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Developmental Neurobiology of Anxiety and Related Disorders

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Summary and Keywords

The majority of anxiety disorders emerge during childhood and adolescence, a developmental period characterized by dynamic changes in frontolimbic circuitry. Frontolimbic circuitry plays a key role in fear learning and has been a focus of recent efforts to understand the neurobiological correlates of anxiety disorders across development. Although less is known about the neurobiological underpinnings of anxiety disorders in youth than in adults, studies of pediatric anxiety have revealed alterations in both the structure and function of frontolimbic circuitry. The amygdala, prefrontal cortex (PFC), anterior cingulate cortex (ACC), and hippocampus contribute to fear conditioning and extinction, and interactions between these regions have been implicated in anxiety during development. Specifically, children and adolescents with anxiety disorders show altered amygdala volumes and exhibit heightened amygdala activation in response to neutral and fearful stimuli, with the magnitude of signal change in amygdala reactivity corresponding to the severity of symptomatology. Abnormalities in the PFC and ACC and their connections with the amygdala may reflect weakened top-down control or compensatory efforts to regulate heightened amygdala reactivity associated with anxiety. Taken together, alterations in frontolimbic connectivity are likely to play a central role in the etiology and maintenance of anxiety disorders. Future studies should aim to translate the emerging understanding of the neurobiological bases of pediatric anxiety disorders to optimize clinical interventions for youth.

Keywords: anxiety, fear, childhood, adolescence, amygdala, prefrontal cortex, trauma, brain development

Developmental Neurobiology of Anxiety and Related Disorders

Anxiety disorders are among the most common pediatric psychiatric disorders (Beesdo, Knappe, & Pine, 2009; Merikangas et al., 2010), with one in three children and adolescents experiencing anxiety-related symptoms before age eighteen, ranging from mild feelings of anxiety to anxiety disorders requiring treatment (Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012; Merikangas et al., 2010). An estimated 10% of youths are diagnosed with an anxiety disorder during the course of childhood and adolescence (Beesdo, Pine, Lieb, & Wittchen, 2010; Kessler et al., 2012). Children with anxiety disorders are at heightened risk for attempting suicide (Foley, Goldston, Costello, & Angold, 2006) and for developing secondary depressive disorders and comorbid anxiety disorders concurrently and later in life (Beesdo et al., 2009, 2010; Gregory, 2007; Pine, Cohen, Gurley, Brook, & Ma, 1998). Anxiety disorders affect family and peer relationships, as well as academic performance (Birmaher, Yelovich, & Renaud, 1998; La Greca & Lopez, 1998; Vernberg, Abwender, Ewell, & Beery, 1992).

Delineating the neurobiological mechanisms underlying pediatric anxiety is key for understanding the emergence of anxiety during development, identifying youth at elevated risk for anxiety disorders, and optimizing clinical interventions for youth. Patterns of atypical structure, function, and connectivity of frontolimbic circuitry have been consistently observed in studies of adults with anxiety disorders. Less is known about the developmental neurobiology underlying the emergence of anxiety during development and how it interacts with dynamic changes in frontolimbic circuitry across childhood and adolescence. Identifying these mechanisms and ways in which the neural bases of pediatric and adult anxiety are distinct is critical for developing targeted clinical interventions for children and adolescents. This article reviews altered neurodevelopment associated with pediatric anxiety disorders as a basis for understanding atypical neurobiological patterns associated with fear learning in anxious populations, in addition to discussing future directions for the study of the developmental neurobiology of youth anxiety disorders. Due to the high degree of overlap between the neural circuitry involved in fear and anxiety, we include anxiety disorders and posttraumatic stress disorder (PTSD), which is classified as a Trauma- and Stressor-Related Disorder in DSM-5. Moreover, fear learning is central to the etiology of both anxiety disorders and PTSD, and they likely share many relevant units of analysis (e.g., conditioning, avoidance, anxious arousal) from a Research Domain Criteria (RDoC) perspective (Cuthbert & Insel, 2013).

Atypical Frontoamygdala Circuitry Associated With Anxiety Disorders

The frontoamygdala circuit plays a critical role in fear learning and the etiology of anxiety disorders. The amygdala responds to affectively salient cues and fear-provoking stimuli in the environment, and the PFC regulates amygdala activation. Given the centrality of this circuit to fear processing implicated in anxiety disorders, this article focuses on findings related to atypical patterns of structure, function, and connectivity of the amygdala and PFC associated with anxiety disorders across development.

Amygdala Structure and Function

Studies of adults with anxiety disorders have consistently identified alterations in amygdala volume, though the direction of these findings has been mixed (Hayano et al., 2009; Massana et al., 2003; O'Doherty, Chitty, Saddiqui, Bennett, & Lagopoulos, 2015; Woon & Hedges, 2009). Similarly, findings on structural abnormalities of the amygdala in pediatric anxiety have been inconclusive. Some studies have found larger amygdala volumes in children and adolescents with generalized anxiety disorder (GAD) (De Bellis et al., 2000; Milham et al., 2005), and a study of post-institutionalized children found that increased amygdala volumes predicted anxiety symptomatology and internalizing behaviors (Tottenham et al., 2010). Most recently, anxiety in early childhood was associated with larger amygdala volumes in a sample of typically developing 7- to 9-year-old children, and amygdala morphometry and frontoamygdala structural connectivity predicted individual differences in anxiety levels (Qin et al., 2014). However, previous studies have also shown decreased amygdala volumes for adolescents with mixed anxiety disorders (Mueller et al., 2013; Strawn et al., 2013).

Investigations of adult amygdala function have shown that increased amygdala activation to emotional stimuli is associated with both normative (i.e., state and trait) and pathological anxiety (Bishop et al., 2004; Dickie & Armony, 2008; Etkin et al., 2004; Somerville, Kim, Johnstone, Alexander, & Whalen, 2004; Stein, Simmons, Feinstein, & Paulus, 2007). A meta-analysis across PTSD, social anxiety disorder (SAD), and specific phobias found that patients with these disorders consistently show increased amygdala and insula activity in response to emotionally salient stimuli (Etkin & Wager, 2007). However, there may also be disorder-specific differences in amygdala reactivity. Findings on amygdala function have been less consistent in patients with GAD (Blair et al., 2008; Nitschke et al., 2009). In addition, increased amygdala activity has been more frequently observed in patients with SAD and specific phobias, as compared to PTSD, whereas individuals with PTSD exhibit hypoactivation of the dorsal and rostral ACC and the ventromedial prefrontal cortex (vmPFC) to a greater degree than individuals with SAD or a specific phobia (Etkin & Wager, 2007). Future research will be essential to determine

the extent to which patients with PTSD versus anxiety disorders not tied to specific traumatic events display similar or different neural alterations.

Pediatric anxiety disorders are characterized by a clear pattern of amygdala hyperactivity (Blair et al., 2011; McClure et al., 2007; Monk, 2008; Thomas, Drevets, & Dahl, 2001), and the degree to which anxious youth show increased amygdala activity corresponds to their symptom severity (Killgore & Yurgelun-Todd, 2005; Thomas et al., 2001). Furthermore, adolescents with comorbid anxiety and depression exhibit elevated amygdala reactivity relative to adolescents with depression alone or healthy controls (Beesdo et al., 2009), pointing to patterns of amygdala reactivity that are specific to anxiety disorders. Although there is compelling evidence for altered amygdala activation in children and adolescents with anxiety, two studies did not observe differences in amygdala activation between adolescents with and without GAD (Monk et al., 2006; Strawn, Wehry, DelBello, Rynn, & Strakowski, 2012). Thus, similar to adults, patterns of amygdala function may be disorder-specific in pediatric populations with anxiety.

Prefrontal Cortex Structure and Function

Findings from the literature on adult anxiety highlight hypoactivity of the PFC across a variety of contexts (Goldin, Manber, Hakimi, Canli, & Gross, 2009; Kim et al., 2008; Shin et al., 2005), as well as atypical patterns of prefrontal connectivity (Kim, Gee, et al., 2011; Kim, Loucks, et al., 2011). Higher levels of anxiety have been associated with decreased activity in the vmPFC and increased activity in the dorsomedial PFC (Simmons et al., 2008; Straube, Schmidt, Weiss, Mentzel, & Miltner, 2009). Children and adolescents with GAD show increased activation of the medial PFC, ventral PFC, and ventrolateral (vlPFC) in response to threatening faces, perhaps due to the need for increased modulation of heightened emotional responses, as well as altered connectivity between the vlPFC and amygdala (McClure et al., 2007; Monk, 2008; Monk et al., 2006; Strawn et al., 2012). In addition to children and adolescents diagnosed with anxiety disorders, children and adolescents at risk for anxiety due to higher trait anxiety (Telzer et al., 2008) or a history of behavioral inhibition (Jarcho et al., 2014) also show altered prefrontal activation.

Structural neuroimaging studies have revealed differences in prefrontal cortical regions for specific pediatric anxiety disorders. Compared to healthy controls, children and adolescents with PTSD (7- to 14-year-olds) have larger prefrontal gray matter volumes but no difference in white matter volume (Richert, Carrion, Karchemskiy, & Reiss, 2006). In contrast, comparing adolescents with mixed anxiety disorders and comorbid depression to adolescents with only depression, youth with co-occurring anxiety had decreased gray matter volumes in the dorsolateral PFC (Wehry et al., 2015). A longitudinal study of associations between subclinical anxiety levels and vmPFC thickness across development also casts light on neurobiological risk for anxiety. Specifically, subclinical anxiety and depression symptoms were negatively correlated with vmPFC thickness for children but positively correlated for adolescents. Furthermore, a slower

rate of vmPFC cortical thinning was observed among children and adolescents with higher rates of anxiety and depression (Ducharme et al., 2014).

Anterior Cingulate Cortex Structure and Function

Studies of adults with anxiety disorders have identified heightened, persistent activation of the dorsal ACC (Paulesu et al., 2010), which is involved in threat processing, and decreased engagement of the rostral ACC, which is involved in inhibiting the fear response (Etkin, Prater, Hoeft, Menon, & Schatzberg, 2010). Structurally, anxious participants with comorbid depression have smaller subgenual ACC volumes than patients with only depression (Jaworska et al., 2016).

In line with these findings, pediatric anxiety disorders have been characterized by atypical structure and function of the ACC (Schienle, Ebner, & Schäfer, 2010). Anxious children and adolescents have shown greater ACC activation than healthy controls in response to threatening faces (Blair et al., 2011; McClure et al., 2007; Mcclure & Pine, 2015; Monk, 2008), possibly due to the need to modulate heightened amygdala reactivity. Adolescents and adults with social phobia have shown increased rostral ACC activation to angry and fearful faces but not to neutral faces, relative to healthy controls (Blair et al., 2011). Anxious children have also shown altered integration of activation across the ACC and limbic regions during disengagement from threat (Price et al., 2014). Among pediatric anxiety patients, higher intolerance for uncertainty has been associated with increased activation of the amygdala and rostral and subgenual ACC (Krain et al., 2008), suggesting that activation of frontal and limbic structures may also vary depending on specific symptom profiles of anxiety across development.

Atypical Frontoamygdala Connectivity

Studies of adults with anxiety disorders have consistently documented a pattern of altered frontoamygdala connectivity, paralleled by patterns of amygdala hyperactivity and prefrontal hypoactivity (Rauch et al., 2006; Shin et al., 2005). In adults, top-down regulation of the amygdala by the PFC is associated with reduced anxiety (Hariri et al., 2002; Pezawas et al., 2005). These findings extend to normative variation in anxiety in adults without psychiatric diagnoses. Higher self-reported trait anxiety in healthy adults has been associated with weaker functional (Kim, Gee, Loucks, Davis, & Whalen, 2011) and structural (Kim & Whalen, 2009) connectivity between the amygdala and medial PFC.

Children and adolescents with anxiety also exhibit atypical patterns of connectivity between the amygdala and various frontal regions, with some evidence for disorder-specific abnormalities. Compared to healthy controls, adolescents with GAD exhibit less negative coupling between the right vlPFC and the amygdala in response to masked angry faces (Monk, Telzer, Mogg, et al., 2008), suggesting that weaker regulatory connectivity may be implicated in generalized anxiety. In contrast, children with social

phobia show increased amygdala activation and increased vlPFC-amygdala connectivity while waiting to interact with social partners they deemed undesirable (Guyer et al., 2008). The differences between these studies might indicate disorder-specific connectivity patterns but could also be due to task-related differences. Research has further documented altered connectivity between the amygdala and other limbic structures in pediatric anxiety. For example, connectivity of the amygdala with the insula and superior temporal gyrus increases with higher anxiety symptomatology among adolescents with GAD (Roy et al., 2013) and other studies have identified increased connectivity of the amygdala with the insula (McClure et al., 2007) and with the posterior cingulate cortex (McClure et al., 2007; Strawn, Wehry, DelBello, Rynn, & Strakowski, 2012) in anxious children and adolescents. Altered amygdala connectivity is also evident in adolescents at risk for anxiety disorders—adolescents with BI show greater connectivity between the amygdala and the dorsolateral PFC and anterior insula (Hardee et al., 2013).

Examinations of age-related change in connectivity suggest that the timecourse of amygdala connectivity also deviates from typical development in youth with anxiety disorders. Healthy controls (ages 8–18) show age-related increases in amygdala connectivity with the vlPFC during threat processing, whereas children and adolescents with PTSD display age-related decreases in amygdala-vlPFC connectivity during threat processing (Wolf & Herringa, 2016). Across both normative and pathological anxiety, amygdala connectivity with regions including the ACC and medial PFC is also altered across development. Functional connectivity between the ACC and amygdala has been found to differ by age during typical development such that younger participants show positive connectivity as they view fearful faces, with a switch to negative (more regulatory) frontoamygdala connectivity around the transition to adolescence (Gee et al., 2013). The developmental switch in frontoamygdala connectivity mediated normative declines in separation anxiety (Gee et al., 2013), suggesting that increasing top-down control of the amygdala by frontal regions may help to regulate anxiety with age. This same circuit was recently implicated in a study of anxious patients that observed a group-by-age interaction in connectivity. Specifically, typically developing children and adolescents show increasingly negative amygdala-ACC connectivity to happy, angry, and fearful faces with age. By contrast, patients with anxiety show increasingly positive connectivity with age, such that adults with anxiety had more positive ACC-amygdala connectivity than healthy adults (Kujawa et al., 2016). These findings suggest a significant deviation in the trajectory of typical frontoamygdala connectivity development and may reflect impairments in top-down regulation that underlie the development of anxiety disorders.

In addition to task-based alterations in functional connectivity, several studies have employed resting-state functional magnetic resonance imaging to examine network connectivity in children and adolescents with anxiety and stress-related disorders. The majority of these studies have focused on amygdala connectivity and find that pediatric anxiety is associated with patterns of increased connectivity between the amygdala, particularly the basolateral amygdala, and neural systems implicated in emotion, attention, and perception, such as the sensory-perceptual association cortex, dorsal

frontoparietal network, ventral striatum, insula, cerebellum, and vmPFC at rest (Qin et al., 2014; Roy et al., 2013). Representing a promising new direction in this line of research, machine learning algorithms have been used to reveal predictive associations between amygdala functional connectivity at rest and individual differences in the severity of anxiety symptomatology during childhood (Qin et al., 2014). Although fewer studies have examined aberrant patterns of connectivity in large-scale networks such as the default mode network (DMN), one study showed hypoconnectivity between the left amygdala and posterior cingulate cortex, a central hub in the DMN, in pediatric anxiety (Hamm et al., 2014). Another study found that contrary to reduced within-network connectivity of the DMN in adults with PTSD (e.g., Sripada et al., 2012), youth with PTSD exhibit increased connectivity within the DMN (Patriat, Birn, Keding, & Herringa, 2016). Future research should aim to build upon the limited body of research on the role of large-scale networks in pediatric anxiety (Sylvester et al., 2012).

Fear Conditioning

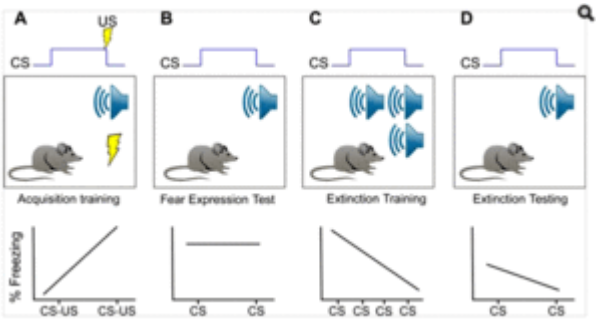

Figure 1. Diagram of fear conditioning and extinction paradigm. Standard fear conditioning procedure for rodent studies used to study the acquisition and extinction of the learned fear response: (A) During the acquisition phase of fear conditioning, a neutral stimulus (the CS) is presented with an aversive UCS (e.g., shock). The repeated pairing of the neutral stimulus and the UCS results in learning that the CS predicts the UCS. (B) Following fear acquisition, the neutral stimulus becomes a CS such that the autonomic and behavioral responses (e.g., freezing) to the UCS become a CR observed in response to the CS alon0065. (C) During fear extinction, the CS is repeatedly presented without the UCS. (D) Through repeated presentations of the CS without the UCS, the CR will gradually decline.

Source: From Morrison and Ressler (2014).

Given the significant body of evidence highlighting disruptions in the frontoamygdala circuit in pediatric anxiety disorders, it is critical to examine how these atypical patterns of neurobiological development may affect behavioral and cognitive processes. Clinical anxiety and stress-related disorders are characterized by disruptions in fear learning, including conditioning and extinction, that are theorized to play a central role in the etiology of anxiety disorders (Rosen & Schulkin, 1998). Although there are other behavioral processes that are highly relevant to anxiety disorders, such as information processing (see Lau & Waters, 2017 for a review) and avoidance (see Krypotos, Effting, Kindt, & Beckers, 2015; and LeDoux, Moscarello, Sears, & Campese,

2017, for reviews), the current review specifically summarizes key findings related to atypical patterns of fear learning and related neurobiology in anxiety disorders. Frontoamygdala circuitry that supports fear learning is highly conserved across species, providing a strong foundation upon which to bridge animal and human studies to understand the neurobiological bases of anxiety disorders during development (Birn et al., 2014; Pine, 2007). Moreover, fear conditioning and related frontoamygdala circuitry have been a primary focus of research on children and adolescents with anxiety disorders (Pattwell et al., 2012; Phelps & LeDoux, 2005).

Classical fear conditioning paradigms involve the presentation of a neutral stimulus that is contingently paired with an aversive stimulus (the unconditioned stimulus, UCS) which, when presented alone, elicits an autonomic and behavioral response. Over time, the repeated pairing of the neutral stimulus and the UCS results in learning that the neutral stimulus predicts the UCS (during a phase known as fear acquisition). Following fear acquisition, the neutral stimulus becomes a conditioned stimulus (CS) such that the autonomic and behavioral responses to the UCS become a conditioned response (CR) observed in response to the CS alone. During fear extinction, the CS is presented without the UCS such that the presentation of the CS no longer elicits a CR (see Figure 1). See Shechner, Hong, Britton, Pine, and Fox (2014) for an in-depth review of fear conditioning and extinction across development.

Contributions From Animal Literature

Seminal findings from conditioning studies in animals first highlighted the amygdala as a critical structure for coordinating the response to threatening external stimuli (LeDoux, 1996, 2003; Phillips & LeDoux, 1992). Animal models have suggested that the amygdala mediates the acquisition phase of fear conditioning but that amygdala activity decreases once the association between the CS and the UCS is established (Büchel & Dolan, 2000). The vmPFC and hippocampus integrate input from other brain structures and modulate amygdala activity to facilitate later phases of fear conditioning (Sierra-Mercado, Padilla-Coreano, & Quirk, 2011). Studies in developing rodents led to the identification of developmental changes in fear conditioning in non-human animals. Around postnatal day 10, rats exhibit an increase in amygdala activation to threatening stimuli, which results in a switch from an approach response to aversive stimuli and the initiation of fear conditioning (Landers & Sullivan, 2012; Moriceau & Sullivan, 2004).

Contributions From Human Literature

Fear conditioning in adults. Providing evidence for the conservation of neurobiological mechanisms underlying fear conditioning across species, human fear-conditioning research conducted in healthy samples has found evidence that fear learning relies on interactions between the amygdala—responsible for identifying and responding to

emotionally salient stimuli (e.g., fear cues)—and the hippocampus—involved in encoding associations between stimuli and contextual factors during fear learning (Corcoran & Quirk, 2007; Sehlmeyer et al., 2009; Weike et al., 2005).

Comparisons of fear conditioning between anxious and non-anxious adult samples have yielded mixed findings. A meta-analysis of fear conditioning in adult anxiety disorders found a modest increase in fear acquisition among adults with anxiety in non-discriminative fear conditioning paradigms (Lissek et al., 2005). Differences have not typically been observed for discriminative conditioning paradigms that directly contrast a CS+, which predicts the UCS, and a CS-, which predicts no UCS (Lissek et al., 2005); however, adults with anxiety disorders have been found to show relatively increased fear responses to safety cues compared with control participants during fear acquisition (Duits et al., 2015). Relative to healthy controls, adults with anxiety disorders display increases in amygdala and hippocampal activation in response to the CS+ during fear conditioning (Schneider et al., 1999) and lower activation of the subgenual ACC and the vmPFC when appraising threat during fear conditioning (Britton et al., 2013). These findings suggest that anxious adults show heightened amygdala activation and decreased activation of regulatory structures that suppress amygdala activation, such as the vmPFC.

Fear conditioning in children and adolescents. Children as young as two years of age have shown the ability to discriminate between a CS+ and CS- (Ingram & Fitzgerald, 1974), but the CR increases with age across development (Gao, Raine, Venables, Dawson, & Mednick, 2010; Glenn et al., 2012). In a study of 5- to 10-year-old children that paired a loud, unpleasant alarm sound with an animated bell, older children reported more fear to the CS+, more accurately discriminated between the CS+ and CS morphs, and had better contingency awareness of the relationship between the CS+ and the UCS than younger children (Michalska et al., 2016). However, changes in fear conditioning are nonlinear and extend into adolescence—adolescents (ages 10–17) show less differential fear than adults in response to the CS+, as compared to the CS- (Lau et al., 2011). Importantly, there are few studies that directly compare fear conditioning across the broader developmental span of childhood, adolescence, and adulthood.

On a neural level, evidence suggests that amygdala reactivity generally decreases across development (Decety, Michalska, & Kinzler, 2012; Gee et al., 2013; Silvers, Shu, Hubbard, Weber, & Ochsner, 2014; Swartz, Carrasco, Wiggins, Thomason, & Monk, 2014; Vink, Derks, Hoogendam, Hillegers, & Kahn, 2014) and that the amygdala becomes less central to fear learning over time (LaBar et al., 1998). Adolescents recruited early-maturing subcortical regions (e.g., amygdala and hippocampus) to a greater degree than adults when distinguishing between the CS+ and CS-, and adults' self-reported fear ratings related to activation during fear learning in later-maturing structures such as the dorsolateral PFC, further evidencing shifts in fear learning across typical development (Lau et al., 2011).

Despite changes during typical development and the hypothesized role of altered fear learning in the etiology of anxiety disorders, results have been inconsistent with regard to group differences in fear conditioning between anxious and non-anxious youth (Craske et al., 2008; Lau et al., 2008; Shechner et al., 2015; Waters, Henry, & Neumann, 2009). Anxious children and adolescents resemble healthy controls in their conditioning to the CS+ versus the CS-, although anxious youth report higher fear ratings and show heightened physiological reactivity (e.g., anticipatory skin conductance response (SCR)) during conditioning (see Lissek et al., 2005, for a review). For example, in a sample of adolescents, anxious participants reported higher fear ratings to both the CS+ and the CS- compared to healthy controls, although there was no interaction between group and stimulus type (i.e., no evidence of differential conditioning) (Lau et al., 2008). Similar findings were observed using SCR in anxious and non-anxious children who were conditioned to geometric figures (Craske et al., 2008; Waters et al., 2009). These results suggest that although anxious children and adolescents may show heightened physiological responses, and self-reported fear ratings during conditioning, they do not show alterations in differential conditioning.

Fear Extinction

Contributions From Animal Literature

During fear extinction, the presentation of the CS+ without the UCS weakens this association, resulting in a decreased CR over time. Animal studies have highlighted the central roles of the amygdala, vmPFC, and hippocampus in extinction learning and recall, with each having a distinct role across differing contexts and developmental periods. Extinction relies more centrally on amygdala functionality earlier in development, with a switch to increased dependence on a broader network of amygdala, vmPFC, and hippocampal functionality later in development (Kim & Richardson, 2010; Milad & Quirk, 2002; Sierra-Mercado et al., 2011). Notably, the capacity for fear extinction learning and associated vmPFC function changes non-linearly across development. Rodents have shown attenuated extinction during adolescence (Kim & Richardson, 2010; McCallum, Kim, & Richardson, 2010; Pattwell et al., 2012), with altered synaptic plasticity of the vmPFC as a potential mediator of this non-linear trajectory (Pattwell et al., 2012). Changes in hippocampal maturity and its role in contextual fear learning and extinction may also play a role in developmental differences in extinction learning (e.g., Delamater, 2004; Rudy & Morledge, 1994). These dynamic changes in frontolimbic circuitry have significant implications for effective extinction learning at distinct developmental periods.

Contributions From Human Literature

Studies of fear extinction in adults. The amygdala, hippocampus, vmPFC, and ACC are involved in extinction learning in adulthood (Gottfried & Dolan, 2004; Kalisch et al., 2006; Phelps et al., 2004). Whereas amygdala activation has been primarily implicated in early extinction, the vmPFC is involved in the retention of extinction (Delgado, Nearing, LeDoux, & Phelps, 2008; Hartley, Fischl, & Phelps, 2011; Kalisch et al., 2006; Milad et al., 2007; Phelps et al., 2004). See Figure 2 for a depiction of the neural structures underlying fear extinction (Quirk & Mueller, 2008).

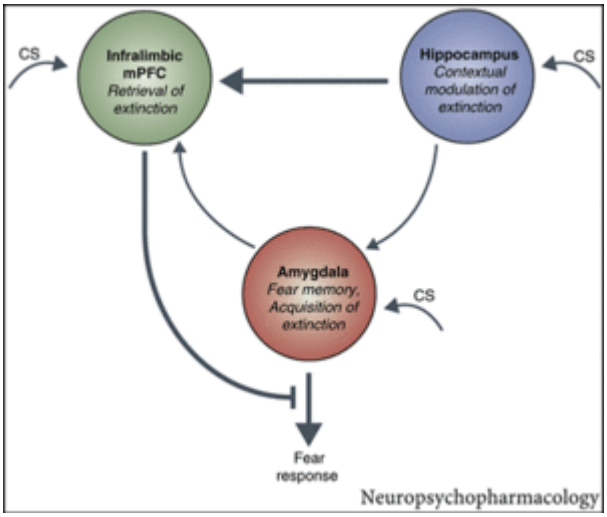

Figure 2. Frontolimbic circuitry underlying fear extinction. Fear extinction relies on the amygdala, hippocampus, and mPFC, with each having a distinct role across differing contexts and developmental periods. Extinction relies more centrally on amygdala functionality earlier in development, with a switch to increased dependence on a broader network of amygdala, vmPFC, and hippocampal functionality later in development.

Source: From Quirk and Mueller (2008).

Clinical anxiety disorders are characterized by disruptions in adaptive fear learning processes, including activation of the fear response that persists in the absence of threat. Adults with anxiety disorders consistently display impairments in fear extinction including heightened SCR during extinction (Michael, Blechert, Vriends, Margraf, & Wilhelm, 2007; Duits et al., 2015), resistance to extinction (Orr et al., 2000), and deficits in extinction recall (Milad et al., 2008, 2009). For example, adults with PTSD exhibit a greater attention bias toward threat and heightened fear-potentiated startle (FPS) to the CS+ during acquisition and early extinction trials, delineating a possible mechanism linking attention biases to threat and trauma-related cues (e.g., McNally, Kaspi, Riemann, & Zeitlin, 1990) and altered fear and extinction learning characteristic of PTSD (Fani et al., 2012). On a neural level, hypoactivity of the vmPFC and hyperactivity in the dorsal ACC may underlie extinction deficits in adults with PTSD (Milad et al., 2009).

Studies of fear extinction in children and adolescents. Cross-species research in mice and humans has found that fear extinction is attenuated in adolescence, compared to childhood and adulthood (Pattwell et al., 2012). Within a narrower age range of childhood (5- to 10-year-olds) in humans, extinction does not appear to differ by age (Michalska et al., 2016). Whether anxious youth show atypical patterns of extinction remains unclear.

Several studies have found that anxious children are more resistant to within-session extinction than healthy controls (Craske et al., 2008; Liberman, Lipp, Spence, & March, 2006; Pliszka, Hatch, Borcherding, & Rogeness, 1993; Waters et al., 2009). For example, anxious children have shown larger orienting and anticipatory SCRs to both the CS+ and CS- during extinction, which persisted up to two weeks later during extinction recall (Craske et al., 2008). Anxious children have also been found to exhibit poorer extinction than healthy controls, despite no differences in self-reported fear ratings (Waters et al., 2009). Other studies, however, have reported no difference in their ability to extinguish the fear response relative to non-anxious children (Britton et al., 2013; Lau et al., 2008; Shechner et al., 2015), though anxious children have reported higher fear during extinction (Shechner et al., 2015). Neurally, anxious children show lower subgenual ACC activation than healthy controls during extinction recall (Britton et al., 2013).

Despite mixed results regarding extinction learning across anxious and healthy samples, there may be key shifts in extinction learning during development (Glenn et al., 2012; Jovanovic et al., 2014) that are dependent on individuals' level of anxiety. In a study of trauma-exposed children, children under 10-years-old show poorer discrimination between the CS+ and CS-, as compared to their older counterparts (Jovanovic et al., 2014). Whereas higher anxiety was associated with reduced FPS during extinction in 8- to 9-year-olds, higher anxiety was associated with increased FPS in children 10- to 13-years-old. These findings point to key developmental differences and underscore abnormalities in learning and extinction as potential risk factors for pediatric anxiety disorders (Jovanovic et al., 2014). In addition to studies of fear extinction, recent research has focused on aberrant patterns of fear response to safety cues in adolescents diagnosed with anxiety disorders. Preliminary findings in this area suggest that the association between age and activation of the PFC differs across age such that adolescents with anxiety disorders exhibit a more negative association between age and PFC activation in response to the CS-, relative to the comparison group (Haddad et al., 2015).

Generalization of the Fear Response

One potential mechanism underlying poor discrimination between threat and safety cues in anxiety is the overgeneralization of the fear response to stimuli resembling the CS. For decades, animal and human studies have noted that the CR can generalize to graded stimuli that resemble the CS (Honig & Urcuioli, 1981; Pavlov & Anrep, 2003). This generalization can be an adaptive response that allows individuals to efficiently avoid danger by classifying new stimuli based on previously learned associations between the CS+ and aversive experiences. However, the transfer of fear to new stimuli without sufficient discrimination between the CS and stimuli resembling the CS can be maladaptive (Lissek, 2012; Lissek & Grillon, 2010). Adults with anxiety disorders show impairments in their discrimination between threat and safety cues (Fani et al., 2012; Jovanovic, Kazama, Bachevalier, & Davis, 2012). A meta-analysis identified

overgeneralization of the fear response as one of the central differences in fear conditioning between healthy and anxious adults, positing that it represents a core mechanism underlying the etiology of pathological anxiety (Lissek et al., 2005).

Adult neuroimaging studies have revealed that the vmPFC plays a central role in threat processing by coordinating interactions between the prefrontal attentional network, the hippocampus and parahippocampal gyrus, the thalamus, and the amygdala (Bishop, Duncan, & Lawrence, 2004; Cross, Brown, Aggleton, & Warburton, 2013; Kalisch et al., 2006; Milad et al., 2007; Mitchell & Gaffan, 2008; Parnaudeau et al., 2013; Sierra-Mercado et al., 2011). This coordinated network mediates the fear response (Phelps, Delgado, Nearing, & LeDoux, 2004; Sierra-Mercado et al., 2011). Empirical studies of aberrant neurobiological mechanisms underlying the overgeneralization of fear in adult patients with GAD have revealed abnormal patterns of vmPFC activation and connectivity in response to both threat and safety cues (Cha et al., 2014; Greenberg, Carlson, Cha, Hajcak, & Mujica-Parodi, 2013).

Evidence from limited developmental work in this area suggests that fear generalization differs as a function of age. When a generalization stimulus (GS) was included in a fear learning paradigm with healthy 8- to 13-year-olds, FPS in older children increased sequentially from CS- to GS to CS+ (similar to adults), in contrast to younger children who show greater FPS to the CS-, as compared to the GS (Glenn et al., 2012). Caregiver-related factors may play an important role in predicting differential responses to threat and safety cues; this effect may be particularly significant during childhood, when parental factors are especially salient in both typically developing and trauma-exposed youth (Gee et al., 2014; Kujawa, Glenn, Hajcak, & Klein, 2015; Rooij et al., 2016). Deficits in discrimination between stimuli may predate the development of anxiety disorders—elevated startle reflex to safe conditions (in the context of safe and threatening cues) predict the longitudinal onset of anxiety disorders for adolescents (Craske et al., 2012; Kujawa, Glenn, Hajcak, & Klein, 2015), and high levels of anxiety symptomatology are associated with adolescents' failure to demonstrate differential startle responses to safety and threat cues (Kadosh et al., 2015). Similarly, controlling for age and trauma exposure in a sample of 8- to 13-year-old children, overgeneralization of the fear response (FPS to both threat and safety cues) predicted trait anxiety (Jovanovic et al., 2014) and anxious adolescents did not show differential patterns of fear potentiated startle to threat and safety cues. Together, these findings highlight fear overgeneralization as a potential mechanism of risk for anxiety in developmental contexts.

Reconsolidation of Fear Memories

A promising line of animal research suggests that fear memories are labile and can be successfully updated with non-fearful information (Dudai, 2006; Monfils, Cowansage, Klann, & LeDoux, 2009; Nader, Schafe, & Le Doux, 2000). Extension of these findings to humans found that extinction trials conducted during the reconsolidation window of an old fear memory prevented spontaneous return of the fear memory, with the effect still evident one year later (Schiller et al., 2010). These studies of the reconsolidation of fear memories suggest that this process updates the initial fear memory with new safety information, which diminishes subsequent fear responses.

Extending this research to developmental contexts, despite adolescents' poorer performance on extinction relative to adults, adolescents who underwent reconsolidation update (i.e., who were reminded of the CS-US association before performing extinction) show significant reductions in fear the following day, as compared to adolescents who performed extinction without the reminder (Johnson & Casey, 2015). Rodent and human studies investigating the neural mechanism underlying fear reconsolidation have implicated the amygdala (Dębiec & Ledoux, 2004; Duvarci & Nader, 2004; Monfils et al., 2009; Nader et al., 2000) independent of PFC involvement (Agren et al., 2012; Schiller et al., 2010), suggesting that the reconsolidation process may have important applications to clinical interventions for adolescents, who show protracted development of the PFC and attenuated extinction (McCallum et al., 2010; Pattwell et al., 2012).

Future Directions

In summary, alterations in frontolimbic connectivity are likely to play a central role in the etiology and maintenance of pediatric anxiety disorders. Pediatric patients with anxiety disorders show alterations in the structure and function of frontolimbic circuitry. Children and adolescents with anxiety disorders typically have larger amygdala volumes than their non-anxious peers and show amygdala hyperactivity that parallels the severity of symptomatology. Abnormalities in the PFC and ACC, and their connections with the amygdala, have also been implicated in pediatric anxiety. Central to the etiology of anxiety disorders, the frontoamygdala circuit plays a key role in fear learning. To date, behavioral studies of fear conditioning and extinction, as well as investigations of the neural correlates of these processes, have yielded mixed results when comparing anxious and non-anxious youth.

Future scientific efforts should focus on further delineating the neurodevelopmental underpinnings of anxiety by employing longitudinal, developmentally informed studies to identify abnormalities in neural structure, function, and circuitry associated with pediatric anxiety disorders, as well as in those at risk for anxiety. Such studies should also

aim to delineate neural mechanisms underlying additional behavioral processes that are relevant to pediatric anxiety disorders, such as avoidance and attention biases. Finally, future research that translates the emerging understanding of the neurobiological bases of pediatric anxiety disorders will be critical to target interventions for particular developmental stages. Specifically, research that marries developmental neuroscience with clinical intervention by delineating neural predictors of treatment response and the neurobiological mechanisms of treatment efficacy has the potential to greatly facilitate the optimization of treatments for children and adolescents with anxiety.

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