Neural Markers of Treatment Response in Pediatric Anxiety and PTSD

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Abstract Pediatric anxiety disorders and post-traumatic stress disorder (PTSD) are associated with elevated threat sensitivity and impaired emotion regulation, accompanied by dysfunction in the neural circuits involved in these processes. Despite established treatments like cognitive behavioral therapy (CBT) and selective serotonin reuptake inhibitors, many children do not achieve remission, underscoring the importance of understanding the neurobiological underpinnings of these disorders. This review synthesizes current research on the neural predictors of treatment response and the neurofunctional changes associated with treatment in pediatric

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anxiety and PTSD during threat and reward processing. Several key findings emerged. First, enhanced threat/safety discrimination in the amygdala predicted better outcomes of pediatric anxiety and PTSD treatments. Second, differences in pretreatment activation within the lateral prefrontal and dorsal anterior cingulate cortices predicted treatment response, likely reflecting baseline executive control differences. Third, post-CBT decreases in activation in default mode, visuo-attentional, and sensorimotor areas may support treatment-related increases in task engagement. Finally, functional connectivity between the amygdala and other limbic, prefrontal, and default mode network nodes predicts treatment response in anxiety and PTSD, highlighting its potential as a biomarker for therapeutic efficacy. Understanding these neurofunctional markers could lead to more targeted interventions, optimizing treatment planning and potentially leading to the development of "pretreatment" strategies to enhance the efficacy of existing treatments. This review highlights the necessity for future research to establish more direct links between neuroimaging findings and clinical outcomes to facilitate the translation of these findings into clinical practice.

Keywords Adolescents · Anxiety disorders · CBT · Children · Post-traumatic stress disorder · Neural biomarkers · SSRI · Reward processing · Threat processing

1 Introduction

Pediatric anxiety disorders are a prevalent mental health concern, affecting roughly 30% of the US population at some point during childhood or adolescence (Kessler et al. 2005; Merikangas et al. 2010). Anxiety disorders typically first emerge during childhood, with a median onset age of 6 years old (Beesdo et al. 2010; Kessler et al. 2012; Merikangas et al. 2010). Anxiety disorders that begin during youth are often chronic (Spence and Rapee 2016), impairing (Kendall et al. 2010; Ranøyen et al. 2018), and can increase risk for other disorders later in life (Kessler et al. 2011), including mood disorders, disruptive behaviors, substance use, and suicidality (Asselmann et al. 2018). Despite the availability of effective treatments, such as cognitive-behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs), approximately 40–50% of people with anxiety disorders do not achieve remission (Ginsburg et al. 2011; Piacentini et al. 2014), highlighting the need to understand the mechanisms by which treatment can be successful. Pediatric anxiety is associated with biases in threat processing, emotion regulation, and executive control, as well as in the neural circuits that support these functions (Ashworth et al. 2021; Fitzgerald et al. 2021; Strawn et al. 2014). However, the mechanisms by which the neurobiology of pediatric anxiety disorders predicts or is modified by successful treatment are not well understood. This review aims to shed light on neural underpinnings and predictors of treatment efficacy in children and adolescents

with anxiety and PTSD to inform future interventions targeted to individual neurobiological profiles.

2 Established Treatments for Pediatric Anxiety and PTSD

The most prevalent treatments for pediatric anxiety are CBT and SSRIs, which can be employed either separately or together, depending on the child's needs and the severity of their anxiety (Birmaher et al. 2003; Compton et al. 2004; Walkup et al. 2008). CBT uses cognitive restructuring to identify and modify negative thought patterns and beliefs fueling anxiety, equipping children with strategies to manage symptoms and minimize avoidance behaviors (Compton et al. 2004). These strategies are intended to promote confrontation and engagement with anxiety-inducing situations (i.e., gradual exposure) to learn that feared outcomes do not occur (Craske et al. 2022; McGuire and Storch 2019). Relaxation techniques are also usually taught to help reduce anxious distress. These components of CBT are typically packaged together for delivery over 10 to 16 weekly sessions (e.g., Nelson and Finch 2008; Rapee and Wignall 2002). Additionally, for children with PTSD, trauma-focused therapy can be integrated with CBT to address and process traumatic events (Cohen et al. 2017). SSRIs, such as fluoxetine, sertraline, and escitalopram, are also frequently prescribed due to their efficacy and safety in children and adolescents with anxiety disorders or PTSD (Strawn et al. 2015). These medications are believed to work by increasing serotonin levels in the brain to improve mood and reduce anxiety. Due to potential side effects of medications, use of SSRIs is typically considered after trying psychotherapy options like CBT and involves careful evaluation of benefits against risks, with monitoring for adverse effects. Other treatments for pediatric anxiety are available (e.g., mindfulness-based cognitive therapy), yet research on the neural mechanisms of their efficacy is limited, and therefore will not be discussed in this review.

In the following section, we will review studies that examine (1) pretreatment neural predictors of treatment response, and (2) pre-to-post-treatment changes in brain function that correlate with treatment response. These studies generally include youth with GAD, SAD, and/or separation anxiety disorders. Neural predictors of trauma-focused CBT have also been tested in adolescents with PTSD. Most studies on the neural predictors of treatment response in pediatric anxiety and other negative valence have focused on neural systems for threat responding (reviewed in La Buissonniere-Ariza et al. 2021; Strawn et al. 2021), based on prevailing theory that anxiety derives from hypersensitivity to threat and deficits of threat regulation. We will first review functional brain activation during threat processing paradigms as a marker (i.e., predictor and mechanism) of treatment response. Next, we will review several studies that have examined the neural correlates of reward responsiveness that predict treatment response. Finally, we will discuss the implications of this research for clinical application and outline potential future directions.

3 Neurofunctional Markers of Treatment Response During Threat Processing

3.1 Amygdala and Insula

The amygdala, a subcortical region responsible for threat detection and fear responding (Davis and Whalen 2001; Ohman 2005), has been implicated in the pathology of pediatric anxiety disorders (Ashworth et al. 2021) and PTSD (Alexandra Kredlow et al. 2022). Research in youth with GAD, SAD, panic disorder, separation anxiety, and post-traumatic stress symptoms have found that viewing (or anticipation of viewing) negative or threatening stimuli elicits amygdala hyperactivation compared to healthy controls (Beesdo et al. 2009; Garrett et al. 2012; Guyer et al. 2008; McClure et al. 2007b; Monk et al. 2008; Thomas et al. 2001), likely contributing to heightened threat perception and increased fear responses characteristic of these disorders (Ohman 2005).

Amygdala function during threat processing has emerged as a predictor of treatment response in pediatric anxiety and PTSD. For children and adolescents with GAD, greater left amygdala responses to fearful relative to happy faces prior to treatment with CBT or fluoxetine predicted greater posttreatment symptom improvement, regardless of treatment type (McClure et al. 2007a). Similarly, greater pretreatment amygdala response to fearful compared to neutral faces predicted greater symptom reduction in adolescent girls with PTSD, following trauma-focused CBT (Cisler et al. 2015). However, in this study, girls with greater amygdala activity to *both* fearful and neutral faces displayed poorer posttreatment symptom reduction, suggesting that greater threat-safety discrimination in the amygdala, rather than hyperactivity alone, may underlie treatment gains. Supporting this notion, PTSD symptom improvement following trauma-focused CBT was associated with decreases in amygdala and hippocampal activation to neutral, but not fearful or angry, faces (Garrett et al. 2019). This may further suggest that CBT reduces anxiety symptoms by improving the ability to discriminate between threat and safety, as evidenced by a reduced response to safe stimuli. Alternatively, amygdala hyperactivation to emotional stimuli may reflect greater symptom severity (Cisler et al. 2015), suggesting more to gain from treatment. It is also possible that greater amygdala activity could reflect greater sensitivity to exposure, widely held to be the most active "ingredient" in CBT (Bilek et al. 2022). Notably, not all studies observe amygdala function as a predictor of treatment response (Burkhouse et al. 2017) and amygdala activation may not change with treatment (Haller et al. 2024).

The insula is a limbic-related region implicated in integrating emotional responses with internal physiological states and the detection of salient stimuli (internal and external) to direct processing between internal and external demands as appropriate to context (Reynolds and Zahm 2005; Seeley 2019). Basic science has shown that the insula has strong reciprocal connections with the amygdala (Reynolds and Zahm 2005). Additionally, functional magnetic resonance imaging (fMRI) studies have used inter-regional correlations between low-frequency blood

oxygenation level-dependent oscillations to characterize insula connectivity with dorsal anterior cingulate cortex to form the cingulo-opercular network which functions to detect salient stimuli from external and internal milieu (Seeley et al. 2007). The cingulo-opercular network may serve as a switch between frontoparietal network regions (e.g., dorsolateral prefrontal cortex, superior parietal cortex) for implementation of cognitive processes, and default mode network regions (e.g., ventromedial prefrontal cortex, posterior cingulate cortex) for internally directed, self-referential processes (Sridharan et al. 2008). In adults with anxiety and PTSD, insula hyperactivation during threat processing has been repeatedly demonstrated (Chavanne and Robinson 2021; Etkin and Wager 2007). This aligns with findings that clinically anxious youth display elevated amygdala-insula connectivity during threat processing compared to healthy controls (McClure et al. 2007b), suggesting that greater connectivity might underlie more severe anxiety, perhaps due to enhanced coupling of threat perception with bodily responses and/or increased influence of amygdala on the insula-based cingulo-opercular network for salience detection.

Functional connectivity between the amygdala and the insula is a marker of CBT outcomes in pediatric anxiety and PTSD. For example, greater pretreatment amygdala-insula connectivity on congruent trials of a threat attention task predicted poorer response to CBT in youth with GAD, SAD, and/or separation anxiety, controlling for pretreatment severity (White et al. 2017). Thus, greater amygdala-insula connectivity prior to CBT may identify a neural target for intervention. This hypothesis is supported by evidence that successful treatment can reduce amygdala-insula connectivity. Specifically, among adolescent girls with PTSD undergoing trauma-focused CBT, greater symptom reduction correlated with pre-to-post-treatment decreases in amygdala-insula connectivity when reappraising negative images (Cisler et al. 2016). Normalization of connectivity between neural pathways involved in threat response and interoception and relatedly, salience detection, may suggest a mechanism by which therapy reduces anxiety symptoms, possibly by attenuating threat sensitivity, including anxiety-induced bodily distress and/or attention to threat.

3.2 Prefrontal and Anterior Cingulate Cortices

Altered function of the prefrontal (PFC) and anterior cingulate cortices (ACC) during emotional tasks has also been implicated in pediatric anxiety (Britton et al. 2013; Burkhouse et al. 2018; McClure et al. 2007b; Monk et al. 2006; Strawn et al. 2012; Swartz et al. 2014) and PTSD (Killgore et al. 2014; Kim et al. 2008; Stevens et al. 2017). Broadly, these regions are involved in emotion regulation, cognitive appraisal, executive functioning, and attentional control processes, and play a pivotal role in managing fear and anxiety (Bishop et al. 2004; Etkin et al. 2006; Haber and Knutson 2010; Kenwood et al. 2022; Shackman et al. 2011). Specifically, the lateral PFC is more involved in cognitive processes (Koechlin et al. 2003), the ACC serves

the spectrum of cognitive to emotional processes along the dorsal to rostral continuum (Bush et al. 2000), and the ventromedial PFC mediates the affective valuation of stimuli for both goal-directed and self-referential processing (D'Argembeau 2013). Altered function in ventral portions of the PFC and ACC during emotional tasks has also been associated with pediatric anxiety symptoms (Britton et al. 2013; Burkhouse et al. 2018; McClure et al. 2007b; Monk et al. 2006; Strawn et al. 2012; Swartz et al. 2014) and PTSD (Killgore et al. 2014; Kim et al. 2008; Stevens et al. 2017). Abnormalities in these regions (e.g., ventrolateral and ventromedial PFC, subgenual and rostral ACC) may contribute to threat biases, difficulties in regulating emotions, and avoidance tendencies that are common in anxiety and PTSD (Blackford and Pine 2012; Kenwood et al. 2022; Liberzon and Sripada 2007).

Activation of the PFC and ACC during threat processing also predicts treatment response in pediatric anxiety, providing insights into the regulatory and cognitive neural mechanisms underlying therapeutic success. For instance, elevated pretreatment activation in the ventrolateral and dorsolateral PFC during the evaluation of threatening emotional faces predicted greater symptom reduction following treatment with CBT or sertraline in youth with GAD, SAD, or separation anxiety disorder (Kujawa et al. 2016). Increased pretreatment activation in the ventrolateral and dorsolateral PFC may suggest greater capacity for cognitive control over emotions (e.g., reappraisal) and emotion regulation, which may enable youth to better engage with their fears and anxieties (i.e., exposure adherence) and thereby benefit from treatment. Moreover, pre-to-post-treatment increases in right ventrolateral PFC activation to angry faces were observed in a study of 14 youth with GAD undergoing CBT or fluoxetine (Maslowsky et al. 2010). Though these changes were not associated with changes in anxiety severity, they may reflect the development of more effective strategies for managing negative emotions, such as cognitive reappraisal, which is a core component of CBT response.

By contrast, *less* pretreatment activation in a cluster encompassing the dorsal ACC and dorsomedial PFC predicted greater symptom reduction following CBT or sertraline in youth with GAD or SAD (Burkhouse et al. 2017). In this study, pretreatment brain function was measured while children matched shapes that were flanked by emotional face distractors. Lower pretreatment dorsal ACC and dorsomedial PFC activation in CBT responders was suggested to identify children with the most to gain from treatment. Given that anxious youth show reduced rostral ACC activation during implicit emotion processing compared to healthy controls (Burkhouse et al. 2018; Swartz et al. 2014), lower pretreatment activation could indicate cognitive or attentional bias to irrelevant emotional stimuli when responding to cognitive demands with clinically significant anxiety, thereby reflecting a treatment target. Consistent with this possibility, increases in rostral ACC activation have been observed during implicit emotion processing following CBT or sertraline among youth with GAD, SAD, and/or separation anxiety (Burkhouse et al. 2018), with greater increases correlating with larger reductions in social anxiety and avoidance symptoms. The rostral ACC plays a role in conflict monitoring, cognitive appraisal, and attention (Bush et al. 2000; Etkin et al. 2011) and dorsomedial PFC is involved in appraising negative emotions (Etkin et al. 2011; Price and Drevets

2010). These abilities may be especially important when trying to exert cognitive control to perform tasks in the presence of negative emotional distractors – a process that is impaired in anxious youth (Cisler and Koster 2010) and targeted by CBT (i.e., cognitive restructuring and successful engagement with exposures).

Discrepancies in the direction of subregional activations in the PFC and ACC in predicting treatment response (e.g., elevated ventrolateral and dorsolateral PFC (Kujawa et al. 2016) versus less dorsal ACC and dorsomedial PFC (Burkhouse et al. 2017)) may stem from variations in task instructions. When participants are instructed to evaluate threat stimuli, as in Kujawa et al. (2016), it may encourage the use of regulatory strategies for engaging with these emotions, leading to greater lateral PFC activation. By contrast, when participants are tasked to ignore emotional stimuli to perform another task (e.g., shape-matching), as in Burkhouse et al. (2018), less activation in regions involved in emotional appraisal or conflict monitoring (e.g., dorsal ACC) may reflect better task engagement and/or less distraction by emotional stimuli. Future research that directly modulates task instructions is needed to elucidate how attentional mechanisms impact spatially localized neural activation and subsequent treatment outcomes.

Functional connectivity between the amygdala and prefrontal cortical structures has also been identified as a predictor of how well youth respond to anxiety treatment. In a sample of adolescents with GAD, more negative (i.e., anti-correlated) pretreatment functional connectivity between the amygdala and a cluster encompassing the bilateral ventromedial PFC (vmPFC) and subgenual ACC (sgACC) during implicit emotion processing predicted greater improvement in anxiety symptoms following treatment with escitalopram, but not for those who received a placebo (Lu et al. 2022). Moreover, participants who received escitalopram also exhibited more negative amygdala-vmPFC/sgACC connectivity at post-treatment compared to the placebo group. The vmPFC and sgACC are involved in emotion processing (Etkin et al. 2011; Hiser and Koenigs 2018) and regulating amygdala response via inhibitory connections (Etkin et al. 2010; Rosenkranz et al. 2003). Anxious youth have been found to display weaker negative coupling between the amygdala and ventrolateral PFC than healthy control subjects during threat processing (Monk et al. 2008), as well as reduced structural connectivity between limbic and prefrontal cortical regions (Aggarwal et al. 2024; Baur et al. 2013; Glenn et al. 2022), which may contribute to impaired prefrontal modulation of amygdala-driven responses to negative stimuli. Thus, larger amygdala-vmPFC/sgACC anti-correlations at baseline may suggest enhanced (i.e., more normalized) inhibitory control over the amygdala, which were further increased by treatment, leading to better treatment outcomes.

Alternatively, as the vmPFC plays a role in self-referential thinking, less positive amygdala-vmPFC/sgAGG connectivity of the amygdala may reflect greater separation of threat processing and introspective networks. This separation could result in less attention to internal distress elicited by threatening stimuli, allowing for better processing of cognitive task demands during implicit emotion processing. In line with this interpretation, among adolescent girls with PTSD undergoing trauma-focused CBT, less pretreatment functional connectivity between the amygdala and

dorsal ACC to fearful faces predicted greater symptom reduction following treatment (Cisler et al. 2015). Whereas the vmPFC is associated with self-referential thinking and the integration of emotional and cognitive processes (Hiser and Koenigs 2018), the dorsal ACC plays a role in error detection, conflict monitoring, and adaptive response selection (Shenhav et al. 2016). These distinct functions may underlie the differential impact of amygdala-PFC/ACC connectivity on treatment outcomes in anxiety and PTSD. Further research is needed to elucidate the precise mechanisms by which amygdala connectivity with specific cortical regions influences treatment response across different psychiatric disorders.

3.3 Frontoparietal and Cingulo-Opercular Networks

Regions in the lateral PFC, posterior parietal cortex, dorsal ACC, and insula are nodes in the frontoparietal and cingulo-opercular networks, respectively, which are task control networks that are engaged when healthy participants perform cognitively demanding tasks. The cingulo-opercular network consists of the dorsal ACC, anterior insula, thalamus, and anterior PFC, and is involved in sustained performance monitoring and attending to salient information (Dosenbach et al. 2006, 2007). The frontoparietal network, which is engaged to adjust control when task demands change, consists of the dorsolateral PFC, posterior parietal cortex, and intraparietal sulcus (Dosenbach et al. 2007; Scolari et al. 2015). Baseline activation of task control networks during threat processing is relevant for treatment because it might indicate cognitive control and/or attentional mechanisms that may influence how youth with anxiety disorders or PTSD engage in CBT. For instance, post-treatment symptom reduction in anxious youth was predicted by elevated baseline cingulo-opercular network function (Burkhouse et al. 2017) but reduced frontoparietal network activity (Kujawa et al. 2016), possibly suggesting differential effects of continuous performance monitoring versus flexible control on one's ability to engage with treatment. Further, differences in functional connectivity between the amygdala and cingulo-opercular network predicted treatment response in anxiety and PTSD (Cisler et al. 2016), suggesting that the interaction between circuitry for threat processing and salience monitoring/cognitive control may be a biomarker for treatment outcomes.

3.4 Default Mode Network

Unlike the cingulo-opercular and frontoparietal networks, the default mode network is deactivated during tasks, and is instead engaged during introspection and self-referential thinking (Raichle et al. 2001; Shulman et al. 1997). Treatments for anxiety and PTSD have been shown to modulate the function of the default mode network, a network primarily consisting of the vmPFC/sgACC, posterior cingulate

cortex, angular gyrus, and precuneus. Youth with psychopathology sometimes fail to suppress the default mode network during externally focused tasks (Han et al. 2016; Liddle et al. 2011; Yin et al. 2017), suggesting difficulties in task engagement and/or diverting attention away from introspection (Greicius and Menon 2004; Singh and Fawcett 2008). Among youth undergoing trauma-focused CBT for PTSD, symptom improvement pre-to-post-treatment was associated with reductions in activation of a cluster encompassing the posterior cingulate cortex and precuneus when viewing emotional faces (Garrett et al. 2019). Reduced activation in default mode network nodes following treatment (and at baseline) may indicate less internally focused and potentially maladaptive rumination on traumatic experiences or anxious thoughts, contributing to symptom improvement.

Treatment-related increases in functional connectivity between the amygdala and discrete nodes within the default mode network have also been observed in a study of medication for youth with pediatric anxiety disorders. Specifically, functional connectivity between the left amygdala and right angular gyrus increased following treatment with escitalopram in anxious youth during a task with emotional and neutral distractors (Lu et al. 2022). Further, increased amygdala-angular gyrus connectivity at the second week of treatment predicted greater posttreatment improvement in anxiety symptoms. The angular gyrus is involved in various aspects of cognition, including attention, spatial cognition, and theory of mind (Seghier 2013). Thus, enhanced connectivity between these regions suggests that escitalopram may influence the integration of emotional and cognitive processing. Speculatively, this may contribute to reductions in anxiety symptoms by regulating the amygdala and reducing maladaptive rumination. These findings also suggest that medications, as compared to CBT, may engage different neural mechanisms. Studies directly comparing medication and CBT treatment for pediatric anxiety disorders will be needed to directly assess this possibility.

3.5 Vision/Attention Networks

Neural activation in visuo-attention networks has also been shown to predict and change with treatment response in anxious youth, possibly due to input from the amygdala. When a threat is detected, the amygdala sends reentrant feedback signals to sensory regions (Vuilleumier 2005), leading to perceptual prioritization of anxiety-provoking stimuli (Anderson and Phelps 2001; Davidson 2002; Ohman 2005; Ohman et al. 2001). Anxious individuals display elevated amygdala activity relative to controls (Brühl et al. 2014; Etkin and Wager 2007), elevated visual cortical engagement (Brühl et al. 2014; Etkin and Wager 2007; Gentili et al. 2016; Straube et al. 2005), and increased functional connectivity between the amygdala and perceptual regions (Brühl et al. 2014) during threat processing.

A recent investigation assessed whole-brain activation in 69 youth with GAD, SAD, and/or separation anxiety disorder while they viewed neutral and angry faces, both before and after undergoing CBT (Haller et al. 2024). Following CBT, anxious

youth displayed decreased activation in regions associated with visual perception and attention. For the superior parietal lobule, anxious youth exhibited elevated pretreatment activation compared to healthy controls, which normalized after therapy. In addition, anxious youth displayed pre-to-post-treatment reductions in function of the inferior parietal lobule, bilateral superior and inferior temporal gyri, and middle occipital gyri compared to healthy controls, despite there being no group differences at baseline. Together, these regions are broadly involved in visual perception, attention, and spatial awareness (Behrmann et al. 2004; Conway 2018; Shapiro et al. 2002), suggesting CBT may influence visual attention during threat processing, possibly by reducing hypervigilance and/or perceptual prioritization.

Similarly, in youth with PTSD, greater connectivity between the amygdala and visual cortex at baseline predicted faster reductions in symptoms during trauma-focused CBT (Cisler et al. 2015). This may suggest that amygdalar influence on visual attention networks identifies the patients that are most likely to respond and could "prime" the brain in ways that facilitate response to CBT. However, it is important to note that predictors do not necessarily equal mechanisms. FMRI studies that assess treatment mechanisms at pre- and post-treatment (i.e., brain changes with symptom changes) have been a challenge in the field and may require more sophisticated analytic methods sensitive to changes in individuals or patient subgroups (Becker et al. 2023).

Reduced cortical thickness in parietal and occipital cortical regions has also been found to predict poorer treatment outcomes following CBT in children and adolescents with GAD, SAD, and/or separation anxiety disorder. These regions included the fusiform gyrus and inferior parietal lobe, which have been shown to play roles in socio-emotional processing and are engaged by emotional face stimuli (Fusar-Poli et al. 2009; Igelström and Graziano 2017; Kanwisher and Yovel 2006). Occipital findings align with studies that observe function in visual cortical regions as a predictor of treatment response in adults with SAD (Doehrmann et al. 2013) and specific phobia (Hauner et al. 2012).

3.6 Sensorimotor Networks

Neurofunctional markers of treatment response have also been observed in the sensorimotor network, a large-scale brain network that processes sensory inputs and coordinates motor functions. For instance, greater pretreatment activation to threat faces in the pre- and postcentral gyri, regions responsible for voluntary movement and sensory processing, respectively (Buhle et al. 2014; Goldin et al. 2008; Kohn et al. 2014), predicted better treatment responses in anxious youth undergoing treatment with CBT or SSRIs (Kujawa et al. 2016). Thus, greater activation in these regions could represent more frequent or better task responding during threat processing, though this hypothesis was not tested and behavioral differences did not predict treatment response. In another sample, anxious youth showed elevated pretreatment activation in the bilateral supplementary motor area

and superior parietal lobule compared to healthy controls during a dot probe paradigm, a task measuring attention to threat. In anxious youth, this hyperactivation normalized following CBT (Haller et al. 2024). The supplementary motor area is involved in planning and executing motor responses (Nachev et al. 2008) and interacts with the dACC, a cingulo-opercular node, during motor coordination (Diwadkar et al. 2017). The superior parietal lobule is a node in the dorsal attention network, which coordinates with the frontoparietal network to regulate attention allocation according to goals and task demands, and plays a role in perceptive, visuomotor, and somatosensory processes (Sulpizio et al. 2023; Wu et al. 2016). Thus, normalization of activation in these regions may have therefore contributed to improved behavioral performance (i.e., less slowing) observed in this sample at posttreatment versus pretreatment, relative to healthy controls (Haller et al. 2024). Alternatively, the pretreatment hyperactivation observed in these cingulo-opercular/frontoparietal-related regions in anxious youth may have indexed compensatory attempts to maintain higher levels of performance despite attention bias to more negative faces, although not entirely effective, as anxious youth responded more slowly than controls. Subsequently, when anxiety symptoms were reduced following treatment, this compensatory hyperactivation of task control networks might not have been necessary, leading to reduced engagement.

4 Neurofunctional Markers of Treatment Response During Reward Processing

While most pediatric anxiety research has focused on threat processing, emerging evidence points to aberrant reward circuitry functioning as a potential factor in anxiety pathophysiology (Bar-Haim et al. 2009; Guyer et al. 2006, 2012; Hardin et al. 2006). In addition to contributing to anxiety symptoms, disruptions in reward processing may affect the ability to engage with and benefit from positive reinforcement strategies commonly used in behavioral therapies (e.g., praise, stickers from therapists). These reinforcement techniques foster treatment engagement and build therapeutic alliance, both of which are linked to improved treatment outcomes (Shirk and Karver 2006). Aberrant reward processing may also reduce motivation to engage in situations that are typically experienced as rewarding (e.g., social interactions) in the face of anxiety about negative outcomes (e.g., embarrassment) in anxious youth. Given that exposure-based therapy for anxiety requires engagement with feared, but potentially rewarding stimuli, less sensitive neural response to reward could drive anxious behaviors and make affected youth less willing to engage with exposure, both naturalistically and in the context of treatment.

The striatum is a subcortical structure involved in motivation and reward processes (Daniel and Pollmann 2014). Emerging research finds that regions within the striatum, including the nucleus accumbens (NAcc), caudate, and putamen, are hyperactive in youth with anxiety (Guyer et al. 2012) and with temperamental risk

factors for anxiety (Bar-Haim et al. 2009; Guyer et al. 2006). The ventral striatum, and NAcc in particular, has been linked to treatment outcomes. Higher pretreatment activation to reward in a cluster encompassing the NAcc and sgACC was observed in anxious youth who responded to treatment (>35% symptom reduction) compared to non-responders (Sequeira et al. 2021), regardless of the type of therapy they participated in. This study included youth with GAD, SAD, and/or, separation anxiety disorder who participated in CBT or a comparison, client-centered psychotherapy. Similarly, greater pretreatment activation to reward anticipation in the entire bilateral ventral striatum, including the NAcc and adjacent regions of the caudate, predicted reduced anxiety severity and a faster rate of improvement in anxiety symptoms following treatment with CBT monotherapy or CBT combined with SSRIs (citalopram or fluoxetine) among youth with depression and comorbid anxiety (Forbes et al. 2010). These findings suggest that ventral striatal responsiveness to reward underlies greater sensitivity to positive outcomes that derive from CBT (e.g., expectation of clinical improvement, in-session therapist approval, anticipation of rewarding outcomes in situations that also increase anxiety) and might facilitate engagement in therapy and thereby better treatment outcomes. For example, greater reward responsiveness could manifest as a more active participation in therapy sessions, a higher likelihood of completing therapeutic homework, or a greater capacity to apply coping strategies outside of the therapeutic setting.

Conversely, in the same study, lower reward-related activation in a region extending from dorsomedial PFC into pregenual ACC before treatment was related to faster improvement of anxiety symptoms (Forbes et al. 2010). The pregenual ACC was considered in relation to the ventromedial PFC node of the default mode network (Raichle 2015), which is involved in self-referential processing (Amodio and Frith 2006). Reduced activation was therefore interpreted to reflect less self-focused thoughts, enabling better task engagement and potentially better engagement with treatment. Alternatively, reduced dorsomedial PFC activation may reflect poorer emotion regulatory capacity (Etkin et al. 2011; Price and Drevets 2010) and therefore more room to benefit from treatment. However, as this finding involves youth with comorbid depression and anxiety, thus its applicability to anxiety disorders warrants further validation.

Relevant to these functional predictors, greater gray matter volume in the left NAcc predicted decreases in anxiety symptoms following treatment with CBT or sertraline, among children and adolescents with GAD or SAD (Burkhouse et al. 2020). As the NAcc is involved in reward processing (Daniel and Pollmann 2014), larger volumes may reflect increased reward sensitivity or reward seeking (Coveleskie et al. 2015; Damme et al. 2022; Thayer et al. 2012). Thus, greater NAcc volume might reflect more responsivity to the positive reinforcement and goal-oriented nature of therapies like CBT. SSRIs also increase serotonin levels in the brain, which can directly affect reward processing pathways, including the NAcc (Kitaichi et al. 2010). NAcc volume may be associated with differences in serotonergic response, potentially enhancing sensitivity to positive effects of SSRIs, though this would need to be tested directly.

5 Summary

We reviewed how the neural circuits responsive to threat and reward processing serve as predictors and/or mechanisms of therapeutic success in pediatric anxiety and PTSD. First, with respect to threat processing, enhanced pretreatment amygdala response to threatening versus safe stimuli predicts improved treatment outcomes in pediatric anxiety and PTSD (Cisler et al. 2015; McClure et al. 2007a), suggesting that accurate threat-safety discrimination may facilitate better engagement with CBT or enable better responses to SSRIs. Trauma-focused CBT led to reductions in amygdala responsiveness to benign stimuli (Garrett et al. 2019), marking a potential mechanism of symptom improvement in PTSD, which may also have implications for anxiety disorders. Second, neural activation in lateral prefrontal and more dorsal anterior cingulate cortices during threat processing likely reflects baseline differences in executive control processes and may be an important biomarker of treatment response for pediatric anxiety, though this may be moderated by attentional focus. Elevated pretreatment activation to threat in the dorsolateral and ventrolateral PFC predicts a better response to CBT/SSRIs (Kujawa et al. 2016), with posttreatment increases in ventrolateral PFC activation suggesting enhancements in cognitive control (Maslowsky et al. 2010). In contrast, during tasks that require ignoring threats, less activation in medial frontal cortex areas (e.g., dorsomedial PFC, dorsal ACC) predicts better responses to CBT and SSRIs (Burkhouse et al. 2017) with rostral ACC function increasing following treatment, corresponding with reductions in symptom severity (Burkhouse et al. 2018). Third, activation in other default mode network nodes (posterior cingulate cortex, precuneus) during threat processing was reduced following trauma-focused CBT for PTSD (Garrett et al. 2019), possibly indicating reduced self-focus or enhanced task engagement. Decreases in visuoattentional and sensorimotor regions have also been observed following the treatment of anxiety with CBT (Haller et al. 2024), with elevated pretreatment sensorimotor activation predicting better responses to CBT and SSRIs (Kujawa et al. 2016). This may further support that treatment leads to improved task engagement, as was observed in one study. Finally, functional connectivity between the amygdala and other limbic, prefrontal, and default mode network nodes is also an important marker of treatment response in youth with anxiety and PTSD. Specifically, reduced pretreatment connectivity between the amygdala and the insula associated with better treatment outcomes for anxiety disorders (White et al. 2017) and reduced amygdala-dorsal ACC connectivity predicted better treatment outcomes for PTSD (Cisler et al. 2015). By contrast, greater anti-correlations between amygdala and vmPFC/sgACC activity are linked to greater symptom reduction for GAD following treatment with SSRIs (Lu et al. 2022). Lastly, increased amygdala connectivity with the default mode network (Lu et al. 2022) and visuospatial areas (Cisler et al. 2015) predicts better treatment responses for anxiety and PTSD, respectively, suggesting these connections could serve as potential biomarkers for predicting therapeutic efficacy.

Emerging evidence suggests that disruptions in reward circuitry, particularly within the ventral striatum, also play a key role in pediatric anxiety and may influence treatment outcomes. Higher pretreatment activation in the ventral striatum, and the NAcc in particular, has been linked to better responses to CBT and other treatments, likely indicating greater sensitivity to positive reinforcement (Forbes et al. 2010; Sequeira et al. 2021). Additionally, greater gray matter volume in the left NAcc predicted decreases in youth's anxiety symptoms following treatment with CBT or SSRIs (Burkhouse et al. 2020).

6 Treatment Implications

The findings of this review support the neurobiological basis of prediction of treatment response (specifically CBT and SSRIs) for youth with anxiety and PTSD. Importantly, the findings of region/network-specific prediction and change articulated in this review have implications for clinical translation. Better understanding of the function of brain regions that lead to better response to treatment (e.g., greater activation of the dorsolateral PFC during threat processing) may be helpful in determining if a given treatment for a child or adolescent with an anxiety disorder or PTSD will be worthwhile or effective. Having predictive information about baseline brain function, prior to the initiation of treatment, will help to identify which youth are more likely to respond to the treatment, helping to distribute scarce clinical resources effectively. Further, understanding the neurobiological mechanisms that help affected youth respond well to treatment could motivate the development of "pretreatment" interventions designed to strengthen the function of certain regions or networks prior to starting treatment, with the goal of improving efficacy of established interventions such as CBT.

The findings of neural change with treatment response also have important treatment implications. By demonstrating change in specific brain regions from pre- to post-treatment in youth with anxiety disorders, this work has potential to identify neurobiological mechanisms that are indirectly or directly related to symptom reduction. If these findings are replicated and a specific mechanism of change is established, novel interventions could be designed with the goal of enhancing this change. For instance, increases in right ventrolateral PFC activity observed with CBT in Maslowsky et al. (2010) indicate that a treatment designed to directly manipulate the right ventrolateral PFC, such as through repetitive transcranial magnetic stimulation, may be a successful and directed future treatment approach. Similarly, these brain regions could be targets of "booster" therapies that help prolong symptom reductions observed with CBT, without requiring affected youth to complete another full course of CBT. However, before these findings can be translated to the clinical space, there are several areas of future study that should be pursued.

7 Future Directions

As discussed in the previous sections of this review, there are some inconsistencies in the findings of prior work, specifically with regard to the direction (greater or weaker) and the specific neural location of brain regions associated with treatment response. For instance, results vary based on the type of task or even the instructions provided for similar task paradigms. This has led to mixed findings that make clinical translation more challenging. To address this, future studies should move toward a more consistent task-based neuroimaging paradigm, and specifically one that closely approximates real-world experiences of anxiety for youth (as discussed in La Buissonniere-Ariza et al. 2021). Alternatively, future studies could prioritize consistency and generalizability by using resting-state neuroimaging, a method that has been understudied in fMRI clinical trials of pediatric anxiety disorders, likely due to uncertainty about the clinical relevance of resting state function, along with challenges related to motion and compliance in youth. More individualized approaches, such as those that utilize repetitive precision scanning of a single individual, could also be considered as a method of better understanding the precise neural correlates of treatment response for a given child or adolescent with anxiety or PTSD. Second, few studies have utilized neuroimaging to examine how pre-to-post-CBT in brain function underpin changes in symptom severity. Even fewer studies have employed randomized control trial designs in which CBT can be directly compared to another intervention. Such work will be needed to isolate treatment-specific effects and determine whether neuroimaging could be used to optimize treatment selection or develop neurally targeted interventions for patients (or groups of patients) with different brain-based vulnerabilities or strengths. Third, a clinical model that relies on a neuroimaging scan prior to treatment will likely always impede feasibility of application. To avoid the need for a neuroimaging scan at the start of treatment, future studies could benefit from identifying symptom or behavior-based measures that associate with patterns of brain activity and that can serve as a proxy for the neural biomarkers of treatment response discussed here. Finally, future research that expands beyond imaging of threat processing is needed to understand the mechanisms of treatment with CBT and SSRIs in pediatric anxiety and PTSD. A promising area for exploration lies in the neural substrates of reward and motivation, which are relevant in youth with depression, but are underexplored in youth with anxiety and PTSD (Sequeira et al. 2021). Furthermore, the neural networks associated with cognitive control function (e.g., cingulo-opercular and frontoparietal networks) and the default mode network have been implicated in threat-processing tasks that involve attentional shifts, but have only recently begun to be examined in the context of anxiety disorders. Given the relevance of the default mode and cognitive control networks in anxiety disorders and CBT (Fitzgerald et al. 2021), investigating the interaction of these tripartite networks both at rest and during cognitive control tasks could yield valuable insights.

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