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A Systems Neuroscience Approach to the Pathophysiology of Pediatric Mood and Anxiety Disorders

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Abstract

Emotional dysregulation is a core feature of pediatric mood and anxiety disorders. Emerging evidence suggests that these disorders are mediated by abnormalities in the functions and structures of the developing brain. This chapter reviews recent behavioral and functional magnetic resonance imaging (fMRI) research on pediatric mood and anxiety disorders, focusing on the neural mechanisms underlying these disorders. Throughout the chapter, we highlight the relationship between neural and behavioral findings, and potential novel treatments. The chapter concludes with directions for future research.

Keywords

Pediatric mood and anxiety disorders; fMRI; Attention orienting; Face emotion processing; Reward processing; Cognitive control

1 Introduction

Mood and anxiety disorders are developmental illnesses (Leonardo and Hen 2008; Miklowitz and Cicchetti 2010; Pavuluri and Passarotti 2008) that are either fully expressed in childhood or adolescence or present in adults following childhood antecedents (Costello et al. 2003; Kessler et al. 2005). Despite the high prevalence and burden of psychiatric disorders (Costello et al. 2003; Merikangas et al. 2009), effective treatments are limited.

Developing a better understanding of the pathophysiology of mood and anxiety disorders holds great promise for identifying targets for novel therapeutics.

From a neuroscience perspective, emotion is mediated by approach and withdrawal systems, with partially overlapping neural circuits that underlie positive and negative affect (Davidson and Irwin 1999; Davidson et al. 2000). Emotion regulation, broadly defined, encompasses “any process that maintains, accentuates, or attenuates emotional responses” (Davidson et al. 2000). Since emotion dysregulation is a core deficit in mood and anxiety disorders, understanding the neural correlates of emotion regulation in health and disease can provide insights into the development and maintenance of these disorders.

Neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), allow investigators to probe the neural activity of emotional processing in real time. fMRI is particularly suited for studies in the developing brain, as it is noninvasive and safe for children and adolescents. Neuroimaging research, combined with clinical and behavioral data, can help elucidate aberrant brain development, thereby facilitating the development of innovative neurobiologically informed treatments for psychiatric disorders.

This chapter focuses on a categorical approach to psychopathology, as the majority of existing clinical research and practice adopts a categorical (i.e., diagnostic) approach. Indeed, categories are needed when treatment and research recruitment decisions have to be made, e.g., who to treat and with what agent. A dimensional approach, however, is also worthwhile and is complementary to a categorical approach in mapping individual variation in neural dysfunction to individual differences in behavioral phenotypes. Future work should continue to pursue both approaches. Here, we provide a selective review of behavioral and fMRI data elucidating neural mechanisms mediating pediatric mood and anxiety disorders, focusing on anxiety disorders, major depressive disorder (MDD), and bipolar disorder (BD). Specifically, for each disorder, we center the discussion on the neural mechanisms mediating psychological domains in which there are prominent illness-related impairments. We conclude the section on each disorder by discussing the implications of neuroimaging research for treatments, and we end the chapter by offering directions for future research.

2 Anxiety and Mood Disorders

2.1 Anxiety Disorders

2.1.1 Clinical Presentation and Behavioral Deficits—Anxiety disorders, including generalized anxiety disorder (GAD), social anxiety disorder, and separation anxiety disorder, are a group of clinical syndromes characterized by extreme distress or avoidance when facing potential threat (Pine 2007; Pine and Klein 2008). Approximately one out of five individuals are affected by anxiety disorders (Pine and Klein 2008), and the disorders often begin in childhood, by age 11 (Kessler et al. 2005). The manner in which emotional information is attended to, interpreted, and responded to play a crucial role in the etiology and maintenance of anxiety disorders (Beck and Clark 1997; Wells and Matthews 1994). Using a variety of behavioral paradigms tapping information processing deficits, research has demonstrated anxiety-specific behavioral impairments. Because considerable work has linked individual differences in anxiety to individual variation in *attention orienting and*

reward processing (Pine 2007; Shechner et al. 2012), this chapter focuses on these two aspects of information processing and the corresponding neural correlates.

2.1.2 Attention Orienting—Dysfunction in attention allocation to threat is implicated in pediatric anxiety disorders (Pine 2007; Pine et al. 2009). To examine deficits in threat-related attention orienting, the dot-probe task has been used widely in research, generating measures for biases toward or away from threatening stimuli. In a typical dot-probe task (Fig. 1), two facial expressions are presented simultaneously, one angry (threat-related) and the other neutral. These are followed by a visual probe which replaces one of the faces. Participants are asked to respond quickly to the probe without compromising accuracy. A faster reaction time to the probe replacing threat-related stimuli (congruent trials), relative to the probe replacing neutral stimuli (incongruent trials), indicates an attentional bias *toward* threat. In contrast, a faster reaction time to the probe replacing neutral stimuli (incongruent trials), relative to the probe replacing threat-related stimuli (congruent trials), indicates an attentional bias *away* from threat.

Behavioral findings: Perturbations in threat-related attention orienting represent some of the most replicated findings in individuals with anxiety (for reviews, see Bar-Haim et al. 2007; Pine 2007; Shechner et al. 2012). Anxious adults, relative to nonanxious adults, exhibit an attentional bias *toward* threat (for a meta-analysis, see Bar-Haim et al. 2007). Although less consistent, research in youth also suggests a bias *toward* threat as a key behavioral marker of pediatric anxiety (Roy et al. 2008; Shechner et al. 2012; Waters et al. 2008). A recent eye-tracking study confirms that, compared to typically developing youths, anxious youths are more likely to direct their initial attention toward angry faces than neutral faces, and are faster to do so (Shechner et al. 2013). Collectively, these behavioral findings validate the clinical observation that pediatric anxiety is characterized by abnormal distress and excessive vigilance toward minor threats.

fMRI findings: Neuroimaging can be used to elucidate the neural circuitry mediating disorder-relevant deficits quantified by standardized behavioral paradigms. Research has emerged to link brain function to anxiety-related behavioral deficits such as attention biases using fMRI. Two highly connected anatomical regions are of particular importance: (a) the amygdala, a central structure implicated in emotional processing (Cardinal et al. 2002; LeDoux 2000) and attention regulation in threat response behavior (Pine 2007); and (b) ventro-lateral prefrontal cortex (vlPFC), involved in modulation of fear (Quirk and Gehlert 2003), as well as response inhibition and cognitive flexibility (Casey et al. 2001; O'Doherty et al. 2003).

Recent research suggests that anxiety disorders are associated with dysfunction in threat circuits encompassing these two regions (McClure et al. 2007b; Monk et al. 2006, 2008; Stein et al. 2002; Straube et al. 2004). Specifically, fMRI studies using slight variants of the dot-probe task demonstrate that adolescents with GAD, relative to healthy controls, exhibit greater amygdala activation during rapid and unconscious processing of threat (Monk et al. 2008) and increased vlPFC activation during prolonged processing of threat (Monk et al. 2006). Moreover, amygdala activation positively predicts attention bias and clinical measures of anxiety severity (Monk et al. 2008), underscoring the critical role that amygdala

plays in detecting threat. Greater vIPFC activation, in contrast, is related to lower severity in anxiety symptoms (Monk et al. 2006), supporting the regulatory role of vIPFC.

By manipulating the length of the exposure to threatening stimuli (500 ms in Monk et al. 2006; 17 ms in Monk et al. 2008), researchers can isolate immediate, rapid, implicit processing from later, more elaborated, explicit attentional and behavioral responses to threatening stimuli. Overall, amygdala activation in pediatric anxiety may reflect processes associated with rapid anxiety-related emotional responses (Monk et al. 2008; Pine et al. 2008). In contrast, vIPFC activation in anxious youth may reflect processes linked to modulation of amygdala activity, regulation of emotional responses to anxiety-provoking stimuli (Monk et al. 2006; Pine et al. 2008), and attention orienting from threat to goal-relevant stimuli (Britton et al. 2012). Together, these findings suggest that anxiety disorders are associated with disturbances in the amygdala-vIPFC circuit, a conclusion which is also supported by functional connectivity data (McClure et al. 2007b) and data indicating disorder-related structural changes in the amygdala and ventral and medial prefrontal cortex (PFC) (Drevets 2001; Rauch et al. 2003).

2.1.3 Reward Processing

Behavioral findings: Reward-related tasks have also been used to examine anxiety-related behavioral deficits. Rewards, like threats, are motivationally salient stimuli that capture attention (Bar-Haim et al. 2009; Shechner et al. 2012). Thus, reward-related tasks allow for probing a deficient allocation of attentional resources toward rewarding stimuli. Additionally, many individuals with anxiety disorders are hypersensitive to performance concerns and exhibit enhanced response monitoring (Ladouceur et al. 2006; McDermott et al. 2009). Such heightened performance monitoring and concerns may be accentuated in reward tasks when rewards are contingent upon task performance (Bar-Haim et al. 2009; Helfinstein et al. 2011, 2012).

Peer acceptance represents the most salient type of rewards in adolescence (Crone and Dahl 2012). Using paradigms incorporating peers as a social reward, researchers have begun to investigate the effects of social factors on affective and reward processing in adolescents. For example, in a “chat room” paradigm, adolescents are led to believe that they are interacting with peers over the internet (Guyer et al. 2008, 2009, 2012a). Relative to healthy adolescents, those with social anxiety evince similar levels of interest in peers on subjective ratings. However, socially anxious adolescents anticipate that their peers will give them low desirability ratings as a chat mate (Guyer et al. 2008). These findings are consistent with the observation that adolescents with high levels of social anxiety have a fear of negative evaluation and feel less accepted by peers and less attractive to others (La Greca and Lopez 1998).

fMRI findings: Paradigms such as the “chat room” afford researchers an opportunity to investigate the neural correlates of reward processing of ecologically valid and salient stimuli such as peer acceptance. Recent fMRI research implicates several brain regions in reward processing, including the amygdala and vIPFC that are recruited during attention orienting (Pine et al. 2009) and the striatum, which plays a central role in coding information

about rewarding stimuli (Delgado 2007; Schultz et al. 1992). During this paradigm, socially anxious adolescents exhibit greater amygdala activation than healthy adolescents when anticipating evaluation from negatively perceived peers (Guyer et al. 2008). In addition, functional connectivity analysis indicates that higher amygdala activation is related to greater vIPFC activation (Guyer et al. 2008), again validating the importance of the amygdala-vIPFC circuit in attention modulation (Miller and Cohen 2001) and behavioral flexibility (Budhani et al. 2007) in emotional contexts.

Risk for anxiety disorders or anxiety itself is manifest as dysfunction in the reward circuit, even when behavioral task performance appears to be intact. For instance, evidence suggests that striatal hyperactivation is associated with social phobia and behavioral inhibition [a temperament style that confers risk for anxiety disorders (Fox et al. 2005)] (Bar-Haim et al. 2009; Guyer et al. 2006, 2012a), even though behavioral differences between affected youths and healthy controls in reward processing of *monetary incentives* have not been documented (Bar-Haim et al. 2009; Guyer et al. 2006, 2012a). This suggests that neural measures may be more sensitive to between-group differences than behavioral measures (Beesdo et al. 2009; Wilkinson and Halligan 2004), highlighting the merits of neuroimaging data in complementing clinical and behavioral data.

2.1.4 Implications—The behavioral and fMRI data reviewed above have generated important insights into the development and refinement of treatments for anxiety disorders. For example, attention bias modification therapy (ABMT), which trains attention *away* from threat or *toward* positive stimuli, has shown promising results in both adult (Hakamata et al. 2010) and pediatric anxiety (Eldar et al. 2012; Waters et al. 2013). ABMT reduces attention bias to threat (Eldar et al. 2012) and increases attention bias toward positive stimuli (Waters et al. 2013) while reducing anxiety symptoms and clinical severity ratings in children with anxiety disorders (Eldar et al. 2012; Waters et al. 2013). Furthermore, changes in attention orienting appear to predate decreases in anxiety (Eldar et al. 2012; Waters et al. 2013). This suggests that attention bias is not an epiphenomenon of anxiety; instead, it may act to cause or maintain anxiety (Bar-Haim 2010; MacLeod et al. 2009). Research has begun to examine changes in brain function associated with ABMT. Such attention training has advantages over cognitive behavioral therapy (CBT) in that it might target rapidly deployed attention processes disrupted in anxiety disorders that would not be targeted by CBT (Pine et al. 2008). Behaviorally based interventions also have great implications for mental health care in pediatric anxiety given the concerns surrounding the effects of psychotropic medications on the developing brain.

In addition to guiding the development of innovative therapies, fMRI may also be used to guide treatment choice. In a preliminary study of 15 youth with anxiety disorders, greater pretreatment activation in the left amygdala during explicit processing (i.e., ratings of subjective fears) of fearful versus happy faces significantly predicts better responses to medication or CBT treatment (McClure et al. 2007a). Such data illustrate that neuroimaging biomarkers have the potential to help identify patients who are most likely to have a favorable response to treatment; and thus more tailored and personalized treatment plans can be developed.

2.2 Major Depressive Disorder

2.2.1 Clinical Presentation and Behavioral Deficits—Adolescence marks a developmental period with a sharp increase in depression (Costello et al. 2003, 2006; Merikangas et al. 2010). Lifetime prevalence of MDD is estimated to be 16.6 % in the general population (Kessler et al. 2005), with an average age of onset between 11 and 14 years (Lewinsohn et al. 1998). Many clinical symptoms of MDD reflect underlying deficits in affective, emotional, and cognitive processing (Mathews and MacLeod 2005; Stuhrmann et al. 2011). Extensive research has documented disturbances in *reward processing* (for a review, see Forbes and Dahl 2012) and *face emotion processing* (for a review, see Stuhrmann et al. 2011) in MDD. We focus on these two domains when discussing behavioral deficits and neural circuits associated with MDD.

2.2.2 Reward Processing

Behavioral findings: Anhedonia, a cardinal symptom of MDD, is defined as diminished interest or pleasure in all, or almost all, activities (American Psychiatric Association 2013) and is thought to reflect disturbed reward processing (Der-Avakian and Markou 2012; Eshel and Roiser 2010; Gabbay et al. 2013). Anhedonia can be quantified and studied using laboratory-based reward paradigms. Considerable research demonstrates that patients with MDD are less incentivized by rewards than are healthy subjects (for a review, see Eshel and Roiser 2010). In responses to monetary incentives, for example, depressed adults prefer highly rewarded stimuli less than healthy adults (Pizzagalli et al. 2009), and are less happy when anticipating rewards (McFarland and Klein 2009).

Research has begun to examine reward processing deficits in children and adolescents with depression. Although the pediatric literature is limited and less consistent than the adult literature, there are some promising results. MDD youth demonstrate low reward seeking (i.e., low bets at favorable odds; Forbes et al. 2007), and this behavior predicts the onset of MDD 1 year later in adolescents with familial risk for depression (Rawal et al. 2013). Low reward seeking also positively predicts anhedonia ratings and negatively predicts social functioning and extra-curricular activities (Rawal et al. 2013). These findings provide preliminary evidence that altered reward processing may also occur in children and adolescents with depression.

fMRI findings: From a neuroscience perspective, anhedonia may reflect a dys-function in reward circuitry (Der-Avakian and Markou 2012), including key structures such as the ventral striatum and orbitofrontal cortex (OFC), as well as regulatory structures such as the anterior cingulate cortex (ACC), dorsal and medial PFC, and amygdala (Haber and Knutson 2010; McClure et al. 2004).

Converging evidence shows that, similar to adults with depression, adolescents with depression exhibit reduced activation in the striatum in multiple phases during anticipation, decision-making, and receiving of rewards (Forbes et al. 2006, 2009; for a review, see Forbes and Dahl 2012). Although blunted responses in the ACC and OFC (Forbes et al. 2006) and increased activation in the dorsolateral and medial PFC have been found during reward processing in adolescents with depression (Forbes et al. 2006), these findings are less

replicated and thus await validation from future research. In addition, enhanced amygdala response to monetary reward is reported in adolescents with MDD (Forbes et al. 2006), parallel with a recent study in adult depression during processing of social reward (Davey et al. 2011).

In sum, fMRI research in pediatric depression implicates dysfunction in the reward circuit encompassing striatum, ACC, OFC, and dorsolateral and medial PFC. These functional data are complemented by data showing reduced ACC, OFC, and striatal volumes in depressed individuals (for a meta-analysis, see Koolschijn et al. 2009), as well as a recent study indicating increased functional connectivity between striatum and dorsomedial PFC/ACC in adolescents with MDD (Gabbay et al. 2013). Greater striatal activation appears to relate positively to adolescents' real-world experiences of positive affect (Forbes et al. 2009) and negatively to depressive symptoms (Forbes et al. 2010b). In addition, girls at familial risk for depression, like depressed adolescents, exhibit blunted striatal activation during reward processing (Gotlib et al. 2010), suggesting that altered reward processing may serve as an endophenotype for depression.

2.2.3 Face Emotion Processing

Behavioral findings: Depression is associated with cognitive deficits and biases, particularly when processing affect-laden stimuli (Elliott et al. 2011; Mathews and MacLeod 2005; Stuhrmann et al. 2011). Such cognitive deficits can be probed using face emotion processing paradigms (Fig. 2) during which participants process facial expressions explicitly (i.e., focusing on the face emotion), implicitly (i.e., focusing on a stimulus feature other than the face emotion, such as gender or age), or passively (i.e., simply viewing the face without constraints on subjects' attention). Ample evidence suggests that adult patients with MDD show attention biases toward sad faces (i.e., faster to detect sad faces; Gotlib et al. 2004a, b). Such bias is specific to sadness, not anger, and occurs in depression but not anxiety (Gotlib et al. 2004a, b). Moreover, depressed adults tend to interpret happy faces as neutral (Gur et al. 1992; Surguladze et al. 2004) and require higher intensity of face emotion to identify happiness (Harmer et al. 2009).

Few studies have examined face emotion processing in children and adolescents with MDD or at risk for MDD, and the results are inconsistent. Some investigators find an oversensitivity to sad faces (i.e., requiring low emotional intensity to identify sadness or having attention biases toward sad faces) in depressed youth or children at risk for MDD (Joormann et al. 2007; Lopez-Duran et al. 2013; Schepman et al. 2012), whereas others report attention biases *away* from sad faces in depressed or at-risk youth (Gibb et al. 2009). Still others find no behavioral differences between youth with and without MDD in accuracy, reaction time, or subjective ratings during face emotion processing (Beesdo et al. 2009; Gaffrey et al. 2013; Yang et al. 2010).

fMRI findings: Compared to the relatively large literature in adults with MDD, fMRI research on face emotion processing in youth with MDD is scarce. Research in adults with depression typically finds elevated amygdala activation while processing fear (for a meta-analysis, see Stuhrmann et al. 2011), and similar findings are reported in some studies in

youths with MDD. In response to fearful faces or across all face emotions, increased amygdala activity has been observed in pre-schoolers with MDD (Gaffrey et al. 2013), children and adolescents with MDD (Beesdo et al. 2009; Roberson-Nay et al. 2006; Yang et al. 2010), and youth at risk for MDD (Monk et al. 2008); however, blunted amygdala responses have also been reported in youth with MDD (Beesdo et al. 2009; Thomas et al. 2001). Discrepancies in the literature may be explained by differences in task demands across studies [e.g., passive viewing (Beesdo et al. 2009; Thomas et al. 2001) versus explicit processing (Beesdo et al. 2009; Yang et al. 2010)]. Nevertheless, amygdala hyperactivation appears to positively predict depressive symptoms (Yang et al. 2010) and negative affect (Gaffrey et al. 2013), and negatively predict emotion regulation (Gaffrey et al. 2013).

In depression, there has been some neural specificity to emotions such as sadness and happiness. For example, relative to those without depression, pre-schoolers with depression show increased activation in the amygdala during viewing of sad faces (Gaffrey et al. 2011). Increased activation in the amygdala (Barch et al. 2012; Gaffrey et al. 2011) and OFC (Barch et al. 2012) are related to greater depression severity in children with and without MDD. Moreover, adolescents at risk for MDD, relative to those without familial risk, exhibit reduced nucleus accumbens (NAcc) responses to happy faces (Monk et al. 2008). NAcc hypoactivation during viewing of happy faces is associated with more depressive symptoms in previously institutionalized adolescents at high risk for MDD (Goff et al. 2013), suggesting that reduced NAcc responses to positive stimuli may be the neural correlates of anhedonia characterizing depression (Wacker et al. 2009).

In sum, these fMRI findings suggest amygdala dysfunction associated with MDD across development, from preschool to adulthood. This is supported by structural imaging data indicating decreased gray matter volumes in the amygdala in children and adolescents with MDD (Rosso et al. 2005). Some evidence suggests that, in addition to the amygdala, other brain regions such as the OFC and NAcc may also be implicated in the dysfunction of face emotion processing in MDD. Findings in at-risk adolescents for MDD highlight the possibility that deficits in face emotion processing and the associated neural activity may represent a stable trait characteristic of depression (Fairchild 2011; Stuhmann et al. 2011).

2.2.4 Implications—In the recent decade, research effort has increased to identify biomarkers to guide treatment selection. A study suggests that affect-related brain activity may predict treatment response in adults with depression (Siegle et al. 2006). Specifically, *decreased* pretreatment reactivity in the subgenual cingulate cortex and *increased* pretreatment reactivity in the amygdala in response to negative words positively predict better recovery with CBT (Siegle et al. 2006). Additionally, a preliminary study in adolescents with depression and anxiety reports greater striatal activation and lower medial PFC activation during a monetary reward task associated with greater reduction of clinical severity and anxiety symptoms (but not depressive symptoms; Forbes et al. 2010a). Such data might facilitate efforts of clinicians to provide personalized treatment.

2.3 Bipolar Disorder

2.3.1 Clinical Presentation and Behavioral Deficits—BD in youth is a relatively rare yet highly debilitating illness (Murray and Lopez 1996) characterized by discrete episodes of depression and hypomania or mania; such episodes represent a clear departure from baseline mood and functioning (American Psychiatric Association 2013; McClellan et al. 2007). Emotional dys-regulation is a hallmark feature of pediatric BD. One of the best-replicated finding in pediatric BD is an impaired ability in processing emotions (including emotion labeling deficits), assessed through *face processing* paradigms (for reviews, see Blond et al. 2012; Chen et al. 2011; Delvecchio et al. 2012; Houenou et al. 2011; Kupferschmidt and Zakzanis 2011; Strakowski et al. 2012). In addition to impaired emotional processing, studies have also revealed *cognitive control* deficits in pediatric BD (for a review, see Passarotti and Pavuluri 2011). In the following, we review behavioral and fMRI findings in pediatric BD, focusing on these two domains of dysfunction: face emotion processing and cognitive control.

2.3.2 Face Emotion Processing

Behavioral findings: Similar to adults with BD (Kohler et al. 2011; Lembke and Ketter 2002), face emotion labeling deficits have been observed in children with BD (Guyer et al. 2007; Rich et al. 2006) and youth at familial risk for BD (Brotman et al. 2008a, b). Youth with BD make more errors identifying emotions, compared to healthy controls (Guyer et al. 2007; McClure et al. 2005) or youth with anxiety and depression (Guyer et al. 2007). These deficits appear to be pervasive across face emotions (Brotman et al. 2008b; Rich et al. 2008) and mood states (Rich et al. 2008; Schenkel et al. 2007). Moreover, BD youths, relative to controls, are more likely to rate neutral faces as hostile and fear-inducing (Brotman et al. 2010, 2013; Rich et al. 2006), and require higher intensity of emotion to be able to identify facial emotions (Brotman et al. 2008b). Together, these difficulties in emotional processing may contribute to the social impairment commonly observed in BD, since the ability to read social cues and facial expressions is essential for adaptive social functioning.

fMRI findings: Research examining the neural circuitry mediating face emotion processing in BD implicates dysfunction in the fronto-limbic-striatal network (for reviews, see Blond et al. 2012; Chen et al. 2011; Delvecchio et al. 2012; Houenou et al. 2011; Kohler et al. 2011; Kupferschmidt and Zakzanis 2011; Pavuluri and Passarotti 2008; Strakowski et al. 2012). Abnormalities in amygdala function during face emotion processing are observed consistently in both children (for a review, see Pavuluri and Passarotti 2008) and adults with BD (for a review, see Strakowski et al. 2012). Research generally indicates amygdala *hyperactivation* in youths with BD, relative to healthy controls, during processing of facial expressions across attentional demands: (1) explicit (Rich et al. 2006), (2) implicit (Garrett et al. 2012; Kalmar et al. 2009; Kim et al. 2012; Pavuluri et al. 2009; Thomas et al. 2013), and (3) passive viewing (Brotman et al. 2013; Pavuluri et al. 2007). Amygdala hyperactivation is also evident in euthymic patients with BD (Chen et al. 2011), suggesting a trait-like deficit in emotion processing subserved by amygdala dysfunction. Structural imaging data further corroborate fMRI findings. Decreased amygdala volume in youth with BD, compared to healthy controls, has been replicated in multiple studies (Blumberg et al. 2005; Chang et al. 2005; Chen et al. 2004; DelBello et al. 2004; Dickstein et al. 2005;

Kalmar et al. 2009). Recent evidence suggests that decreased amygdala volume is associated with increased amygdala activation during face processing in youth with BD (Kalmar et al. 2009), implicating both functional and structural amygdala abnormalities in pediatric BD.

In contrast to the relatively consistent finding of amygdala hyperactivation in BD, the precise direction of dysfunction in the PFC and striatum is less clear. Some studies report hyperactivation in these regions (Ladouceur et al. 2011; Pavuluri et al. 2007; Rich et al. 2006), whereas others report hypoactivation (Garrett et al. 2012; Pavuluri et al. 2007; Pavuluri et al. 2009). This discrepancy may be explained by differences in attention demands across face emotion paradigms (Brotman et al. 2013), as a recent study reveals that, while ACC and striatal hyperactivation is evident in youth and adults with BD when attention is unconstrained (i.e., passive viewing), BD patients show hypoactivation in the same regions when attention is constrained (i.e., explicit or implicit processing; Brotman et al. 2013).

Together, fMRI research with face emotion processing paradigms in pediatric BD implicates aberrant neural activation in the amygdala, PFC, ACC, and striatum. While amygdala hyperactivity is consistently reported, both hyperactivity and hypoactivity in the PFC, ACC, and striatum are observed in pediatric BD. Although clearly more research is warranted to discern the effects of different paradigms and attention demands on these findings, the data suggest that deficient PFC regulation of heightened amygdala responses to emotional stimuli may contribute to disrupted emotional processing in pediatric BD (Garrett et al. 2012).

2.3.3 Cognitive Control

Behavioral findings: Broadly speaking, cognitive control is the ability to orchestrate thought and action in accordance with internal goals (Miller and Cohen 2001). It is typically probed using tasks that tap working memory, response inhibition, and set shifting (Sabb et al. 2008). Although emotional dysfunction is a prominent feature of BD, impaired cognitive control is also a common correlate (for a review, see Passarotti and Pavuluri 2011). Behavioral paradigms assessing response inhibition, a type of cognitive control, have been used in research with BD. A typical response inhibition task (e.g., Go/No-Go task or Stop Signal task) requires participants to execute a motor response (i.e., go trials) or inhibit a pre-potent motor response (i.e., no-go or stop trials). On response inhibition tasks, adult patients with BD have a slower reaction time and make more omission errors compared to healthy controls (Welanders-Vatn et al. 2013). Likewise, youths with BD, relative to healthy controls, are less accurate during the go trials (Leibenluft et al. 2007), the stop trials (Pavuluri et al. 2010), or both types of trials (Passarotti et al. 2010) on the Stop Signal task. These data suggest that youths with BD show impairment in motor execution and/or motor inhibition. Youths with BD also perform more poorly on neurocognitive tasks assessing sustained attention, executive function, and working memory (Pavuluri et al. 2006). In sum, behavioral data suggest that cognitive control functions including sustained attention, executive function, and response inhibition is impaired in pediatric BD. Research on cognitive control may contribute to the understanding of impulsivity and irritability in pediatric BD.

fMRI findings: In healthy subjects, the PFC and ACC are key regions in the circuit mediating cognitive control (Kerns et al. 2004). Consistent with this, research in adults with BD indicates that, relative to controls, BD adults exhibit hypoactivation in the OFC and ACC during response inhibition tasks (e.g., Go/No-Go; Altshuler et al. 2005). Similarly, in BD youths compared to healthy controls, deficits in motor response inhibition are linked to reduced activation in the vIPFC (Leibenluft et al. 2007; Passarotti et al. 2010), striatum (Blumberg et al. 2003; Deveney et al. 2012; Leibenluft et al. 2007), and ACC (Blumberg et al. 2003; Deveney et al. 2012; Leibenluft et al. 2007; Passarotti et al. 2010).

Neuroimaging research may help clarify the diagnostic boundaries between pediatric BD and attention-deficit/hyperactivity disorder (ADHD), a common comorbidity of pediatric BD. Preliminary evidence suggests that youths with BD and youths with ADHD both exhibit deficient response inhibition, but the underlying neural correlates are distinct (Passarotti et al. 2010). Specifically, youths with ADHD activate vIPFC and dorsolateral PFC (dlPFC) less than do youths with BD, suggesting greater prefrontal dysfunction associated with ADHD than with BD (Passarotti et al. 2010).

Overall, fMRI research implicates abnormalities in the fronto-striatal network involving vIPFC, dlPFC, ACC, and striatum in contributing to dysfunction in cognitive control in pediatric BD (Passarotti and Pavuluri 2011). Future research investigating the complex, dynamic interaction between cognition and emotion would be informative in elucidating the pathophysiology of BD, since impairment in these two domains is prominent. Better understanding of the neurobiological bases of cognitive and emotional dysfunction in pediatric BD will inform more effective and innovative treatments targeting specific neural circuits involved in pediatric BD.

2.3.4 Implications—Emerging research attempts to understand the effect of treatments on neural function. For example, lamotrigine monotherapy may normalize BD patients' hypoactivity in the PFC and temporal regions during response inhibition (Pavuluri et al. 2010). Increased vIPFC activation with lamotrigine treatment is correlated with reduction in manic and hypomanic symptoms (Pavuluri et al. 2010). These findings suggest that mood stabilizers not only improve functions and symptoms in affective and emotional domains, but also influence the brain networks involved in cognitive control (Pavuluri et al. 2010). Continuing effort on linking basic pathophysiological research to translational research will likely contribute to the development of biosignatures of treatment responses in pediatric BD.

3 Future Directions and Conclusions

In this chapter, we reviewed research on the pathophysiology of pediatric mood and anxiety disorders, disorders that are characterized by deficits in emotional regulation. An essential step in pathophysiological research is to identify paradigms that capture these deficits so that investigators can map clinical symptoms onto brain function. By linking disturbances in cognitive and emotional processes to brain function, neuroimaging research has provided unique insights into the neuropsychological mechanisms of pediatric mood and anxiety disorders. Although great strides have been made, more research is needed. Studies in pediatric populations with psychopathology, relative to the adult populations, are less

confounded by the effect of longstanding or repeated treatments. Future studies employing longitudinal designs would allow us to better chart the developmental trajectories of clinical symptoms and the underlying neural mechanisms over time. Together, a better understanding of aberrant neural systems underlying clinical phenotypes will help identify biomarkers of mental illness, which in turn has great potential to index risks for mental illness, improve the diagnostic accuracy, and provide targets for neurobiologically informed interventions and for monitoring treatment response.

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Fig. 1. Dot-probe task. Mean reaction time of the incongruent trials – mean reaction time of the congruent trials = attention bias. Positive values indicate a bias *toward* threat; negative values indicate a bias *away* from threat

Fig. 2.
Face emotion processing paradigms and examples