].

The early-childhood behavioral inhibition findings described above suggest that sensitivity of the striatum may be a neural marker in addition to amygdala sensitivity [41, 102] that links early-childhood behavioral inhibition specifically to later anxiety. Indeed, both social phobia and social subordination, which shares behavioral features of social phobia, are associated with dysfunctions in the striatal dopaminergic system [103–106] and altered striatal function [107]. Thus, identifying alterations in striatal function during anticipatory performance-based or social situations could reveal pathophysiological traits common to both social phobia and behavioral inhibition. Recent work confirmed this hypothesis by showing striatal hypersensitivity to anticipated incentives in adolescents with SoPh but not GAD [52]. It may be that striatal function is a biomarker that differentiates between

these two anxiety diagnoses while the amygdala is involved in anxiety in a nonspecific fashion that does not differentiate between the anxiety disorders. Moreover, the findings in socially anxious adolescents closely resemble those in children with behavioral inhibition. As such, adolescents with social phobia and adolescents with early-life behavioral inhibition show similar patterns in certain striatal regions during reward processing which indicates the importance of considering more than one affectively relevant neural system as well as additional psychological processes in pediatric anxiety.

Related to reward processing and anticipating outcomes, intolerance to uncertainty is a trait associated with anxiety, extreme worry, and impaired decision-making. In a study of adolescents with GAD or SoPh, the relationship between intolerance to uncertainty and neural responses to uncertainty was examined [49]. High levels of intolerance to uncertainty were associated with increased activation in frontal and limbic regions including the anterior cingulate cortex, orbitofrontal cortex, and amygdala in response to uncertainty during a decision-making task. Intolerance of uncertainty emerged as a cognitive trait associated with neural regions that may contribute to the maintenance of pediatric anxiety disorders. These results also highlight the variability related to trait characteristics that exist within adolescents with anxiety disorders and suggest that using such an approach for characterization of pediatric anxiety may prove fruitful in tailoring treatments to subgroups of patients depending on their profiles of key traits and neural response patterns.

Functional Connectivity in Pediatric Anxiety

Recently, studies have begun to examine functional connectivity in the context of anxiety disorders. Typically, the goal of studies examining functional connectivity is to determine the degree of co-activation among various brain regions. Functional connectivity can be measured during two conditions: (1) a specific task (task-dependent functional connectivity or TDFC), typically one related to emotion salience or emotion regulation in the case of anxiety disorders (i.e., how does activity in one region relate to or "regulate" activity in another region during different task-related events), or (2) a state of rest (resting state functional connectivity or RSFC) when the individual is not engaged in any particular assigned task (i.e., what neural interactions occur spontaneously while an individual has their eyes closed or is fixating on a cross). While measuring either TDFC or RSFC, the co-activations of regions within a particular known neural network may be investigated. Or, alternatively, a specific "seed" region may be identified so that the degree of covariation between activity in this seed region and activity in other regions may be measured, which can lead to the identification of new interrelated networks.

Task-Dependent Functional Connectivity

Among the handful of studies that have examined patterns of TDFC in patients with anxiety disorders versus controls, connections have been examined across a range of neural networks. Adults with anxiety disorders exhibit stronger connections between limbic regions (i.e., anterior insula) and frontal and parietal regions [108], as well as weaker TDFC within prefrontal networks [109] and within superior temporal networks [110]. Despite this range of findings, however, the majority of work on this topic has focused largely on links between subcortical/limbic regions (responsible for processing salience and affect) and cortical/frontal regions (responsible for control or regulation of affect and implicit drives). This is likely because an imbalance in the functioning of these regions

(e.g., hyperactivation of the amygdala combined with hypoactivation of the medial and lateral prefrontal cortices) is often thought to characterize anxiety disorders, as discussed in other sections of this chapter and recent reviews [111–113]. For example, one recent study of adults examined a specific type of emotion regulation during reappraisal of negative self-beliefs—one of the hallmark characteristics of social phobia. Results indicated less TDFC between the prefrontal cortex and the amygdala among patients with SoPh versus controls [114], consistent with the notion that patients are less able to regulate amygdala responses to negative emotions. Similarly, other work examining patients with GAD has shown a similar pattern such that patients fail to engage regulatory regions in response to heightened displays of amygdala activity resulting from emotional stimuli [115].

A small number of studies have examined functional connectivity in pediatric samples. Similar to the work described in adults, one study found that compared to healthy controls, adolescents with GAD displayed a relatively weaker negative TDFC between the lateral prefrontal cortices and the amygdala during an emotional attention orienting task [36], which is consistent with the notion that individuals with anxiety are less able to regulate neural responses to emotion, even prior to adulthood. Interestingly, however, another study that examined pediatric patients with social anxiety disorders found a somewhat different pattern of results. Specifically, socially anxious patients displayed stronger positive TDFC between the lateral prefrontal regions and the amygdala during the anticipation of social evaluation by peers than healthy controls who showed relatively little TDFC [45]. While more research will help clarify these patterns of results, it is possible that the distinct processes that are involved in responding to negatively valenced stimuli (i.e., anticipating, versus actually responding to, a negative stimulus) may be characterized by distinct patterns of TDFC in anxious individuals.

Resting State Functional Connectivity

In studies of clinical populations, RSFC may be a particularly useful way of studying neural interactions for several reasons [116–118]. First, RSFC analyses permit investigators to examine patterns of intrinsic functional connectivity underlying different, simultaneous functions. Thus, there is less need to isolate a particular construct of interest using a specific task. Second, when examining brain activity while individuals are resting, biases among particular clinical populations in terms of how they interpret task instructions or respond to certain stimuli will be significantly reduced. Thus, these biases will be less likely to produce group differences that are solely task dependent. Third, examining resting brain activity increases the probability of enrolling patients in studies who have a limited ability to comply with certain task demands. In other words, studies of RSFC may permit the inclusion of individuals who are more impaired than those typically included in clinical neuroimaging studies. Finally, given that RSFC is not task dependent, there is greater reliability across research sites and scanners, which facilitates the study of larger samples [119]. This is particularly important for studies of pediatric anxiety disorders that often suffer from small sample sizes.

Similar to the TDFC studies described above, most of the RSFC studies examining neural function in relation to anxiety disorders have found results that are consistent with the notion that anxiety disorders may be characterized by dysregulation between frontal and limbic networks, resulting in an inability to regulate responses to emotional events [111–113]. Here we briefly discuss some of the RSFC studies most relevant for understanding limbic/frontal connections in the context of anxiety disorders, given that this has been the focus of the majority of this work thus far. Moreover, it is worth noting that studies examining RSFC have so far focused exclusively on adult populations; nevertheless, we review them here because of their potential relevance for exploring pediatric populations in future research.

First, a few studies have specifically focused on SoPh. One of these studies found that the amygdala showed reduced RSFC with two regions commonly linked with higher-level control processing, both the medial orbitofrontal cortex and the portion of the medial posterior parietal cortex that includes both the posterior cingulate cortex and the precuneus [120]. The connectivity between these regions was particularly reduced among individuals with higher state anxiety. Similarly, another study found that adults with SoPh show reduced RSFC between the amygdala and the inferior temporal gyrus and increased RSFC between the amygdala and occipital regions [121]. This is consistent with the commonly reported finding that individuals with SoPh have exaggerated affective responses to visually observed stimuli combined with an inability to properly regulate these affective responses which likely contributes to their heightened anxiety in social situations. Other work has further demonstrated irregularities in the RSFC of several brain systems among individuals with SoPh, including altered connections between limbic/subcortical and frontal/cortical networks [122, 123], as well as disrupted connectivity within different regions of the frontal lobe, and between frontal and visual networks [124]. Moreover, many of these findings have also been associated with the degree of patients' symptom severity [122, 124].

Results from a recent study of adults with GAD indicate increased RSFC between the amygdala and a frontoparietal control network and decreased RSFC between the amygdala and regions linked with stimulus salience, including the insula and the cingulate, as compared to healthy comparisons [125]. At first glance, this finding seems to run counter to the idea that anxious individuals have weaker neural connections between limbic/subcortical regions and control/frontal regions (as well as heightened connections within the salience/affective network). However, the authors suggest a compensatory role of the frontoparietal network and suggest that heightened connectivity between limbic and control regions may reflect additional regulatory resources needed to compensate for the heightened affective responses that typify this population. Liao and colleagues [123] also propose a compensatory model in which cortical regions are more strongly connected with limbic regions among individuals with SoPh; however, it is not yet clear when compensatory models might be most relevant (i.e., compared to models focusing on the hyperactivation of limbic regions and the hypoactivation of control regions). In fact, the results from another recent study examining RSFC in healthy individuals did not appear to be consistent with this compensatory model. Specifically, this study demonstrated that healthy individuals who reported high levels of anxiety showed negative correlations between activity in the amygdala and ventromedial prefrontal cortex during rest whereas those who reported low levels of anxiety showed positively correlated activity [126]. High anxious individuals also showed uncorrelated activity in the amygdala and dorsomedial prefrontal cortex while low anxious individuals showed negatively correlated activity. One additional study has shown heightened state activity during an off-task period after an initial task involving worrying among individuals with GAD in both limbic (i.e., the anterior cingulate cortex) and frontal (i.e., the dorsomedial prefrontal cortex) regions [127], which implies that those with GAD continue to worry; however, this study did not examine functional connectivity. Thus, additional research will be helpful in better elucidating irregularities of neural connectivity among individuals suffering from anxiety disorders.

Resting state EEG has also been used to assess underlying functional connections across the brain related to anxiety. These studies focus on the relationship between slow and fast waveform activity, which is believed to index the functional connectivity between subcortical/limbic regions and cortical/frontal regions. Thus, the relationship between slow and fast activity may reflect patterns of inhibitory control over motivational goals [128]. To our knowledge, EEG investigations of RSFC have not been carried out in clinically anxious populations; however, two recent studies examined aspects of anxious functioning among healthy individuals. One study demonstrated that healthy individuals with higher ratings of anxiety displayed EEG recordings consistent with weaker connectivity (i.e., a higher ratio between slow and fast waveforms) between frontal and limbic regions [129]. A second study provided evidence that resting state EEG activity among individuals displaying greater anxiety-related threat biases (i.e., avoidance of threatening stimulus displays) was similarly indicative of a

weaker cortical/limbic connection [130]. Thus, together these studies are consistent with data from fMRI research indicating that individuals with greater anxiety may have reduced frontal control over affective processes.

Treatment of Pediatric Anxiety: Implications for the Brain

The field of clinical cognitive neuroscience has been moving in an exciting direction by examining clinically relevant cognitions, emotions, and behaviors that characterize anxiety and relate to impaired functioning. This approach offers the potential for conceptualizing and pinpointing ways in which cognitions, emotions, and behaviors could be targeted in interventions for pediatric anxiety such as CBT or pharmacological interventions (e.g., SSRIs), both of which are very effective for treating anxiety [131–138]. For example, CBT offers patients tools such as cognitive reframing and self-monitoring to gain control over their symptoms. The well-documented pattern of amygdala hyperactivation in pediatric anxiety elicited during a range of psychological processes (e.g., face emotion processing, attentional bias) represents a possible biological marker for targeted intervention efforts. Indeed, emerging evidence suggests some potential pathways for intervening that are guided by knowledge of the pathophysiology of anxiety and relate to treatment response. The application of neuroimaging to testing treatment-related changes in brain function is relatively new, but there are some intriguing patterns emerging from the existing literature.

One study, which used the same face emotion task described earlier to assess fearful face processing, found that greater pretreatment amygdala activation in pediatric anxiety-disordered patients was associated with better response to both CBT and pharmacological treatments [139]. Amygdala hyperactivation was specific to conditions during which patients attended to their internally experience fear of salient emotional faces. Furthermore, both a decrease in symptoms across treatment course and posttreatment anxiety symptom severity were associated with this pattern. Nonetheless, it is important to consider that the documented amygdala perturbations may be present in a portion of pediatric anxiety cases that respond effectively to CBT or psychopharmacological treatment, whereas other cases who are more treatment resistant may react more positively to treatments that elicit input from other brain regions.

Another study focused on treatment-related brain response changes in association with attention orienting using a dot-probe task. Here, adolescents with GAD exhibited a significant increase in right vlPFC activation in response to angry versus neutral faces following effective treatment with either CBT or an SSRI [140]. As in past neuroimaging results comparing pediatric anxiety patients and controls, these treatment-related results also suggest the vlPFC may facilitate effective neural and affective responding via other brain regions (e.g., amygdala), perhaps through regulating overwhelming emotions or reframing biased cognitions. Thus, targeting the ventral regions of the PFC may offer one mechanism by which negative emotions such as anxiety can be reduced.

Striatal responses to reward have also been examined in the context of treatment for adolescent depression [141]. In this study, a monetary reward task was administered to assess striatal response during the anticipation of reward outcomes prior to the start of 8-week open label treatment with either CBT or CBT plus an SSRI. During each of the eight weeks of treatment, clinician ratings of symptom severity and improvement and self-reported anxiety and depressive symptoms were obtained. Greater pre-treatment striatal response to reward anticipation was associated with lower clinician-rated severity and lower anxiety symptom levels after the course of treatment. Interestingly, greater striatal response was associated with a faster reduction in anxiety symptom levels. These results suggest that a typical striatal response (increased rather than reduced as seen in depression) is associated with a better response to treatment, in terms of anxiety symptoms. It also suggests a

role of anxiety in the reward-related pathophysiology of adolescent depression, which underscores recent findings showing elevated striatal response to monetary incentives in adolescents with diagnosed anxiety disorders [52].

Conclusions and Future Directions

Clinical cognitive neuroscience provides an exciting bridge between basic and clinical domains of psychiatric and psychological research, particularly in the area of anxiety. Our current understanding of brain-behavior relationships is possible because of the applicability of animal models of fear responses to humans. As this chapter described, neurobiological research using tools such as fMRI has allowed for the testing of hypotheses about how specific neural circuits underlie psychological processes that shape behavior. Adding a developmental component to this approach has further deepened our understanding of the nature of neural structures and circuits and their connections in relation to pediatric anxiety.

Future work in this area will benefit from the inclusion of larger samples as well as of pure patient groups for cross-comparisons where possible. In addition, although the normative, longitudinal progression of brain structure has been fairly well characterized [21, 28, 79, 142–144], studies mapping longitudinal trajectories of brain function in response to the types of tasks described in this chapter need to be conducted in both pediatric health and anxiety. It would also be beneficial to chart longitudinal changes in anatomy among anxiety-disordered youth to pinpoint whether anxiety has long-term influences on neural structures such as the amygdala, striatum, or vPFC or whether these structures drive anxiety over time. More research that employs techniques such as diffusion tensor imaging would be beneficial for understanding anatomical connections within pediatric anxiety samples as well as work that focuses on the relationships between function and structure. Finally, additional work is necessary to determine the stability of neural functional change due to the effects of treatment once it has been completed.

In sum, we have described work that aims to pinpoint what psychological processes are at play in modulating and mapping neural structure and function in clinical pediatric anxiety. We hope that in the next generation of research of this kind, the information gathered to date will be translated into the development of effective, targeted treatments for pediatric anxiety.

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