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Neural Mechanisms Underlying Biased Fear Perception in Youth With Anxiety

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ABSTRACT OF THE DISSERTATION

Neural Mechanisms Underlying Biased Fear Perception in Youth with Anxiety

by

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Accurate recognition of facial affect can inform our understanding of others' emotions and state of mind. Children and adults with anxiety are more likely to interpret ambiguous or neutral stimuli as threatening and are less able to regulate emotional responses to perceived threats which may contribute to the etiology and/or maintenance of anxiety. For instance, perceiving ambiguous social cues, like facial affect, as threatening may cause avoidance of social situations, limiting opportunities to reduce fears through habituation or reappraisal. Threat biases in anxiety may be subserved by elevated activation in arousal and salience-processing brain regions, aberrations in regulatory control brain regions, and impaired connections between these networks. However, less is known about perceptual sources of threat biases in anxiety because existing correlational studies cannot directionally test associations. Current research also suffers from additional limitations including homogenous samples of white, upper-middle-class, treatment-seeking youth, raising important questions about whether extant

models of threat bias in anxiety are generalizable beyond the specific ecology of middle SES European American groups. To address these limitations, this dissertation probed the neurodevelopmental correlates of biases in threat perception in diverse samples of anxious youth. Chapter 1 probed the effects of trait anxiety and pre-scan anticipatory state anxiety on neural response to ambiguously fearful facial affect in preadolescent Latina girls. Results supported that trait anxiety is associated with increased insula sensitivity to fear and reduced activation in the inferior frontal gyrus. Further, pre-scan anticipatory state anxiety influenced perceptual networks and moderated the effect of trait anxiety on activation in executive control regions. In Chapter 2, structural brain analyses conducted in a subset of participants from Chapter 1 revealed that anxious girls displayed reduced integrity in the cingulum, a white matter tract that facilitates communication between limbic and regulatory prefrontal regions. Finally, in Chapter 3, anticipatory state anxiety was experimentally induced in socially-anxious young adults to probe subsequent threat biases in emotion perception. Results revealed that elevations in anticipatory anxiety predicted an increased tendency to label ambiguous facial affect as fearful but not angry. Together, these chapters suggest that threat biases may be subserved by reduced prefrontal regulation of hyperactive arousal networks coupled with aberrations in fear perception. Results also reveal that transient fluctuations in anticipatory state anxiety elicit threat biases in the perception of ambiguously fearful facial affect. Implications for research considerations and avenues for possible treatments are discussed.

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General Introduction

Anxiety Disorders are a prevalent mental health concern in the United States, with approximately 30% of adolescents and adults experiencing an anxiety disorder in their lifetime (Kessler et al., 2005; Merikangas et al., 2010). Anxiety disorders have their onset during middle childhood and early adolescence (Kessler et al., 2005; Merikangas & Avenevoli, 2002; Ost, 1987) when neural networks underlying emotion processing and social cognition are developing and socio-emotional skills are maturing (Casey et al., 2000, 2008; Ernst et al., 2006; Herba & Phillips, 2004; E. E. Nelson et al., 2005; Pfeifer & Blakemore, 2012a). Childhood anxiety disorders are often chronic (Spence & Rapee, 2016), even following treatment (Hudson et al., 2015), and present a significant risk factor for negative social outcomes and later psychopathology in adulthood (Beidel et al., 1999; Mancini et al., 2005). Given the adverse sequelae associated with childhood anxiety disorders, it is crucial to understand the neurodevelopmental mechanisms underlying anxiety and its behavioral correlates in order to create effective measures to prevent and treat it. Two known key features of anxiety disorders are threat biases in the perception of ambiguous or negative emotional stimuli (Maoz et al., 2016; Yoon et al., 2014), coupled with impaired emotion regulation abilities (Eden et al., 2015; Hung et al., 2020; Schäfer et al., 2017). Anxiety-related behavioral differences during emotion processing are subserved by hyperactivity in salience-processing brain regions like the amygdala and insula (Brühl et al., 2014; Etkin & Wager, 2007; Killgore & Yurgelun-Todd, 2005; K. M. Thomas et al., 2001), aberrations in prefrontal, regulatory control networks (Klumpp et al., 2013; Monk et al., 2006; Swartz et al., 2014), and reduced

limbic-prefrontal functional coupling (Guyer, Lau, et al., 2008; Monk et al., 2008; Pagliaccio et al., 2015; Roy et al., 2013) suggesting impaired downregulation of threat reactivity by regulatory regions. However, less is known about developmental influences on anxiety-related differences in prefrontal function and connectivity with salience-processing regions. Further, the perceptual sources of threat biases in anxiety are not well understood because much of the existing literature relies on correlational research, which cannot test directional associations. Finally, pediatric anxiety research is frequently conducted in white, treatment-seeking youth from advantaged socioeconomic backgrounds, limiting the generalizability of results. Across three studies, this dissertation leverages functional and structural neuroimaging, precise behavioral testing, and experimental manipulation to examine the mechanisms underlying the development of anxiety disorders across the lifespan in diverse samples.

Anxious youth and adults display increased attention to fearful and angry facial affect relative to controls (Bar-Haim et al., 2007; Brotman et al., 2007; Eysenck et al., 2007; Roy et al., 2008; Shechner et al., 2013; Telzer et al., 2008) and are more likely to interpret emotional stimuli as negative or threatening (Cooney et al., 2006; Maoz et al., 2016; Muris et al., 2000; Reeb-Sutherland et al., 2015; Taghavi et al., 2000; Yoon et al., 2014). A growing evidence base also suggests that anxiety may be associated with perceptual enhancements for threat-relevant stimuli (Etkin & Wager, 2007; Gentili et al., 2016). Perceiving ambiguous emotional expressions as threatening could contribute to the onset and/or maintenance of anxiety. Misidentifying social cues could impair communication between interaction partners, possibly leading to uncomfortable or

embarrassing social interactions. For instance, anxious people may misperceive ambiguous or low-intensity facial expressions as signs of social disapproval and may respond inappropriately. Further, perceiving social cues as threatening may cause anxious people to avoid social situations, reducing opportunities to habituate or reappraise fears and further exacerbating anxiety symptoms (Stirling et al., 2006). Thus, targeting threat biases in emotion perception may be a possible avenue for treating anxiety symptoms and improving social skills.

In addition to displaying threat biases in emotion recognition, anxious individuals also display decrements in executive control functions, including a reduced ability to regulate negative emotions (Cisler et al., 2010; Schäfer et al., 2017; Suveg & Zeman, 2004) and inhibit responses to task-irrelevant stimuli, especially when they are negative (Cisler & Koster, 2010). The ability to self-regulate threat responses may be especially important during unpleasant or ambiguous social situations. When distressed, anxious individuals display impairments engaging in goal-directed behaviors, controlling impulsive behaviors, and selecting effective regulation strategies (Salters-Pedneault et al., 2006), thereby reducing their ability to control elevated emotional reactivity. Problematically, abnormalities in emotion regulation may even amplify the influence of negative emotional responses on anxiety symptoms (Cisler et al., 2009; Kashdan et al., 2008; Kashdan & Steger, 2006). In addition to regulatory impairments, children and adults with anxiety display impaired task performance when presented with emotional distractors (Krug & Carter, 2012; Ladouceur et al., 2009) due to a reduced ability to flexibly deploy and shift attention in the presence of potential external threats (Eysenck et

al., 2007). Together, these findings suggest that anxiety is subserved by enhanced threat processing and emotional reactivity coupled with a reduced ability to control these processes.

In line with behavioral findings, anxiety disorders are mediated by hyperactivation in brain regions responsible for emotion processing and arousal, along with aberrant recruitment of top-down cortical networks that regulate arousal and anticipation of threat. Upon viewing negative or ambiguous facial affect, children and adults with generalized anxiety and social anxiety reliably display elevated blood oxygenation level dependent response (BOLD) response in brain regions implicated in emotional arousal and salience detection, including the amygdala and insula (Brühl et al., 2014; Dickie & Armony, 2008; Etkin et al., 2004; Etkin & Wager, 2007; Günther et al., 2020; Killgore & Yurgelun-Todd, 2005; K. M. Thomas et al., 2001). These regions are core structures in detecting the emotional significance of a stimulus and generating an affective response (Murray, 2007; Phillips et al., 2003) and are central for processing threats or other negative affective stimuli (Etkin, 2010, 2012). Threatening or emotional stimuli signal the amygdala to activate a threat response, allocate attentional resources, and increase vigilance (Davis & Whalen, 2001; Vuilleumier et al., 2004), enabling rapid detection of potential threats and preparation of fight or flight responses (LeDoux, 1996). Although this is an adaptive response to danger in the general population, for individuals with anxiety this adaptive response is overly intense and can become maladaptive. The amygdala has strong, bidirectional connections with the insula (Reynolds & Zahm, 2005), a region involved in detecting and interpreting certain bodily states (Craig, 2002) and

experiencing subjective emotions (Tayah et al., 2013; Uddin et al., 2017). The insula receives information about the salience and value of stimuli and integrates this information with the predicted influence that stimuli may have on the body (Paulus & Stein, 2006). The insula is involved in the anticipation of emotionally aversive events (Grupe & Nitschke, 2013; J. B. Nitschke et al., 2006; Ploghaus et al., 1999; Simmons et al., 2004), and insula hyperactivation may lead anxious people to misinterpret bodily signals, triggering anxious affect, worry, and avoidance behaviors (Paulus & Stein, 2006). Together, elevated amygdala and insula activity may underlie anxiety symptoms, whereby negative social information is assigned greater salience than neutral or safe cues.

Of particular relevance to this dissertation, hyperactivation of the amygdala may additionally contribute to biases in perceptual processing in anxiety. Emerging research suggests that anxiety may influence sensory systems to prioritize threat-relevant stimuli, which may alter perceptual representations of threat (see Sussman et al., 2016 for a review). In the general population, the amygdala rapidly detects threat-relevant stimuli via a neural pathway that processes low-spatial frequency information without requiring cortical input (de Gelder et al., 1999; LeDoux, 2000; Sander et al., 2003; Vuilleumier et al., 2003). After the amygdala detects a threat, it can influence processing in sensory regions by sending re-entrant feedback signals (Vuilleumier, 2005), leading to perceptual prioritization (A. K. Anderson & Phelps, 2001; Davidson, 2002; Ohman, 2005; Ohman et al., 2001). During emotion viewing, anxious individuals display elevated amygdala activity relative to controls (Brühl et al., 2014; Etkin & Wager, 2007), elevated visual cortical engagement (Brühl et al., 2014; Etkin & Wager, 2007; Gentili et al., 2016;

Straube et al., 2005) and increased functional connectivity between the amygdala and perceptual regions (Brühl et al., 2014). Further, people with elevated anxiety display enhanced unconscious processing of subliminal fearful facial affect (Li, Zinbarg, et al., 2008) and other threat cues (Mathews & MacLeod, 1986), suggesting threat biases can arise prior to conscious cognition. Despite evidence for differences in bottom-up perception in anxiety, most anxiety research has focused on attentional (Cisler & Koster, 2010; Mueller et al., 2009; Pishyar et al., 2004; Taylor et al., 2016) and interpretative biases (Amin et al., 1998; Constans et al., 1999; D. Roth et al., 2001; Stopa & Clark, 2000) and less is known about the contribution of perceptual biases. Targeting perceptual biases in anxiety may have important implications for its prevention and treatment. For instance, reducing the perceptual salience of threatening features of ambiguous stimuli relative to safe or neutral features might lead to downstream differences in interpreting social situations.

In addition to biases in salience detection, anxious children and adults also display aberrant activation in prefrontal regions that are involved in appraising and regulating emotional responses during emotion processing (Brühl et al., 2014; Etkin & Wager, 2007; Fonzo & Etkin, 2017). In healthy populations, regulating negative affective states leads to increased engagement of prefrontal regions like the dorsal anterior cingulate cortex (dACC), dorsolateral prefrontal cortex (dlPFC), and inferior frontal gyrus (IFG)/ventrolateral prefrontal cortex (vlPFC) (Buhle et al., 2014; Diekhof et al., 2011; Etkin et al., 2015; Ochsner et al., 2012). These regions are involved in executive function processes like emotion regulation, selective attention, and response inhibition (Aron et

al., 2014; Botvinick et al., 2004; Pessoa et al., 2003; Thompson-Schill et al., 2005). Anxious youth and adults display abnormal recruitment of these prefrontal, regulatory networks during emotion processing (Brühl et al., 2014; Etkin & Wager, 2007; Fonzo & Etkin, 2017). However, the literature is mixed as to whether anxiety is associated with heightened prefrontal activation (Buff et al., 2016; McClure et al., 2007; Monk et al., 2006; Strawn et al., 2012) or reduced engagement (Bishop, Duncan, Brett, et al., 2004; Etkin et al., 2010; Klumpp et al., 2011; Palm et al., 2011; Swartz et al., 2014). Differences among studies may be a result of differences in instructed task behaviors (e.g., implicit versus explicit emotion processing; Klumpp et al., 2013; Swartz et al., 2014) or the type of emotional stimuli employed (Glenn et al., 2021).

In the general population, engagement of prefrontal, regulatory regions leads to deactivation in limbic-related arousal networks like the amygdala and the insula (Craig, 2003, Haber and Knutson, 2010, Morrison and Salzman, 2010). Anxious people also display reduced functional (Cha et al., 2016; Hahn et al., 2011; Monk et al., 2008) and structural connectivity (Baur et al., 2012; Glenn et al., 2022; Phan et al., 2009) between regulatory networks and limbic regions involved in arousal, which may underlie impaired executive control in anxiety. The cingulum and uncinate fasciculus are two white matter tracts that enable the downregulation of negative emotions by facilitating prefrontal-limbic communication. Diffusion-weighted imaging studies find that adults with anxiety display reduced white matter integrity in these tracts (Baur et al., 2011; Phan et al., 2009; Tromp et al., 2012; Wang et al., 2016; Y. Zhang et al., 2013). However, relationships between childhood anxiety and white matter microstructure are less systematic

(Aggarwal et al., 2022; Andre et al., 2020; Liao et al., 2014; Mohamed Ali et al., 2019; Tromp, Williams, et al., 2019), possibly due to developmental changes in brain structure during puberty.

During middle childhood and early adolescence children undergo important developments in their cognition, biology, and social networks, which may contribute to elevated risk for developing anxiety disorders (Kessler et al., 2005; Merikangas & Avenevoli, 2002; Ost, 1987). As children enter middle and later childhood, peer networks grow in size and become more diverse (Brown & Larson, 2009; Furman et al., 2009; Parker et al., 2015). These differences contribute to the creation of social hierarchies (McHale et al., 2003) and to groups that are segregated by certain factors like sex and race-ethnicity (Abrams et al., 2003; Horn, 2003), requiring children to employ more nuanced social skills to navigate group dynamics. In conjunction with changing social networks, alterations in the normative development of brain structure, function, and connectivity likely contribute to the emergence of anxiety during middle childhood. For example, studies of gray and white matter development demonstrate great change during the transition from childhood to adolescence, with brain regions involved in social cognition and emotion regulation developing alongside maturing socioemotional skills (Casey et al., 2008; Gee et al., 2013b; Gogtay et al., 2004; E. E. Nelson et al., 2005, 2016; Pfeifer & Blakemore, 2012b). Changing social motivations coupled with a mismatch in the developmental timing of brain maturation—more mature subcortical structures and less mature PFC structures—is thought to create a sensitive period for the development of anxiety disorders (E. E. Nelson et al., 2005, 2016).

The ability to process and identify facial affect is one important social skill that develops throughout childhood and into adolescence (Herba et al., 2006; Herba & Phillips, 2004; L. A. Thomas et al., 2007). Neuroimaging studies in typically developing youth have provided information on the neurodevelopment of the neural networks responsible for perceiving, identifying, and interpreting others' emotions, including the amygdala, insula, and prefrontal cortices. Although it is a relatively early-developing structure, the amygdala continues to undergo functional changes throughout childhood and adolescence that may contribute to changes in processing socioemotional stimuli. For instance, amygdala engagement to threatening facial affect is elevated in youth relative to adults, with some studies finding a linear decrease in amygdala activation from childhood to adulthood (Gee et al., 2013b), and others observing a curvilinear trend that peaks in adolescence (Guyer, Monk, et al., 2008; Hare et al., 2008; Monk et al., 2003). The insula undergoes structural refinement throughout childhood and adolescence (Churchwell & Yurgelun-Todd, 2013; Shaw et al., 2008) that may parallel developmental increases in the ability to identify and regulate emotions (Giuliani et al., 2011; Mayer et al., 1999; Zimmermann & Iwanski, 2014). Developmental increases in neural response to negative or emotional stimuli have been observed in the insula (Decety & Michalska, 2010; Fischer et al., 2010; Lewis et al., 2008) as well as regions in the prefrontal cortex (Vink et al., 2014; Yurgelun-Todd & Killgore, 2006). The dorsal anterior cingulate cortex (dACC) is also reliably engaged by emotional stimuli and plays a role in the appraisal of emotional stimuli (R. J. R. Blair et al., 1999; Lane et al., 1997; Pessoa et al., 2002). Elevations in BOLD response in the dACC to threatening facial affect is greater in youth

than in adults (Monk et al., 2003; E. E. Nelson et al., 2003), though see (Hung et al., 2012). By contrast, activation in the prefrontal cortex elicited by emotional stimuli increases with age (Vink et al., 2014; Yurgelun-Todd & Killgore, 2006). The prefrontal cortex, which is broadly responsible for higher-order cognition (Dixon et al., 2017) has a protracted developmental course and continues to develop into early adulthood (Gogtay et al., 2004; Lenroot & Giedd, 2006; Sowell et al., 2003). Given these critical developmental changes in brain function, more research is needed to understand the neural substrates underlying threat biases in preadolescent youth and whether they are associated with anxiety.

A key feature of anxiety disorders is a tendency to display maladaptively excessive anticipation of threatening or negative future outcomes under conditions of uncertainty (Grupe & Nitschke, 2013; Michalska et al., 2023). When healthy controls experience short-term elevations in anticipatory anxiety, it resembles behavioral, physiological, and neural outcomes experienced in anxiety disorders. For instance, anticipation of and exposure to social threat reliably increases subjective anxiety, physiological reactivity (Kemeny, 2003; Kudielka, Hellhammer, & Kirschbaum, 2007; Leitenberg, 2013; Somerville et al., 2013), and induces changes in BOLD response in the neural circuitry thought to contribute to anxiety (Burklund et al., 2017; Fehlner et al., 2020; Gianaros et al., 2008; Somerville et al., 2013; Wager et al., 2009). In fact, many researchers experimentally elicit anticipatory state anxiety as a translational model for anxiety disorders (Chavanne & Robinson, 2021). Despite this, pediatric anxiety research rarely tests the influence of short-term fluctuations in anticipatory anxiety on neural

outcomes, so little is known about whether state elevations in anticipatory anxiety emulate or interact with trait anxiety symptoms. Preliminary evidence suggests that elevations in anticipatory anxiety may exaggerate biases for individuals with pathological anxiety (i.e., anxiety disorders or high trait anxiety) (Dyer et al., 2022; Egloff & Hock, 2001). However, it is also possible that short-term fluctuations in state anxiety might have a greater influence on healthy controls, as people with pathological anxiety may experience sustained high levels of anticipatory anxiety.

Understanding how momentary elevations in anxiety contribute to threat biases may have important implications for minoritized groups like Latinx participants who are underrepresented in research and display greater mistrust in scientific institutions than white participants (Loue & Sajatovic, 2008; Preloran et al., 2001; Yancey et al., 2006). Greater levels of mistrust and unfamiliarity with research among minoritized participants may lead to systematic differences in anticipatory state anxiety across demographic groups. Such differences may influence emotion processing and/or cognitive functioning and complicate inferences drawn from MRI scans and other biometric measures. In addition, many Latinx communities disproportionately face acculturative and socioeconomic stressors (Pérez et al., 2008; Torres et al., 2012), which may contribute to elevated risk for anxiety disorders (Mendoza et al., 2017). Some studies find that Latinx samples report more anxiety symptoms than other ethnic groups and are at higher risk for experiencing health disparities that create barriers to treatment (Alegria et al., 2006; Lewis-Fernandez et al., 2005; Pina & Silverman, 2004; Varela et al., 2008). However, despite making up 25% of the child population and almost 20% of the adult population in

the United States (*Child Trends*, 2018), few studies focus on the mental health trajectories of Latinx youth or adults. Prevention and treatment efforts developed from research in white samples may not be generalizable to Latinx populations, potentially exposing this group to greater risk. This gap in the literature indicates a critical need to understand the correlates of anxiety in underrepresented communities.

In three chapters, this dissertation will examine the neurodevelopmental correlates of threat biases in emotion perception in anxiety in ethnically-diverse samples of participants (most from Latinx backgrounds) ranging from preadolescence to young adulthood. I leverage functional and structural data analyses, experimental manipulation, and precise behavioral testing to examine how threat biases in emotion perception contribute to the development and maintenance of anxiety disorders. Chapter 1 examines functional correlates of trait anxiety during implicit fear processing in preadolescent girls, and whether associations are influenced by pre-scan anticipatory state anxiety. Chapter 2 leverages diffusion weighted imaging to test whether anxious girls display structural aberrations in white matter tracts connecting brain regions that generate and regulate threat responses. I also assess the influence of pubertal development on associations between anxiety and white matter integrity. Finally, in Chapter 3, I experimentally induce anticipatory state anxiety among socially anxious young adults to test whether transient increases in anticipatory state anxiety lead to threat biases in the perception of ambiguous facial affect. By targeting both behavioral threat biases and structural and functional neural correlates of emotion processing difficulties, the approaches outlined provide

fundamental insight into the development of anxiety and reveal new possible targets for treatment.

Chapter 1 probes the independent and interactive effects of trait anxiety and pre-scan anticipatory state anxiety on neural response to ambiguously fearful facial affect. Unfamiliarity with academic research may contribute to higher levels of anticipatory state anxiety about affective neuroimaging tasks. However, few studies on pediatric anxiety test how pre-scan state anxiety influences emotion processing, so little is known about the influence of state features associated with apprehension of the research environment. In Chapter 1, a community sample of preadolescent Latina girls with elevated trait anxiety underwent functional neuroimaging while viewing fearful faces ranging from low to high intensity. Fear was processed implicitly; girls were instructed to attend to the gender of the face stimuli rather than the emotional content. Results are expected to demonstrate that variations in trait anxiety are dually subserved by hypervigilance to threat in salience-processing regions and reduced activation in regulatory regions. We further hypothesize that elevated pre-scan anticipatory state anxiety will predict brain activity and moderate associations between trait anxiety and neural activity.

Chapter 2 tests whether anxiety symptoms and pubertal stage influence white matter microstructure in a sample of preadolescent Latina girls. We assess microstructural integrity of the cingulum and uncinate fasciculus because they facilitate communication between limbic and regulatory regions in the lateral and medial prefrontal cortex, which are critical in the generation and regulation of threat responses, respectively. Diffusion-weighted imaging studies find that adults with anxiety display

reduced white matter microstructure in these tracts (Baur et al., 2011; Phan et al., 2009; Tromp et al., 2012; Wang et al., 2016; Y. Zhang et al., 2013) but developmental work is mixed (Aggarwal et al., 2022; Andre et al., 2020; Liao et al., 2014; Mohamed Ali et al., 2019; Tromp, Fox, et al., 2019), possibly due to pubertal influences. To address this gap in the literature, we test whether anxiety is associated with decrements in white matter microstructure in cingulum and uncinate fasciculus, and whether pubertal stage moderates this association. Results are expected to demonstrate that decrements in white matter microstructure underlie the development of anxiety in preadolescent girls, possibly via impairments in prefrontal control over limbic regions.

Finally, Chapter 3 tests the effects of experimentally induced anticipatory state anxiety on threat biases in the perception of facial affect among young adults with elevated social anxiety symptoms. Experimental study design is an important method for understanding causal mechanisms. Although experimental design is often used when testing animal models of anxiety, translation between animal models of anxiety and pathological anxiety is difficult. Recent meta-analytic evidence finds that induced anxiety in healthy adults and pathological anxiety display overlapping neural activations (Chavanne & Robinson, 2021), suggesting that experimentally inducing anxiety may serve as an intermediate translational model of anxiety disorders. Participants in Chapter 3 judged the emotion of faces morphed between happy and fearful or angry facial expressions before and after a social threat manipulation or a control task. We first assessed baseline associations between trait social anxiety and threat biases in the perception of ambiguously fearful and angry facial affect. We further tested whether

threat biases could be induced by experimentally manipulating participants' anticipatory anxiety via a social threat. We aimed to target perceptual sources of threat biases so, to reduce the influence of top-down, interpretive biases on participants' emotion ratings, stimuli were presented rapidly and were backward-masked to interrupt stimulus processing (Liss, 1968). We predict that trait social anxiety and induced anticipatory anxiety would be associated with subsequent threat biases in the perception of ambiguous facial affect.

Together, these chapters inform the behavioral and neurodevelopmental correlates of biases in threat perception across development, specifically probing the influence of anticipatory state anxiety. Importantly, all three chapters test anxiety-related biases in emotion perception in samples with a large proportion of participants from Latinx descent, informing the generalizability of existing work. By targeting both behavioral and neural sources of threat biases, the approaches outlined may reveal new targets for prevention and/or treatment of anxiety across diverse samples.

Chapter 1: Pre-scan state anxiety influences perceptual brain networks and moderates the effect of trait anxiety on neural substrates of implicit fear processing in Latina girls

Abstract

Unfamiliarity with academic research may contribute to higher levels of anticipatory state anxiety about affective functional neuroimaging tasks. Children with high trait anxiety display aberrant brain responses to fearful facial affect, but little is known about the influence of state anxiety on this association. Because reduced engagement in scientific research and greater mistrust among minoritized groups may lead to systematic differences in pre-scan state anxiety, it is crucial to understand the neural correlates of state anxiety during emotion processing to disambiguate sources of individual differences. The present study probed the independent and interactive effects of pre-scan state anxiety and trait anxiety on neural activation during implicit fear processing in a community sample of preadolescent Latina girls with elevated trait anxiety. Trait-anxious children displayed increased insula sensitivity to changes in fearful facial affect and reduced activation in the left inferior parietal lobule, suggesting trait anxiety may be subserved by hypersensitivity in salience regions coupled with reduced ability to recruit executive control networks. Pre-scan state anxiety influenced neural activation in face-perception regions and interacted with trait anxiety to predict activation in networks involved in mentalizing and executive control. Imaging researchers should control for state anxiety so that systematic differences in brain activation resulting from MRI apprehension are not misleadingly attributed to demographic or environmental characteristics.

Introduction

Accurate recognition of others' emotional expressions provides us with cues to salient features of the environment and the emotional state of our interaction partners. Children with anxiety exhibit threat biases in processing and interpreting ambiguous facial affect (Brotman et al., 2007; Reeb-Sutherland et al., 2015; Roy et al., 2008; Shechner et al., 2013) and display aberrant neural activation when viewing such stimuli (Blackford & Pine, 2012). Perceiving ambiguous social cues as threatening may cause anxious children to avoid social situations, reducing opportunities to habituate or reappraise fears and further exacerbating anxiety symptoms (Stirling et al., 2006). Momentary feelings of anxiety in healthy children, or *state anxiety*, can also elicit behavioral and neural responses to negative emotional stimuli resembling those seen in pathological anxiety (e.g., trait anxiety and anxiety disorders) (Bishop, Duncan, & Lawrence, 2004; Skouras et al., 2013; Somerville et al., 2004; Suzuki & Tanaka, 2021). Further, state anxiety can interact with pathological anxiety to predict behavioral responses to negative emotional stimuli (Dyer et al., 2022; Egloff & Hock, 2001; Rutherford et al., 2004). Many children experience elevated state anxiety while undergoing functional magnetic resonance imaging scanning (fMRI; Meléndez & McCrank, 1993). However, few developmental studies on anxiety test how pre-scan state anxiety influences emotion processing, so it is unknown whether previous findings capture trait features of anxiety or state features associated with apprehension of the neuroimaging environment, or both. Given that some demographic groups may experience greater state anxiety about scanning due to limited experience with research or

medical mistrust (Loue & Sajatovic, 2008; Preloran et al., 2001; Yancey et al., 2006), it is critical to understand the neural correlates of elevated state anxiety and whether they are distinct from, or overlapping with, those seen in trait anxiety. In the present study, a community sample of Latina girls (8–13 years) with elevated trait anxiety completed an fMRI implicit face emotion viewing task, during which they viewed fearful faces varying in emotion intensity and reported on the face's gender. We tested the interactive and independent effects of state and trait anxiety on girls' neural response to fearful facial affect.

Anxious children display increased attention allocation to fearful and angry facial affect relative to controls (Abend, Bajaj, Matsumoto, et al., 2021; Brotman et al., 2007; Roy et al., 2008; Shechner et al., 2013; Telzer et al., 2008) and are more likely to appraise emotional stimuli as negative or threatening (Muris et al., 2000; Reeb-Sutherland et al., 2015; Taghavi et al., 2000). Several brain networks underlie threat biases in children and adults with pathological anxiety. Upon viewing negative or ambiguous facial affect, children and adults with anxiety disorders display elevated blood oxygenation level-dependent response (BOLD) response in the amygdala and insula (Brühl et al., 2014; Buff et al., 2016; Dickie & Armony, 2008; Etkin et al., 2004; Etkin & Wager, 2007; Fonzo et al., 2015; Günther et al., 2020; Killgore & Yurgelun-Todd, 2005; Monk et al., 2008; K. M. Thomas et al., 2001). The amygdala and insula are highly interconnected structures that contribute to the peripheral expression of emotion and salience detection (Etkin, 2010, 2012; Knight et al., 2005). Upon viewing a negative or threatening stimulus, the amygdala signals the production of a threat response and

increases vigilance (Davis & Whalen, 2001). The insula is involved in interoception and is thought to play a crucial role in subjective emotions (Tayah et al., 2013; Uddin et al., 2017). Given the central role of these regions in identifying the emotional significance of a stimulus and generating an affective response (Murray, 2007; Phillips et al., 2003), they are hypothesized to be important for processing negative affective information. Thus, aberrations in amygdala and insula activity may underlie anxiety symptoms, whereby negative or ambiguous social information is assigned greater salience as a result of hyperactivation in these regions.

Compared to non-anxious controls, anxious youth and adults also show differences in the function of prefrontal cortex (PFC) regions involved in appraising and regulating emotional responses during emotion processing (Brühl et al., 2014; Etkin & Wager, 2007; Fonzo & Etkin, 2017; Glenn et al., 2020), as well as structural differences in tracts connecting these regulatory regions to the amygdala (Baur et al., 2012; Eden et al., 2015; Glenn et al., 2022; Phan et al., 2009). However, the literature is mixed as to whether anxiety is associated with heightened prefrontal activation to negative emotional stimuli (Buff et al., 2016; McClure et al., 2007; Monk et al., 2006; Strawn et al., 2012) or reduced engagement (Bishop, Duncan, Brett, et al., 2004; Britton et al., 2013; Etkin et al., 2010; Klumpp et al., 2011; Palm et al., 2011; Swartz et al., 2014). Variable results across studies may be due to task-related differences in targeted behaviors (e.g., implicit viewing versus explicit labeling; (Klumpp et al., 2013; Swartz et al., 2014), the type of emotional stimuli employed (Glenn et al., 2021), or developmental differences across samples (Britton et al., 2013). For instance, youth and adults with anxiety disorders

displayed less activation in the rostral anterior cingulate cortex during implicit emotion processing (matching shapes in the context of emotional face distractor) than explicit emotion face-matching, relative to controls (Klumpp et al., 2013; Swartz et al., 2014). Thus, biases in implicit or automatic responses to emotional stimuli are a possible etiological account for anxiety disorders (Li, Zinbarg, et al., 2008).

The MRI context itself can elicit temporary feelings of state anxiety, discomfort, or even panic among children (Meléndez & McCrank, 1993; Tyc et al., 1995), which may elicit patterns of activation that are unique from (Saviola et al., 2020), or overlapping with, pathological anxiety (Chavanne & Robinson, 2021). State anxiety in the fMRI context is an especially important consideration in pediatric anxiety research but, to date, it is understudied (see Michalska et al., 2020 for a detailed review of methodological considerations and challenges of the scanning environment). Children undergoing fMRI scans are often alone in the confined space in the scanner bore, where they must tolerate loud noises and restricted motion (Raz et al., 2005). This experience can elicit physical discomfort (Chou et al., 2014) and anxiety (Meléndez & McCrank, 1993; Tyc et al., 1995), and increase biological indices of stress like cortisol (Eatough et al., 2009; Lueken et al., 2012). Elevated state anxiety can impact task performance (Attwood et al., 2017; Dyer et al., 2022) and influence attentional (A. L. Nelson et al., 2015; Quigley et al., 2012), perceptual (Cornwell et al., 2017; Karvay et al., 2022; Kobald et al., 2016; Li, Howard, et al., 2008), and interpretative mechanisms (Attwood et al., 2017; Kavcıoğlu et al., 2021; Muris et al., 2003), as well as their neural bases (Gossett et al., 2018). State anxiety also elicits changes in BOLD response while participants view threatening or

emotional stimuli (Bishop, Duncan, & Lawrence, 2004; Skouras et al., 2013; Somerville et al., 2004; Suzuki & Tanaka, 2021) and even during rest (Baur et al., 2013; Saviola et al., 2020). Importantly, although undergoing MRI scanning induces stress in about 30% of participants (Meléndez & McCrank, 1993), few studies test how pre-scan state anxiety impacts task performance.

Undergoing an MRI scan is anxiety-inducing for not just children (Marshall et al., 1995; Tyc et al., 1995) but also more generally people who are unfamiliar with the scanning environment (Chapman et al., 2010; Rosenberg et al., 1997). Because minoritized groups like Latinx participants are underrepresented in research and, for historic reasons, display greater mistrust in medical, academic, and scientific institutions than white participants (Loue & Sajatovic, 2008; Preloran et al., 2001; Yancey et al., 2006), there may be systematic differences in state anxiety across demographic groups that lead to inaccurate interpretations of results. For instance, higher rates of pre-scan state anxiety among a minoritized group in a study may lead to greater alterations in emotion processing or cognitive functioning in that group. Without accounting for state anxiety, such task-related differences could be misattributed to temperamental, environmental, or cultural factors rather than apprehension of the research environment.

In the present study, a community sample of Latina girls (8–13 years) with elevated trait anxiety completed an implicit face emotion viewing task while undergoing fMRI scanning. In this task, children viewed graded levels of happy and fearful faces varying in emotion intensity and reported on the face's gender. We tested the independent and interactive effects of trait anxiety and state anxiety on whole-brain neural response to

fearful affect. Two separate models tested mean BOLD response across all fearful affect and fear intensity-modulated response (i.e., the slope of the neural activation across varying fear intensities). We focused only on fearful affect as threat biases in anxiety are largely specific to threat perception (Doty et al., 2013; Reeb-Sutherland et al., 2015; Richards et al., 2002; Surcinelli et al., 2006). First, we hypothesized that, relative to low trait-anxious children, high trait-anxious children would display overall increased amygdala and insula response to fearful facial affect (Dickie & Armony, 2008; Killgore & Yurgelun-Todd, 2005; Stein et al., 2007; K. M. Thomas et al., 2001), reduced activation in prefrontal regions like the vlPFC and ACC (Klumpp et al., 2013; Monk et al., 2006; Swartz et al., 2014), and less intensity-modulation in all hypothesized regions (Bishop et al., 2015; Michalska et al., 2023). Second, as meta-analytic evidence finds that state and trait anxiety elicit overlapping patterns of neural activation in the insula (Chavanne & Robinson, 2021), we hypothesized that *state* anxiety would also elicit high insula response to fearful facial affect. Third, we tested whether state and trait anxiety interacted to predict neural responses. Following prior work showing that state anxiety increases attentional and interpretive threat biases only for trait-anxious people (Dyer et al., 2022; Egloff & Hock, 2001), we predicted elevations in both state and trait anxiety would interact to predict neural increased activation in regions involved in salience detection (e.g., insula, amygdala) and reduced activation in attentional control regions (e.g., vlPFC, ACC).

Methods

Participants and Procedure

Fifty-five 8-13-year-old Latina girls and their primary caregivers were recruited from the Inland Empire of Southern California to participate in a longitudinal study of emotional development. Participants were recruited via the University's shared database of child participants recruited from the community, as well as through fliers in local outpatient mental health clinics and hospitals. Participant eligibility was determined by phone screening with the primary caregiver. Children were eligible for participation if they were between 8 and 13 years old, fluent in English, right-handed, and had no contraindications for neuroimaging (e.g., no ferrous metal in the body, not pregnant, not claustrophobic). Children also needed to be at least 50% Latinx origin and self-identify as Latina to be eligible for participation (see Table 1.1 for ethnic-racial identity of participants in the final sample). Exclusionary criteria included current psychiatric diagnosis of Tourette's syndrome, obsessive-compulsive disorder, lifetime history of mania, psychosis, or pervasive developmental disorder. Menstruation onset was initially used as an exclusionary criterion but was dropped to increase sample size, and two postmenarchal participants were recruited.

Table 1.1. Racial and ethnic background of study participants ($N = 46$).

Ethnic-Racial Background	***N***
Latina	39
Mexican American	31
South/Central American	2
Mixed ethnicity (Mexican American & other Latinx)	6
Mixed race (Latina & white)	7

Participants completed a laboratory testing session and a scanning session. During the laboratory session, children and caregivers reported on family demographics and children's behavior, anxiety, and other mental health outcome measures not reported here. During the scanning session, children completed an implicit face emotion viewing task while undergoing fMRI data collection. fMRI scans were not collected from seven participants because they did not return for the scan visit (n = 4), or due to participants' distress (n = 1), dental braces (n = 1), or experimenter error (n = 1). Two participants were excluded due to low response rate on the task (> 25% missed trials), resulting in a final sample of 46 participants (M_{age} = 9.9 $\pm$ 1.2 years; Table 1.2) and their caregivers (40 mothers, 6 fathers). The visit structure was changed part-way through data collection so 10 participants completed the laboratory session and scanning session at two visits, approximately two weeks apart (M = 19.3 days, $\pm$ 4.8). The remaining 36 participants completed the laboratory and scanning sessions in one visit. Upon participant arrival at each wave, written parent consent and child assent were obtained. At the end of each session, participants were compensated with a gift card and a toy. All study procedures were approved by the Institutional Review Board.

Table 1.2. Sample demographic characteristics and descriptive statistics for study variables.

Characteristic	Descriptive Statistics
N	46
Female (%)	100
Age, years	
Mean (SD)	9.9 (1.2)
Range	8 - 12
Household income (*N*=45)	
Mean (SD)	$60,666 ($46,277)
STAIC-Trait	
Mean (SD)	38.4 (7.2)
Range	22-54
STAIC-State (*N*=43)	
Mean (SD)	29.5 (5.3)
Range	20-48
SCARED	
Mean (SD)	36.8 (14.6)
Range	4 - 71

Note. STAIC = State-Trait Anxiety Inventory for Children. SCARED = Screen for Child Anxiety Related Disorders. Household income was not available for one participant. STAIC-State measures were not collected from three participants.

Measures

State and Trait Anxiety Symptoms

Children's state and trait anxiety symptoms were measured via child self-report on the State-Trait Anxiety Inventory for Children (STAIC; (Spielberger et al., 1972). The STAIC is comprised of two 20-item scales that assess state anxiety (STAIC-State) and trait anxiety (STAIC-Trait). Children respond to all items on a three-point Likert scale,

and each subscale is summed to a total score (range: 20–60). Both measures display excellent internal consistency ($\alpha \geq .81$; (Spielberger et al., 1973).

The STAIC-State measures children's state anxiety by asking children to indicate how they feel "right now…at this moment." The STAIC-State was measured in the imaging facility immediately before the scan. The STAIC-State was added to the protocol shortly after data collection began, so three participants did not complete it and their scores were imputed with mean-replacement.

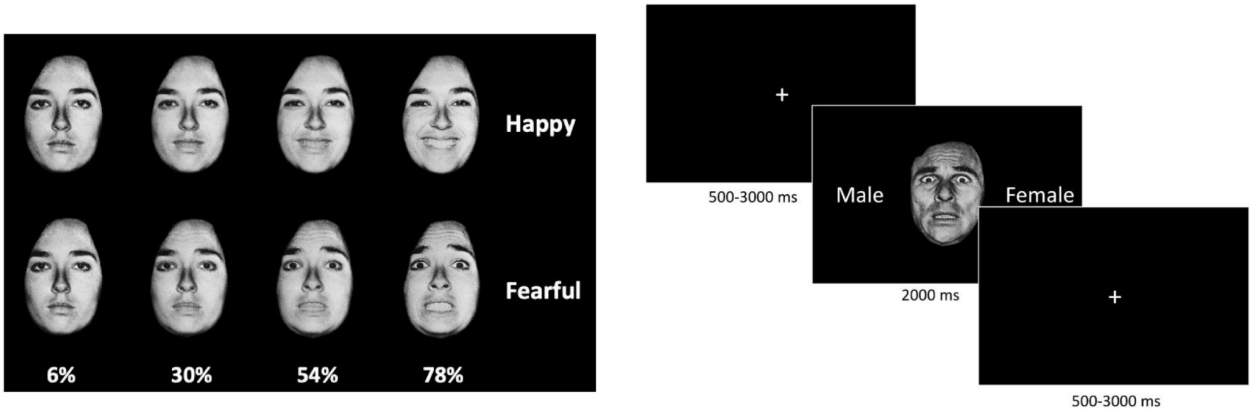
The STAIC-Trait assesses trait levels of anxiety by probing how the child usually feels. Children completed the STAIC-Trait in the lab, prior to the scan. The STAIC-Trait demonstrates concurrent validity with other anxiety measures ($r = .88$; Spielberger et al., 1973). In our sample, the STAIC-Trait is highly correlated with child report on the Screen for Child Anxiety Related Disorders ($r = .81$, $p < .001$; SCARED; Birmaher et al., 1997), which assesses anxiety disorder symptomatology. Although our sample was a non-treatment-seeking community sample, anxiety scores were elevated. The threshold for clinically-significant levels of anxiety on the SCARED (≥ 25) was met in 38 child-reported scores (Table 1.2). Of note, state and trait anxiety scores (STAIC) were uncorrelated in our sample ($r = .04$, $p = .77$).

Implicit Face Emotion Viewing Task

While undergoing fMRI scanning, children completed an implicit face emotion viewing task (R. J. R. Blair et al., 2001; Stoddard et al., 2017) during which they labeled the gender of ten actors' face emotion pictures (100% white; 60% female). Faces were morphed between fearful or happy and neutral expressions at 6%, 30%, 54%, and 78%

emotion intensity (Figure 1.1). Because of our focus on probing anxiety-related biases in threat processing, the present analyses focus only on fearful facial affect (Doty et al., 2013; Richards et al., 2002; Surcinelli et al., 2006). Faces were presented in random order for 2000 ms each, followed by a 500-3000 ms jittered interstimulus interval (ISI) during which a white fixation cross was presented against a black background. In one run, children viewed 20 trials of each morphed fearful and happy stimulus, summing to 160 trials total and 80 trials of fear morphs. The task was programmed in E-prime (version 2.0.10; PST Inc., Pittsburgh, PA). Participants viewed the back-projected screen via a mirror mounted on the head coil and pressed a button box with their right hand to indicate the gender of the face (male/female).

Figure 1.1. Implicit face emotion viewing paradigm.



Note. Participants labeled the gender of faces that were blended between neutral and fearful or happy emotional expressions at 6%, 30%, 54% and 78% intensities. Faces were presented in random order for 2000 ms each, followed by a 500-3000 ms jittered interstimulus interval (ISI).

Imaging Data

MRI Data Acquisition and Preprocessing

Whole-brain neuroimaging data were collected using a 3T Siemens Prisma scanner and 32-channel head coil. Two hundred and forty functional image volumes were collected during one run of 9 min 44 s. Functional image volumes with 62 contiguous interleaved axial slices were obtained with a T2*-weighted echo-planar sequence (TR = 2500 ms; TE = 32 ms; flip angle = 80; Field of View [FOV] = 204 x 228 mm; matrix = 102 x 114; voxel size = 2 x 2 x 2 mm^3). Using a magnetization-prepared gradient echo sequence, functional data were anatomically localized and coregistered to a high-resolution T1-weighted volumetric scan of the whole brain that was collected prior to the functional volumes (MPRAGE: TR = 2400 ms; TE = 2.72 ms; TI = 1060 ms; flip angle = 8; FOV = 240 x 256 mm; matrix = 300 x 320; voxel size = .8 x .8 x .8 mm^3).

Individual echo-planar images were preprocessed and analyzed using AFNI (Analysis of Functional NeuroImages; version 22.0; Cox, 1996). Preprocessing included despiking, slicetime correction, motion correction, and smoothing with a 4 mm full-width at half-maximum (FWHM) kernel. All MRI data were transformed to Montreal Neurological Institute (MNI) space. BOLD data was scaled at the voxel-wise time series by their temporal means so effect estimates can be interpreted as percent signal change. Every TR on which motion exceeded 2 mm was censored and excessive motion was defined as more than 20% of TRs censored for motion/outliers (n = 0). One participant had 20.4% of TRs censored and was included in all analyses. Average head motion was not correlated with state anxiety (r = .15, p = .30) or trait anxiety (r = .24, p = .10).

Using the AFNI 3dDeconvolve function, a general linear model was generated to estimate BOLD signal change with amplitude modulation based on fear intensity level of the stimulus (i.e., 6%, 30%, 54%, 78%). We generated two regressors using the amplitude modulation option (AM2) in AFNI: mean task-related activation across all fear intensities and fear intensity-modulated BOLD response. Fear intensity-modulated BOLD response tested amplitude modulation by trial-wise emotion intensity, allowing us to examine trial-by-trial associations between variation in BOLD response and variation in emotion intensity. Regression coefficients for the effects of intensity-modulation indicate differences in percent signal change per emotion intensity increase above one's mean response to fear, indexing the strength of the emotion intensity-BOLD association. Positive fear intensity-modulation indicates increasing activation with greater fear intensity and vice versa. Third-order Legendre polynomials modeled baseline drift and six head motion parameters.

Statistical Analyses

To correct for multiple comparisons, familywise error correction was performed using Monte Carlo simulation on gray matter-masked, whole-brain data (3dClustSim in AFNI). The gray matter mask was created by segmenting the MNI152_2009c anatomical template into gray matter and non-gray matter. Masked output maps included gray matter voxels of the whole brain. The voxel threshold of $p < .005$ resulted in an average cluster threshold of 50 voxels at the whole-brain corrected alpha level of .05. Peak coordinates (x, y, z) are reported based on the MNI atlas in left, posterior, inferior (LPI) orientation.

Two linear mixed-effects models were conducted using AFNI's 3dLME program (Chen et al., 2013). The first model tested the independent and interactive effects of state and trait anxiety in predicting mean task-related activation, averaged across all fear intensity levels. The second model tested the independent and interactive effects of state and trait anxiety on fear intensity-modulated BOLD response. Gray matter-masked, whole-brain voxel-wise tests were used for all fMRI analyses and age was included as a continuous covariate of no interest. Follow-up simple slopes analyses were conducted in clusters with significant state-by-trait anxiety interactions to obtain the model-predicted slope for children with high (+1 SD), moderate (0 SD), and low (-1 SD) trait anxiety levels.

Dependent measures for behavioral analyses were gender labeling accuracy (percent correct gender identification across all fear trials), percent overall trials responded to, and mean reaction time. Children's state (STAIC-S) and trait (STAIC-T) anxiety levels were correlated with each behavioral measure.

Results

Behavior

Children showed high task engagement (M = 94.1% response rate $\pm$ 5.6%) and were accurate at labeling the gender of faces (M = 91.0% $\pm$ 8.8%). Two participants responded to fewer than 75% of trials and were excluded from the final analyses with N = 46. State anxiety was inversely associated with average response rate across all fear trials, r = -.31, p = .039, such that participants with greater state anxiety responded to fewer trials. Trait anxiety was not associated with response rate (r = -.12, p = .41). Gender

labeling accuracy was not correlated with state anxiety (r = -.09, p = .55) or trait anxiety (r = -.25, p = .08). Reaction time (M = 1081.9 ms $\pm$ 134.9 ms) was also unrelated to state anxiety (r = .07, p = .62) and trait anxiety (r = .03, p = .85).

Brain Activation

Main Effects of Trait Anxiety

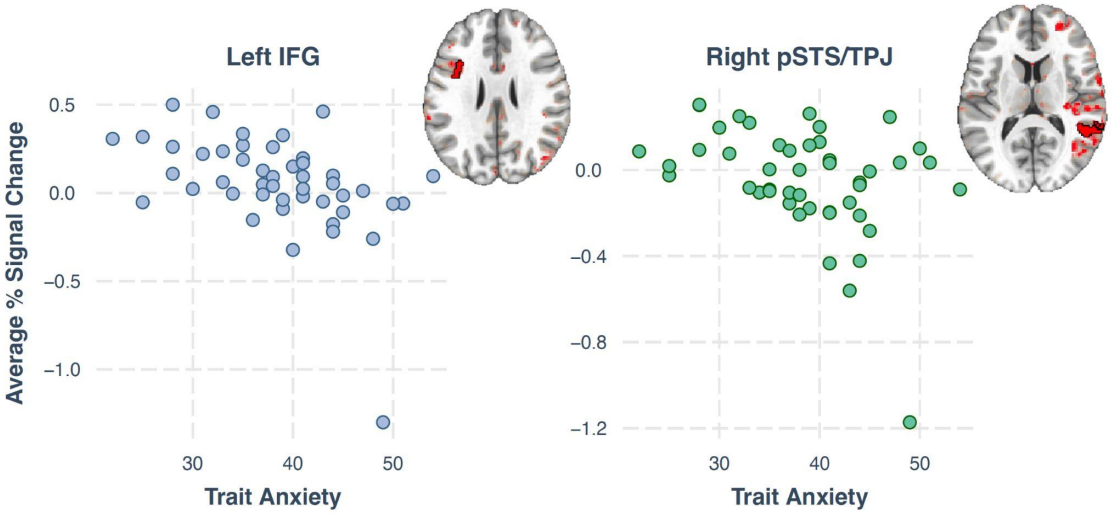
We observed a main effect of trait anxiety on mean hemodynamic response to fear faces in two clusters, after controlling for state anxiety and age. The first cluster was in the left opercular inferior frontal gyrus (IFG) and the second cluster included the right posterior superior temporal sulcus (pSTS) and right temporoparietal junction (TPJ). Trait anxiety was inversely associated with BOLD response in the left IFG (r = -.47, p = .001) and right pSTS/TPJ (r = -.39, p = .007) (Table 1.3, Figure 1.2). Trait anxiety was also positively associated with fear intensity-modulated activation in a cluster in the right insula (r = .48, p < .001; Figure 1.3). Children with high trait anxiety displayed greater increases in right insula activation with increasing fear intensity compared to children with low trait anxiety.

Table 1.3. Effects of trait and state anxiety on neural activation.

Region	Regressor Type	Size (k)	Peak Coordinates (LPI x, y, z)		
Trait Anxiety					
Right pSTS/TPJ	Mean Activation	102	59	-45	9
Left IFG	Mean Activation	61	-39	3	25
Right Insula	Intensity-Modulation	205	31	3	-5
State Anxiety					
Left IOG/FG	Intensity-Modulation	98	-45	-81	-15
Trait x State Anxiety					
Right Operculum	Mean Activation	170	51	-17	3
Right pSTS/TPJ	Mean Activation	130	57	-51	11
Right Caudate	Mean Activation	82	17	19	3
Right Angular Gyrus	Mean Activation	55	47	-75	27

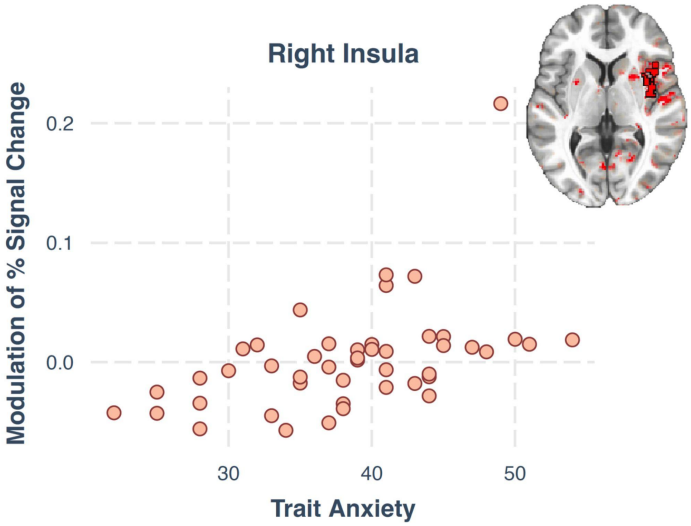
Note. pSTS = posterior superior temporal sulcus; TPJ = temporoparietal junction; IFG = inferior frontal gyrus; IOG = inferior occipital gyrus; FG = fusiform gyrus. The threshold of $p < .005$ resulted in an average cluster threshold of 50 voxels at a whole-brain corrected alpha level of .05.

Figure 1.2. Inverse associations between trait anxiety and mean neural response to fearful facial affect in the left IFG and right pSTS/TPJ.



Note. A gray matter-masked whole brain analysis revealed inverse associations between trait anxiety and BOLD response (averaged across 6%, 30%, 54%, 78% fear intensities) in the left inferior frontal gyrus (IFG; r = -.47, p = .001) and right posterior superior temporal sulcus (pSTS) / temporoparietal junction (TPJ; r = -.39, p = .007). Correlations remain significant when the outlier was removed (ps < .03).

Figure 1.3. Trait anxiety was positively correlated with fear intensity-modulated BOLD response in the right insula.

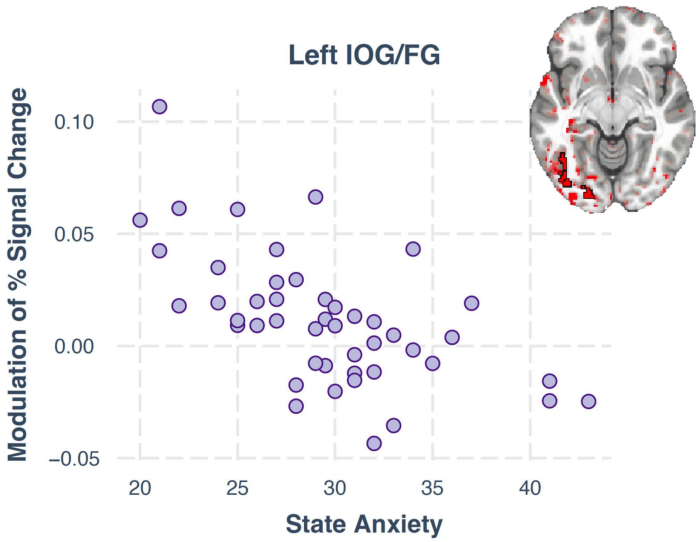


Note. Children with high trait anxiety displayed greater increases in right insula activation with increasing fear intensity compared to children with low trait anxiety (r = .48, p < .001). Removing the outlier did not change associations.

Main Effects of State Anxiety

No main effects of state anxiety on mean activation emerged. A main effect of state anxiety on fear intensity-modulation emerged in one cluster that encompassed portions of the left inferior occipital gyrus (IOG) and left fusiform gyrus (FG) and included the fusiform face area. State anxiety was negatively associated with fear intensity-modulated activation, such that children with low state anxiety displayed greater increases in BOLD in the left IOG/FG as stimuli displayed greater levels of fear (r = -.61, p < .001; Figure 1.4).

Figure 1.4. State anxiety was inversely associated with fear intensity-modulated BOLD response in the left IOG/FG.

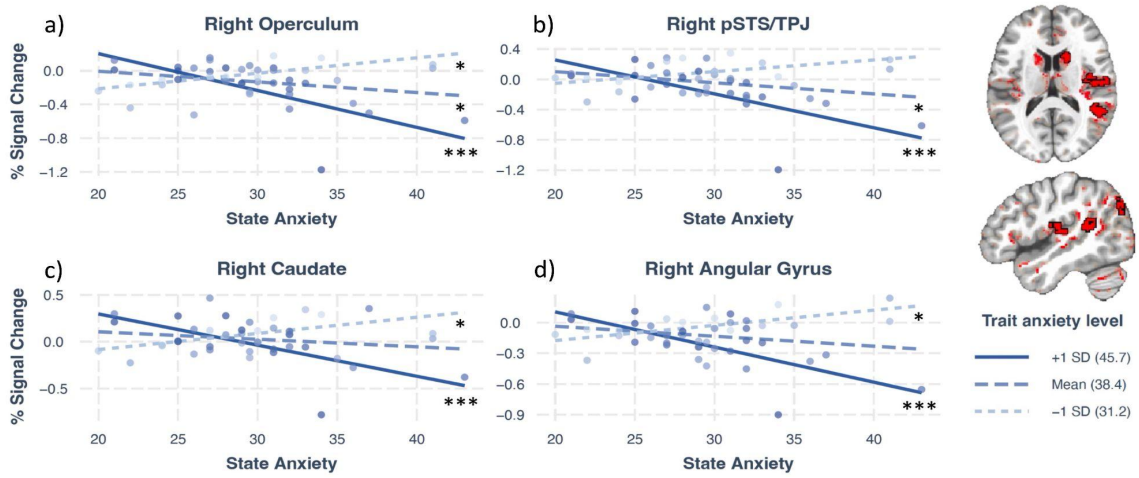


Note. Children with low trait anxiety displayed greater fear intensity-modulation in the left IOG/FG than children with high trait anxiety (r = -.61, p < .001). The correlation remained significant when the outlier was removed.

Trait-State Anxiety Interactions

Trait and state anxiety interacted to predict mean BOLD response in four clusters: the right operculum, the right pSTS/TPJ, the right caudate, and the right angular gyrus (*ps* < .005, corrected). Follow-up simple slopes were conducted in each region to test the model-predicted association between state anxiety and mean BOLD response for children with low (-1 SD: STAIC-Trait = 31.2), mean (0 SD: STAIC-Trait = 38.4), and high (+1 SD: STAIC-Trait = 45.7) levels of trait anxiety. In the right operculum, simple slopes revealed that children with low trait anxiety displayed a positive association between state anxiety and mean BOLD response (*p*s < .05), whereas children with mean and high trait anxiety displayed an inverse association between state anxiety and mean BOLD response (*p* < .001) (Figure 1.5a). In the pSTS/TPJ, simple slopes revealed that children with mean and high levels of trait anxiety (*p*s < .001) displayed an inverse association between state anxiety and mean BOLD response, whereas children with low trait anxiety showed no association between state anxiety and mean BOLD response (*p* = .08) (Figure 1.5b). In the right caudate and right angular gyrus, children with low trait anxiety displayed a positive association between state anxiety and mean BOLD activation (*ps* < .05) and children with high trait anxiety displayed a negative slope (*ps* < .001) (Figure 1.5c,d). State anxiety and mean activation were unrelated for children with mean levels of trait anxiety in the right caudate and right angular gyrus (Figure 1.5c,d). State and trait anxiety did not interact to predict fear intensity-modulated hemodynamic response.

Figure 5. Interactive influence of state and trait anxiety on mean BOLD response.



Note. State and trait anxiety interacted to predict mean BOLD response in four clusters: a) right operculum, b) right posterior superior temporal sulcus / temporoparietal junction (pSTS/TPJ), c) right caudate, and d) right angular gyrus. Simple slopes predict the association between state anxiety and mean neural activation for children with low (-1 SD), moderate (0 SD), or high (+1 SD) trait anxiety. ***$p \leq .001$, **$p \leq .01$, *$p \leq .05$.

Discussion

Youth who are unfamiliar with academic and biobehavioral research settings may experience elevated levels of state anxiety in anticipation of affective neuroimaging tasks, complicating inferences. The present study probed the independent and interactive effects of trait and state anxiety on neural activation during implicit fear processing in a community sample of preadolescent Latina girls with elevated trait anxiety. Four key findings emerged. First, trait anxiety was inversely associated with mean activation in the left opercular IFG and right pSTS/TPJ. Second, trait anxiety was positively associated with fear intensity-modulated activation in the right insula. That is, high trait-anxious children displayed greater linear increases in right insula activity with intensifying fear expressions compared to low trait-anxious children. Third, state anxiety was inversely

associated with fear intensity-modulation in the left IOG/FG, such that low state-anxious children displayed greater increases in activity with increasingly fearful affect than high state-anxious children. Finally, state and trait anxiety interacted to predict activation in the right pSTS/TPJ, right operculum, right caudate, and right angular gyrus. Overall, state anxiety was negatively associated with BOLD responses for high trait-anxious children and positively associated for low trait-anxious children.

The inferior frontal cortex is a prefrontal region that enables task control and emotion regulation in the face of task-irrelevant emotional distractors (Aron et al., 2004; Dolcos et al., 2006; Morawetz et al., 2017; Winecoff et al., 2011) by down-regulating amygdala activity (Cohen et al., 2016; Gold et al., 2015; Morawetz et al., 2017; Mujica-Parodi et al., 2009) and this regulatory capacity may be reduced in people with anxiety (Cha et al., 2016; Monk et al., 2008; Mujica-Parodi et al., 2009). Activation appears to be lateralized such that the left inferior frontal cortex controls the impact of distracting emotions on cognitive performance (Dolcos et al., 2006). The pSTS/TPJ is also involved in re-orienting attention to behaviorally-relevant stimuli (Constantinidis & Steinmetz, 2001; Corbetta et al., 2008; Patel et al., 2015). Children and adults with anxiety display impaired task performance when presented with emotional distractors (Krug & Carter, 2012; Ladouceur et al., 2009) due to a reduced ability to flexibly deploy and shift attention in the presence of external threats (Eysenck et al., 2007). While viewing negative or emotional stimuli, anxious individuals display aberrant activity in the IFG (Fales et al., 2010; J. M. Fitzgerald et al., 2017; Mujica-Parodi et al., 2009) and pSTS/TPJ (Gentili et al., 2008; Straube et al., 2004), though the directionality of these

findings are mixed (discussed in greater detail below). Additionally, inverse associations between anxiety and IFG activity have been observed when down-regulating negative emotions (Ziv et al., 2013) and during tasks with emotional distractors (Bishop et al., 2007; Monk et al., 2006; Strawn et al., 2012). Together, inverse associations between trait anxiety and activity in the IFG and/or pSTS/TPJ may suggest poorer emotion regulation capabilities and/or a reduced ability to attend to task-relevant stimulus features when presented with fearful affect. Alternatively, reduced activity in the IFG and pSTS/TPJ may indicate that anxious children have impairments inferring the emotions of others, given that these regions are involved in processing socio-emotional facial cues (Direito et al., 2019; Haxby et al., 2002; Müller et al., 2018; Pelphrey et al., 2004; Pitcher et al., 2017) and representing the emotions and mental states of others (Jabbi et al., 2008; Jabbi & Keysers, 2008; Leroy et al., 2015; Saxe & Kanwisher, 2003; Schurz et al., 2014). However, we are not able to disentangle these possibilities because we did not probe children's attention or mentalization abilities. Trait anxiety also did not predict differences in task performance, though there was a trending inverse association between trait anxiety and gender labeling accuracy (r = -.25, p = .08). Future work should probe behavioral and physiological correlates of hypoactivation in the IFG and pSTS/TPJ in trait-anxious girls.

As mentioned previously, not all studies find reduced IFG or pSTS/TPJ response in anxiety. Some research finds that anxious adults display stronger IFG activity when viewing negative stimuli (Fales et al., 2010; J. M. Fitzgerald et al., 2017). Further, socially anxious adults have displayed increased TPJ activation upon the presentation of a

threatening distractor (Kim et al., 2018) and increased STS activity when viewing both positive and negative emotional stimuli (Gentili et al., 2008). Discrepant findings may result from task-related differences across studies. Reductions in IFG and pSTS/TPJ response may be specific to fear stimuli, as fear and anger elicit distinct neural signatures (Saarimäki et al., 2016; Sprengelmeyer et al., 1998). Additionally, given that these regions both play a role in attentional mechanisms, neural responses may be modulated by task instructions (Ewbank et al., 2009; Klumpp et al., 2013; Swartz et al., 2014). For instance, anxiety was associated with reduced IFG activation while participants passively viewed fearful faces (Mujica-Parodi et al., 2009), but with increased IFG activation when they attended to their own emotional state (J. M. Fitzgerald et al., 2017) or matched emotional faces (Fales et al., 2010). Finally, developmental changes in STS function may underlie discrepant findings. Research in socially anxious adults has found increased STS activity associated with anxiety symptoms during emotion processing (Gentili et al., 2008; Straube et al., 2004), which diverges from the inverse association we observed between children's trait anxiety and right pSTS/TPJ activity. STS activation increases with age in response to fearful faces (Gee et al., 2013b). Further, anxiety changes the direction of the association between age and children's STS activity during error processing (Smith et al., 2020). Developmental differences may reflect an age-related compensatory mechanism by which these networks are enlisted to reduce anxiety symptoms in adolescents and adults.

Second, in addition to associations with mean neural activation, trait anxiety was positively associated with fear intensity-modulation in the right insula. Children with

high trait anxiety displayed greater fear intensity-modulation in the right insula (i.e., greater increases in neural activity with increases in fear intensity) compared to low trait-anxious children. There is robust evidence for insular involvement in emotion processing (Botvinick et al., 2005; Gorno-Tempini et al., 2001; Phan et al., 2002; Straube et al., 2004) and interoceptive awareness – the detection and interpretation of internal bodily states (Critchley, 2003; Critchley et al., 2005). Clinical and trait anxiety are associated with biases in threat processing (Cisler & Koster, 2010; Shechner et al., 2012) and interoceptive awareness (Domschke et al., 2010; Paulus & Stein, 2010), as well as exaggerated insula reactivity (Etkin & Wager, 2007; Paulus & Stein, 2006, 2010), suggesting that insula dysfunction is a key feature of pathological anxiety. Increased fear intensity-modulation in trait-anxious youth might suggest greater neural sensitivity to subtle changes in emotional affect. It is also possible that, among trait-anxious children, increases in fearful affect elicit greater sympathetic responses to stimuli or greater interoceptive awareness of physical discomfort than children with low trait anxiety (Domschke et al., 2010; Michalska et al., 2022).

Third, we observed that state anxiety was inversely associated with fear intensity-modulation in the left IOG/FG, key regions in the perception of visual emotional stimuli (Adolphs, 2002). Children with low state anxiety displayed increases in left IOG/FG activity with increasing fear intensity, whereas high state-anxious children did not. One possible reason that high state-anxious children did not display fear intensity-modulated responses in these emotion perception regions is that they displayed elevated responses even at low levels of fear. Threat-induced anxiety can enhance sensory processing and

facilitate threat detection (Li, Howard, et al., 2008; Phelps et al., 2006). People with elevated state anxiety identify threat at lower levels of emotion intensity than people with low state anxiety (Muris et al., 2003) and are more likely to generalize learned threats to ambiguous stimuli (Xu et al., 2016). Thus, state anxiety may increase perceptual responses to ambiguously fearful affect more so than full-intensity fearful expressions. Because all stimuli in the present analyses were fearful to some degree, state-anxious children may have displayed elevated left IOG/FG activation at low levels of fear, thereby reducing intensity-modulated activity in these face-processing regions.

Finding that state anxiety influences activation in face-processing regions may be problematic for research with people that are especially nervous prior to scanning, like children or groups that are unfamiliar with the scanning environment. Pre-scan state anxiety is rarely included in imaging analyses so perceptual effects that stem from baseline differences in state anxiety might be misattributed to demographic variables like age or ethnic background. Differences in visual perception can have downstream consequences for people's attitudes and behaviors across a variety of tasks, underscoring the importance of controlling for individual- and group-level differences in state anxiety.

Finally, state and trait anxiety interacted to predict average neural activity in the right pSTS/TPJ, right operculum, right caudate, and right angular gyrus. In the right pSTS/TPJ, state anxiety was inversely associated with mean activity for moderately and high trait-anxious children, but not low trait-anxious children. The pSTS/TPJ is engaged in emotion processing (Direito et al., 2019; Haxby et al., 2002; Müller et al., 2018; Pelphrey et al., 2004; Pitcher et al., 2017) and inferring the mental states of others (Leroy

et al., 2015; Saxe & Kanwisher, 2003; Schurz et al., 2014). Thus, when high and moderately trait-anxious children are momentarily stressed, they may be less likely or less able to engage in other-focused socioemotional processing, resorting to a more ego-centric focus as a means of regulating emotions. In support of this, adults who were treated with an adrenal stress hormone blocker showed greater empathy towards strangers' pain (Martin et al., 2015; J. P. Nitschke & Bartz, 2023), suggesting that stress may inhibit people's ability to put themselves in another's shoes. Our results suggest that children with low trait anxiety may be buffered from this effect.

State and trait anxiety also interacted to predict average neural activity in the right operculum, right caudate, and right angular gyrus, such that increases in state anxiety predicted increased neural activation for low trait-anxious children and decreased activation for high trait-anxious children. The operculum and caudate contribute to various aspects of executive control function. The operculum is a node in the cingulo-opercular network, which plays a role in error monitoring (Neta et al., 2014; Sylvester et al., 2012). Children with anxiety display aberrations in the cingulo-opercular network (Besteher et al., 2017), which may impair children's ability to employ executive control during tasks with emotional distractors (Sylvester et al., 2012). Positive associations between state anxiety and right opercular activity in low trait-anxious children suggest that increasing state anxiety may enable better executive function during a simple gender labeling task, in line with the Yerkes-Dodson Law (Yerkes & Dodson, 1908), whereas the inverse is true for high trait-anxious children. The caudate is a region in the striatum, which is also involved in processes that are fundamental for task-relevant cognitive goals

(i.e., directing attention away from threat) (Grahn et al., 2008) as well as responding to negative and positive incentives. Inducing anxiety enhances striatal activity to both negative and positive outcomes (Gorka et al., 2018), which may reflect increases in the subjective salience of these stimuli. Among low trait-anxious children, state anxiety was associated with increased right caudate activation, possibly indicating that fearful affect is more salient during discrete periods of elevated anxiety among non-trait-anxious children. However, children with both high state anxiety and high trait anxiety may show dysregulated responses in this region. Finally, the angular gyrus is a part of the default mode network, which is implicated in emotion regulation (Delgado et al., 2008) and displays dysfunction in anxiety (Krug & Carter, 2010; Osuch et al., 2000; Simmons et al., 2008; Zhao et al., 2007). Reduced default mode network activation may manifest as difficulty regulating emotions based on current goals (Sylvester et al., 2012). For low trait-anxious children, greater state anxiety may necessitate greater recruitment of these regulatory networks in order to maintain task performance (Simpson et al., 2001). Conversely, for high trait-anxious children, state anxiety may exacerbate pre-existing deficits in these regions (Egloff & Hock, 2001).

Several limitations of the current study and future research considerations should be acknowledged. First, sample size was modest. Recent studies suggest that brain-behavior effects can sometimes be inflated and contribute to problems with replicability (Marek et al., 2022). However, our sample was unique and consisted of Latina girls -- a demographic group that was under-represented in research. Low representation of Latinx children in anxiety research is especially troubling given that they display a high

prevalence of anxiety (Glover et al., 1999; McLaughlin et al., 2007; Pina & Silverman, 2004; Potochnick & Perreira, 2010; Varela et al., 2008) and are one of the largest and fastest-growing ethnic groups in the United States (Colby & Ortman, 2015). Thus, results may inform future large-scale studies by identifying preliminary effects within a well-characterized sample of Latina girls. Second, the cross-sectional study design limited our ability to make inferences about developmental processes. Future work should test longitudinal changes in the effects of state and trait anxiety on implicit fear processing, especially within executive control networks, which may display changing associations with anxiety across development. Third, because state anxiety measures were collected prior to the scan, we cannot be sure that such levels were sustained throughout the task. Thus, our results capture the effects of anticipatory, pre-scan anxiety on neural response during implicit fear processing. A final limitation of this study is that all the faces presented in this experiment were non-Hispanic white people. All girls in this study identified as Latina and most were 100% Latina (~85%, $N = 39$), with the remainder of girls from both white and Latinx backgrounds (~15%, $N = 7$). Thus, for most participants, stimuli were from an outgroup (other race). People respond differently to face stimuli that depict members of their own race compared with those of an outgroup race (Fiske, 1998). Outgroup members are more readily associated with aversive stimuli (Navarrete et al., 2012) and anxious arousal (Olsson et al., 2005) than members of one's own race. People also display differences in neural activation to racial ingroup versus outgroup faces (Golby et al., 2001; Hart et al., 2000). Thus, differences in participants' experiences or familiarity with white people may have influenced their neural response to the face

stimuli. Future work should sample faces from a variety of races and ethnicities and/or covary for participants' experiences with racial outgroup members.

In summary, the present study examined the influences of trait anxiety and anticipatory, pre-scan state anxiety on Latina girls' neural activity during implicit fear processing. Our results suggest that trait and state anxiety independently and interactively influence BOLD response to fearful affect in regions that are central in salience detection, emotion regulation, and executive control. Trait anxiety may be subserved by increased insula sensitivity to changes in threatening facial affect, coupled with reduced ability to recruit executive control networks. Future work could test whether aberrant neural responses can be modified through interventions that dually reduce sensitivity to threatening affect and enhance cognitive control capacities. In addition, state anxiety influences BOLD response in face-perception regions and interacts with trait anxiety to predict activation in networks involved in mentalizing, executive control, and regulation. Results suggest that state anxiety may exacerbate deficits observed in trait anxiety during implicit fear processing and attune these skills in low trait-anxious children, though further data is necessary to understand the behavioral correlates of these differences in brain function. Regardless, pre-scan state anxiety has important influences on networks that are aberrant in anxiety, potentially contributing to variable results across studies. Minoritized groups often have reduced engagement in scientific research and more mistrust (Loue & Sajatovic, 2008; Preloran et al., 2001; Yancey et al., 2006), and thus may experience greater levels of pre-scan state anxiety. Imaging researchers should control for state anxiety so that systematic differences in subgroups' neural response

resulting from MRI apprehension are not incorrectly attributed to demographic or environmental characteristics.

Chapter 2: Anxiety symptoms and puberty interactively predict lower cingulum microstructure in preadolescent Latina girls

Abstract

Preadolescence is a period of increased vulnerability for anxiety, especially among Latina girls. Reduced microstructure (fractional anisotropy; FA) of white matter tracts between limbic and prefrontal regions may underlie regulatory impairments in anxiety. However, developmental research on the association between anxiety and white matter microstructure is mixed, possibly due to interactive influences with puberty. In a sample of 39 Latina girls (8-13 years), we tested whether pubertal stage moderated the association between parent- and child-reported anxiety symptoms and FA in the cingulum and uncinate fasciculus. Parent- but not child-reported anxiety symptoms predicted lower cingulum FA, and this effect was moderated by pubertal stage, such that this association was only significant for prepubertal girls. Neither anxiety nor pubertal stage predicted uncinate fasciculus FA. These findings suggest that anxiety is associated with disruptions in girls' cingulum white matter microstructure and that this relationship undergoes maturational changes during puberty.

Introduction

Anxiety disorders are a prevalent mental health concern in the United States (World Health Organization, 2017), with an estimated one-third of girls experiencing an anxiety disorder by adolescence (Merikangas et al., 2010). Greater vulnerability for anxiety symptoms in girls begins in middle childhood (6-12 years) and increases into adolescence (13-18 years) (Kessler et al., 2005; Merikangas & Avenevoli, 2002; Ost, 1987) when youth undergo major puberty-related structural brain changes, including in white matter tracts critical for emotion processing and regulation (Asato et al., 2010; Giorgio et al., 2010; Herting et al., 2012; Lebel et al., 2008, 2012; Lebel & Beaulieu, 2011; Oyefiade et al., 2018). However, the limited developmental work examining white matter microstructure in anxiety is mixed (Aggarwal et al., 2021; Liao et al., 2014; Tromp, Williams, et al., 2019) and no studies to our knowledge have focused on ethnic minority youth. Thus, the current study sought to examine associations among anxiety symptoms, pubertal status, and white matter microstructure in a community sample of Latina girls - a demographic group with elevated anxiety symptoms (Glover et al., 1999; McLaughlin et al., 2007; Pina & Silverman, 2004; Potochnick & Perreira, 2010; Varela et al., 2008).

A characteristic feature of anxiety disorders is a reduced ability to downregulate negative emotions (Abend, Bajaj, Harrewijn, et al., 2021; Carthy et al., 2010; Cisler et al., 2010), which is thought to be partially mediated by white matter tracts that facilitate communication between limbic (e.g., amygdala) and emotion regulatory regions in the lateral and medial prefrontal cortex (PFC). Two such white matter tracts are the

cingulum, a large-scale fronto-limbic tract that runs in the cingulate gyrus and connects the cingulate cortex with medial prefrontal, parietal, and temporal regions; and the uncinate fasciculus, a smaller-scale fronto-limbic tract that projects from anterior temporal to prefrontal and orbitofrontal regions (Baur et al., 2011; Phan et al., 2009; Tromp et al., 2012; Wang et al., 2016; Y. Zhang et al., 2013). Diffusion weighted imaging studies have reported that adults with anxiety display reduced fractional anisotropy (FA) in these two tracts (Baur et al., 2011; Phan et al., 2009; Tromp et al., 2012; Wang et al., 2016; Y. Zhang et al., 2013). FA is a diffusion tensor imaging metric that reflects the degree to which water diffusion is restricted, or anisotropic, and indirectly indexes white matter pathway microstructural integrity (Beaulieu, 2002). Relationships between anxiety and white matter microstructure are less systematic in the developmental literature, with researchers observing that anxiety is associated with reductions in uncinate fasciculus FA among adolescents (Liao et al., 2014) and preadolescent boys (Tromp, Williams, et al., 2019), but not girls (Aggarwal et al., 2022; Tromp, Williams, et al., 2019). In other work, girls' anxious and depressive (internalizing) symptoms were correlated with reduced cingulum and uncinate fasciculus FA (Mohamed Ali et al., 2019), and the inverse relationship between internalizing symptoms and cingulum FA was stronger for girls than boys (Andre et al., 2020). Thus, although these findings support a structural contribution from cingulum and uncinate fasciculus to the well-documented difficulties with emotion regulation in anxiety (Eden et al., 2015; Hung et al., 2020; Schäfer et al., 2017), the association between anxiety symptoms and microstructure in these tracts remains unclear in preadolescent girls.

Puberty-driven influences on white matter microstructure in early adolescence may alter connections between emotion processing and regulatory regions (Asato et al., 2010; Chahal et al., 2018), and influence anxiety symptoms. White matter microstructure of the cingulum and uncinate fasciculus exhibit protracted development throughout adolescence and into adulthood (Lebel et al., 2008, 2012) and shows sex differences during puberty (Asato et al., 2010; Herting et al., 2012; Ho et al., 2020), suggesting that previous work finding anxiety-related sexual dimorphism in FA may be attributable to puberty-specific structural changes. Puberty also spurs changes in the valence of functional connectivity between the amygdala and ACC, regions that are connected by the cingulum, with children exhibiting positive connectivity and adolescents and adults exhibiting negative connectivity (Gee et al., 2013a; M. Wu et al., 2016). This association is moderated by anxiety, such that age is negatively related to amygdala-ACC functional connectivity in healthy youth (Gee et al., 2013a; Jalbrzikowski et al., 2017; Kujawa et al., 2016a) but positively related in anxious youth (Kujawa et al., 2016a). As preliminary work in preadolescent girls suggests that there are longitudinal changes in the association between anxiety and cingulum FA (Aggarwal et al., 2021; prior to multiple comparison correction), it is also possible that puberty and anxiety interact to predict cingulum microstructure. However, few studies have tested whether pubertal stage moderates the association between anxiety and white matter development.

In a sample of Latina girls aged 8-13 years, we first examined associations between anxiety symptoms (parent- and child-reported) and FA in the cingulum and uncinate fasciculus. We then tested whether anxiety-FA relationships were moderated by

pubertal stage. Based on prior findings in the cingulum (Aggarwal et al., 2021; Albaugh et al., 2017; Kujawa et al., 2016a; Tromp, Williams, et al., 2019; Vanes et al., 2020), we hypothesized that (1) anxiety symptoms will be associated with decrements in cingulum microstructure, and (2) that pubertal stage will influence the association between anxiety and cingulum FA. Given the nascent evidence base on puberty effects on cingulum FA (Chahal et al., 2018), we did not make specific directional predictions. To extend prior work on uncinate fasciculus microstructure in anxious preadolescent girls (Aggarwal et al., 2021; Mohamed Ali et al., 2019; Tromp, Williams, et al., 2019), we tested independent and interactive influences of anxiety and pubertal stage on uncinate fasciculus FA. Because of prior mixed findings, we considered these analyses exploratory.

Method

Participants and Procedures

Fifty-five Latina girls were recruited from the Inland Empire region of Southern California to participate in the first wave of a longitudinal study on emotional development. Girls aged 8-13 years were initially eligible to participate if they were medication-free, reported no contraindications for neuroimaging (e.g., no ferrous metal in the body, not pregnant, not claustrophobic), were not experiencing active medical problems or suicidal ideation, and were free from a current psychiatric diagnosis of Tourette's syndrome or obsessive-compulsive disorder and lifetime history of mania, psychosis, or pervasive developmental disorder. Although menstruation was initially used

as an exclusionary criterion, it was later dropped to increase sample size and two postmenarchal participants were recruited.

Across two visits, participants completed a laboratory testing session and MRI data collection. During the laboratory session, children and their caregivers completed a battery of self-report questionnaires assessing demographics, behavior, anxiety, and other mental health outcome measures not reported here. During the MRI session, children underwent T1-weighted and diffusion weighted imaging data acquisition. Diffusion weighted imaging scans were not collected from 16 participants because they did not return for the second visit (n = 12), or due to participants' distress (n = 2), time constraints (n = 1), or inability to continue data collection during the COVID-19 pandemic (n = 1), resulting in a final sample of 39 participants.

Because of our larger focus on social determinants of mental health in Latina youth, children also had to have at least 50% Latinx heritage and identify as Latina or Hispanic in order to participate. Our sample consisted of 26 Mexican American girls, 8 girls of other, mixed, or unspecified Latinx descent, and 5 girls of mixed racial descent (Table 2.1).

At the end of each visit, participants were compensated with a gift card and a small prize. Study procedures were approved by the University of California, Riverside Institutional Review Board and written informed consent and assent were obtained at the start of the first visit from parents and children, respectively.

Table 2.1. Sample demographic characteristics and descriptive statistics for study variables.

					Anxiety symptoms (SCARED)	
N	Age	Female	Pubertal stage (Tanner scale)	Household income	Parent-report	Child-report
39	10.1 (1.2)	100%	1.9 (0.8)	$64,474 ($45,778)	18.6 (13.7)	37.6 (15.5)

Note. Variables are displayed as mean (standard deviation). SCARED = Screen for Child Anxiety Related Disorders.

Measures

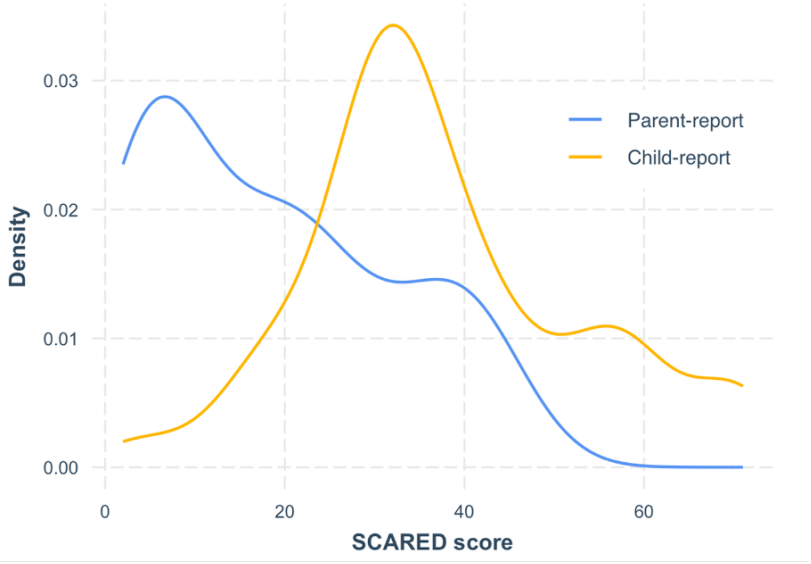
Pubertal Staging

Girls' pubertal stage was measured via self- and parent-assessed Tanner staging (Morris & Udry, 1980). Meta-analytic evidence has found that Tanner staging is a more sensitive predictor of internalizing psychopathology for girls than hormone levels, subjective reports of pubertal timing, or age at menarche (Barendse et al., 2021). The female version of the Tanner stage line drawings consists of five drawings depicting breasts and five drawings depicting pubic hair. For each set, girls and their caregivers selected the image that reflected the child's current stage of development. Scores range from 1 (prepubertal) to 5 (postpubertal). An overall pubertal stage composite was created by averaging child- and parent-reported breast and pubic hair development. Scores of dyads with a missing informant report (n = 3 children, 1 parent) were composed of the remaining informant's scores.

Anxiety Symptoms

Children's anxiety symptoms were collected via self- and parent-report on the Screen for Child Anxiety Related Disorders (SCARED). The SCARED included 41-items assessing recent anxiety symptoms (past 3 months) rated on a 3-point Likert scale and it has strong psychometric properties (Birmaher et al., 1997, 1999). Item scores were summed to a total score (range: 0–82). Missing parent-report was imputed with mean-replacement (n = 1). The normality of parent- and child-reported SCARED were tested with the Shapiro-Wilk test (Razali et al., 2014) and by visual inspection of skewness (Figure 2.1). Parent-reported SCARED scores were log-transformed to reduce a positive skew in raw scores (p = .002). Child-reported SCARED scores were normally distributed (p = .11) and were not transformed. The threshold for clinically-significant levels of anxiety ($\geq$ 25) were met in 33 child-reported scores and 13 parent-reported scores.

Figure 2.1. Density distribution of parent- and child-reported scores on the Screen for Child Anxiety Related Disorders (SCARED).



Note. Shapiro-Wilk statistical testing for normality revealed skewed distribution of the parent-report (p = .002) but not child-report (p = .11). Parent-reported SCARED scores were log-transformed to reduce data skewness.

Children and caregivers may provide distinct information about children's anxiety symptoms. Child-report on the SCARED has predicted longitudinal changes in whole-brain white matter microstructure (Aggarwal et al., 2021), which may be because children are more knowledgeable about feelings of anxiety not externally observable to their parents. Conversely, parent-report on the SCARED has demonstrated higher sensitivity, higher specificity, and matches more closely with clinical cutoffs than child-report (Bodden et al., 2009; Rappaport et al., 2017). Thus, we implemented two separate models with parent-and child-reported anxiety symptoms. We conducted Bonferroni corrections for multiple comparisons across two informant groups (child-report, parent-report) and two regions of interest (cingulum, uncinate fasciculus), ($p < 0.0125$).

Imaging Data

Acquisition. Whole-brain neuroimaging data were collected using a 3T Siemens Prisma scanner and 32-channel receive-only head coil. A high-resolution T1-weighted scan of the whole-brain was acquired using a magnetization prepared gradient echo sequence (MP-RAGE) with the following parameters: TE / TR = 2.72 / 2400 ms, flip angle = 8, FOV = 256 x 240 mm, matrix = 320 x 300, voxel size = 0.8 mm^3, and scan time = 6:28.

A single diffusion-weighted single-shot spin-echo, echo planar imaging (EPI) image was acquired with the following parameters: TE / TR = 102 / 3500 ms, FOV = 218 × 187 mm, matrix size = 128 × 110, voxel size = 1.7 mm^3, multiband factor = 4, 72 slices with no gap, and scan time = 8:42. Bipolar diffusion-weighting gradients were applied in 64 directions with b values of 1500 s/mm^2 and 3000 s/mm^2 with six b = 0 images.

Processing. For each participant, non-brain tissue was removed and a whole-brain mask was generated using Analysis of Functional NeuroImages (AFNI; Cox, 1996). Next, we corrected for head movement, EPI distortions, and eddy-current induced distortions using the TOPUP and EDDY commands in FMRIB's Software Library (FSL; www.fmrib.ox.ac.uk/fsl). Finally, FSL's DTIFIT was used to estimate a single diffusion tensor for each voxel, using data from both b values, with the whole-brain mask limiting tensor fitting to brain tissue. The output included a voxel-wise image for FA.

Regions of Interest (ROI). ROI creation followed a pipeline that has been successfully implemented by our group (Franco et al., 2021; Merenstein et al., 2022.; Venkatesh et al., 2021). Standard bilateral masks of the cingulum and uncinate fasciculus

were first created from the JHU ICBM-DTI-81 white matter labels atlas in FSL (Mori et al., 2008). For each participant, the standard cingulum and uncinate fasciculus white matter masks were aligned to native diffusion space using the following registration steps: (1) the MP-RAGE image was aligned to the Montreal Neurological Institute (MNI) 152 1mm^3 resolution standard image using an affine transformation with 12 degrees of freedom, (2) the preprocessed diffusion image with no diffusion weighting applied (i.e., my_hifi_b0) was aligned to the MP-RAGE image using a boundary-based registration with six degrees of freedom, (3) the diffusion-to-MP-RAGE and MP-RAGE-to-MNI transformations were concatenated, (4) the concatenated transformation was inverted, and (5) the inverted transformation was applied to align the standard JHU ICBM white matter masks to native diffusion space. Cingulum and uncinate fasciculus alignment and mask coverage were visually inspected and all masks were of usable quality.

Prior to extracting FA values, gray matter tissue and cerebrospinal fluid were excluded from the native space masks by multiplying them by a white matter mask generated for each participant from their MP-RAGE image via FSL's Automated Segmentation Tool (FAST; Y. Zhang et al., 2001). The partial volume estimate of this white matter mask was thresholded at 0.5, aligned to diffusion space by applying the inversion of the diffusion-to-MP-RAGE transformation described above, and multiplied by the bilateral cingulum and uncinate fasciculus masks. The resulting masks were then separately multiplied by each participant's voxel-wise dtifit_FA image and FA values were averaged across voxels separately within each mask. The volume of each mask, measured as the number of voxels, was also extracted using fslstats.

Data Analysis

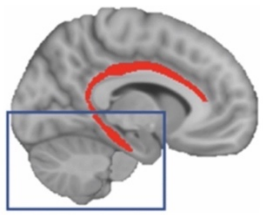
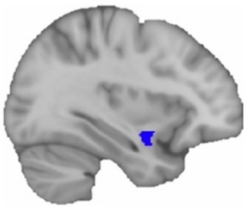
To examine the effects of pubertal staging and anxiety on white matter microstructure, we implemented multiple linear regression analyses in RStudio (Team, 2021). Anxiety symptoms and pubertal stage were tested as independent and interactive predictors of ROI FA. To test the relations among anxiety, pubertal stage, and white matter microstructure independent of individual differences in white matter volume, all analyses controlled for ROI volume. We tested each informant type (child-report, parent-report) and ROI (cingulum, uncinate fasciculus) in four separate models. Pubertal stage and age were strongly correlated in our sample ($r = .65$, $p < .001$), so we did not include age as a covariate in our model to avoid multicollinearity. Exploratory analyses were conducted to determine whether significant effects of pubertal stage were confounded by age or pubertal timing, the relative measure of pubertal development compared to same-age, same-sex peers (Graber et al., 2018) (Appendix A). To probe significant interactions, simple slopes were examined to assess predictions of white matter microstructure from anxiety symptoms across three levels of pubertal staging (−1 SD, 0 SD, +1 SD). No outliers were observed in children's anxiety scores or FA values ($\pm$ 3 SD).

Results

Linear regression models tested whether anxiety symptoms and pubertal stage interacted to predict FA in each ROI (cingulum, uncinate fasciculus), separately for parent- and child-reported SCARED anxiety scores. Parent-reported SCARED scores were log-transformed to reduce data skewness.

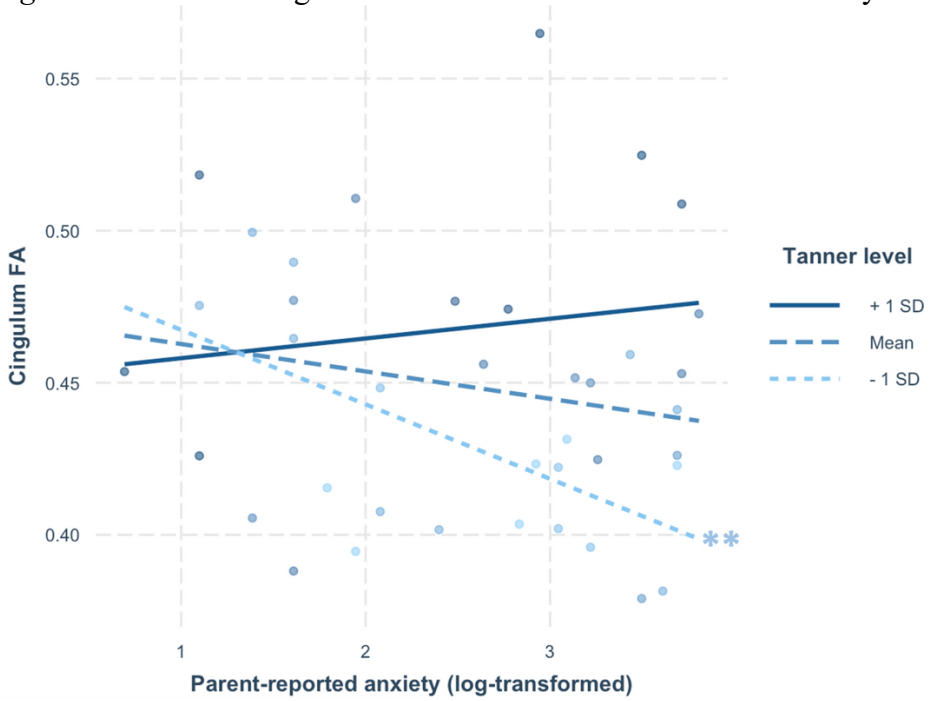
When cingulum FA was the outcome variable (M_{FA} = .45 $\pm$ .04), the model that included log-transformed parent-reported anxiety symptoms and pubertal stage as predictors was significant, R^2 = 0.663, $F(4, 34) = 16.78$, $p < .001$. Higher levels of parent-reported anxiety symptoms predicted lower cingulum FA, $p = .001$, and this effect was moderated by pubertal stage, $p = .001$ (Table 2.2). Cingulum volume also significantly positively predicted cingulum FA, $p < .001$. Follow-up simple slopes analyses revealed that children's parent-reported anxiety symptoms were significantly associated with reduced white matter microstructure in the cingulum at early pubertal stages (Tanner = 1.14), $\beta = -.02$, $t = -3.24$, $p = .003$, and not significantly related to FA at mean (Tanner = 1.94), $\beta = -.01$, $t = -1.81$, $p = .08$, and late pubertal stages (Tanner = 2.73), $\beta = .01$, $t = 1.14$, $p = .26$ (Figure 2.2). Volume was the only predictor of FA in the cingulum when this model was repeated with child-reported anxiety symptoms in place of parent-reported anxiety symptoms ($p = .001$), and no other main effects or interactions emerged ($ps > .19$). All significant cingulum effects survived Bonferroni correction for multiple comparisons across informants and regions, $p < 0.0125$.

Table 2.2. Pubertal stage and parent-reported anxiety symptoms independently and interactively predict FA in the cingulum but not uncinate fasciculus

Cingulum FA		***SE***	***t***	***R²***	***p***
	Anxiety	.001	-3.55		0.001***
	Pubertal stage	.001	-1.69		0.10
	Pubertal stage*Anxiety	<.001	3.47		0.001***
	Cingulum volume	.005	4.31		<0.001***
	Overall model			0.664	<0.001***
Uncinate fasciculus FA		***SE***	***t***	***R²***	***p***
	Anxiety	.025	-0.30		0.76
	Pubertal stage	.028	-0.11		0.91
	Pubertal stage*Anxiety	.010	0.47		0.64
	Cingulum volume	<.001	2.02		0.05*
	Overall model			0.172	0.16

Note. Statistics are shown for each predictor (*SE*, *t*, *p*) and the overall model (R^2, *p*). For visualization, the standard JHU-ICBM hippocampal cingulum is overlaid on a sagittal view of the standard superior cingulum using a MNI 152 brain ($1mm^3$ resolution) as the underlay. FA = fractional anisotropy. *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq .001$.

Figure 2.2. Pubertal stage moderates the association between anxiety and cingulum FA.



Note. Simple slopes tested the association between anxiety and cingulum FA at Tanner levels of 1.14 (-1 SD), 1.94 (0 SD), and 2.73 (+1 SD). Anxiety symptoms predicted reduced cingulum FA for children in early pubertal stages (-1 SD). $^{**}p < .01$.

When uncinate fasciculus FA was the outcome variable ($M_{FA} = .43 \pm .05$), no significant effects of anxiety or pubertal stage emerged for either informant report (*p*s > .70). In both models, uncinate fasciculus volume positively predicted FA (*p*s < .05) but did not survive Bonferroni correction.

Exploratory analyses testing the influence of age and pubertal timing (residualized pubertal stage) on white matter microstructure in place of pubertal stage did not reveal any significant effects of anxiety, age, or pubertal timing (Appendix A). This suggests that the significant effects of parent-reported anxiety and pubertal stage were not due to individual differences in age or pubertal timing.

Discussion

The present study leveraged diffusion weighted imaging to examine anxiety symptoms and pubertal stage as interactive predictors of cingulum and uncinate fasciculus white matter microstructure in preadolescent Latina girls. We observed that parent-reported child anxiety symptoms predicted reduced FA in the cingulum but not the uncinate fasciculus. Further, the association between anxiety symptoms and cingulum microstructure was moderated by pubertal stage, such that only prepubertal girls (-1 SD; Tanner = 1.14) displayed an inverse association between anxiety symptoms and cingulum FA. We suggest that pediatric anxiety symptoms manifest as disruptions in cingulum white matter microstructure in preadolescent girls and identify maturational moderators of this microstructure. Our results were specific to girls and highlight the importance of examining sexes separately when measuring associations between anxiety, pubertal status, and brain development.

Our first key finding was that elevated parent-reported child anxiety symptoms predicted decrements in white matter microstructure in the cingulum but not in the uncinate fasciculus.

Anxiety symptoms have been associated with reduced cingulum FA in adults (Wang et al., 2016; Zhang et al., 2013) and children (Aggarwal et al., 2022; Albaugh et al., 2017; Mohamed Ali et al., 2019; Tromp, Williams, et al., 2019). However, developmental studies of cingulum microstructure tested primarily white, high socioeconomic samples of treatment-seeking youth, and several of these findings did not hold for multiple comparison corrections (Aggarwal et al., 2022; Tromp, Williams, et al., 2019). The

present study replicated the association between childhood anxiety and reduced cingulum FA and extended these findings to preadolescent Latina girls. Elucidating markers of anxiety in Latinx youth is critical because an emerging evidence base indicates that Latinx youth experience elevated anxiety compared to other ethnic groups (Anderson & Mayes, 2010; McLaughlin et al., 2007; Pina & Silverman, 2004; Potochnick & Perreira, 2010; Varela et al., 2008), which is likely exacerbated by economic or acculturative stress (Mendoza et al., 2017; Suarez-Morales & Lopez, 2009; Torres et al., 2012) and barriers to treatment access (Chavira et al., 2014; Miranda & Green, 1999; Ojeda & McGuire, 2006; Zhou et al., 2021). Indeed, 33% of children in our community sample met clinical thresholds for an anxiety disorder (≥ 25) across both informant reports. Identifying reduced cingulum microstructure as a vulnerability marker for pediatric anxiety in this high-risk population may inform and increase the generalizability of diagnosis and treatment. For example, because white matter microstructure exhibits plasticity in youth and can be altered by training (Huber et al., 2018; Mackey et al., 2012; Scholz et al., 2009; Tymofiyeva & Gaschler, 2020), targeting cingulum microstructure may be an effective cross-cultural method in the treatment for pediatric anxiety.

Lower cingulum microstructure is associated with reduced use of emotion regulatory strategies (Eden et al., 2015) and emotional dysregulation (Hung et al., 2020). The cingulum stretches from the orbitofrontal cortex, along the dorsal surface of the corpus callosum, and down the temporal lobe. The cingulum is broadly implicated in cognitive control, attention, and emotion regulation (Charlton et al., 2010; Chiang et al., 2016; Hung et al., 2020; Takahashi et al., 2010; Yamamoto et al., 2015), all of which are

disrupted in pediatric anxiety (e.g., K. D. Fitzgerald et al., 2013; Golombek et al., 2020; McClure et al., 2007; Roy et al., 2008; Toren et al., 2000). Thus, reduced FA in the cingulum could reflect underlying neural makers of pediatric anxiety, including impaired downregulation of amygdala hyperactivity by regions like the ACC, dorsolateral PFC, and ventromedial PFC (Beesdo et al., 2009; Blair et al., 2011; Britton et al., 2013; Glenn et al., 2020; Guyer, Lau, et al., 2008; McClure et al., 2007; Michalska et al., 2019; Telzer et al., 2008; Thomas et al., 2001) and reduced amygdala-prefrontal functional coupling (Guyer, Lau, et al., 2008; Monk et al., 2008; Pagliaccio et al., 2015; Roy et al., 2013). Convergent evidence suggests that white matter microstructure of fronto-limbic tracts is positively associated with cognitive reappraisal, a form of emotion regulation, and inversely associated with anxiety traits (Eden et al., 2015). Consistent with prior reports, the current study showed reduced cingulum white matter microstructure in girls with higher anxiety symptoms. Plausible mediators of this association include impaired emotion regulation and cognitive control reflecting diminished recruitment of PFC subregions and ensuing microstructural differences in tracts subserving them. In other words, inefficient recruitment of regulation strategies in anxious preadolescent girls may alter neural communication and affect microstructural properties within important white matter pathways including the cingulum (Albaugh et al., 2017). Future work combining diffusion data and task-related functional imaging could further elucidate the dynamics between cingulum microstructure and limbic-prefrontal functional connectivity in anxious children.

In the present study, only parent-reported anxiety symptoms predicted cingulum FA, whereas child-reported anxiety was not significantly associated with white matter microstructure in either tract of interest. This contrasts with a study by Aggarwal and colleagues (2022), who observed that child- but not parent-reported SCARED scores were associated with whole-brain and uncorrected cingulum FA in preadolescent girls. However, other studies have observed associations between parent-reported internalizing symptoms and cingulum FA via alternative measures (Albaugh et al., 2017; Mohamed Ali et al., 2019). Parent- and child-reported anxiety symptoms often diverge because children tend to report more severe symptoms than parents (Choudhury et al., 2003; Cosi et al., 2010), and this discrepancy may be larger for healthy children (Rappaport et al., 2017). Thus, parents may more accurately estimate clinical cutoffs for anxiety severity compared to children (Bodden et al., 2009; Rappaport et al., 2017). Conversely, children may be more knowledgeable about feelings of anxiety not externally observable to their parents. Our findings underscore the importance of testing both child and parent reports and highlight the need for future work to probe sources of disagreement between informants.

The relationship between anxiety symptoms and cingulum FA was also moderated by pubertal stage, such that an inverse association only emerged for prepubertal girls. Microstructural integrity in the cingulum increases from childhood to adulthood (Lebel et al., 2008), and is longitudinally associated with girls' testosterone levels (Ho et al., 2020) and pubertal timing (Chahal et al., 2018; Mendle et al., 2007). Of note, both baseline anxiety symptoms and longitudinal increases in symptoms predict

reductions in preadolescent girls' cingulum microstructure (Aggarwal et al., 2022; Albaugh et al., 2017; Vanes et al., 2020), suggesting that protracted maturation of cingulum microstructure may correspond with changes in pediatric anxiety symptoms. Simple slopes analyses revealed that anxiety symptoms predicted cingulum microstructure for prepubertal girls, but not those who were in early or middle stages of pubertal development. Anxiety may be a particularly potent risk factor for white matter alterations in prepubertal girls because anxiety disorders that onset earlier in childhood are more chronic and persistent (Beesdo et al., 2007; Spence & Rapee, 2016), and may therefore have more pronounced implications for neurodevelopment. To be conclusive, this possibility would need to be followed up longitudinally, through comparison of cingulum FA in postpubertal girls with a history of anxiety in prepubescence versus no history of prior anxiety. Alternatively, pubertal timing, a relative comparison of pubertal development with same-age, same-sex peers (Graber et al., 2018), may underlie differences in cingulum microstructural properties (Chahal et al., 2018) in girls with anxiety. However, no main or interactive effects of pubertal timing or age emerged in our sample, suggesting that variations in these variables do not underlie the interactive effects of pubertal stage (Appendix A).

The observed maturational differences parallel changes in the function of regulatory networks. Several functional imaging studies have observed age-related compensatory changes in the activation of top-down control networks like the ACC and ventromedial PFC, whereby these networks are underactive in anxious children but become enlisted to mitigate anxiety symptoms in anxious adolescents and adults (Etkin et

al., 2009; K. D. Fitzgerald et al., 2021). Similarly, during emotion viewing, amygdala-ACC functional connectivity is reduced in anxious children and increased in anxious adults, relative to their non-anxious counterparts, suggesting a change in valence during adolescence (Kujawa et al., 2016b). Under this notion, early anxiety-related structural alterations in the cingulum could increase susceptibility to regulatory impairments that are mitigated by increases in white matter microstructure during puberty. The present study illustrates the importance of examining the relationship between anxiety and brain structure as a function of puberty, rather than solely including puberty as a covariate, as this association may have important changes across pubertal development.

Finally, we did not observe an association between anxiety and FA in the uncinate fasciculus. Decrements in uncinate fasciculus microstructure have been observed in boys with anxiety (Tromp, Williams, et al., 2019), adolescent girls and boys with anxiety (Liao et al., 2014), and girls with internalizing symptoms (Mohamed Ali et al., 2019). However, studies in anxious, preadolescent girls have not found significantly reduced uncinate fasciculus FA (Aggarwal et al., 2021; Tromp, Williams, et al., 2019), and have revealed evidence for the lack of an association (Aggarwal et al., 2021). Sexual dimorphism has been observed in the association between anxiety and uncinate fasciculus FA in preadolescents (Tromp, Williams, et al., 2019) and young monkeys (Tromp, Fox, et al., 2019), but interestingly, these differences were not explained by age, sex hormones, or the heritability of uncinate fasciculus FA. The mechanisms underlying sex differences in uncinate fasciculus structure are not known. One possibility is that structural differences reflect sex differences in the prevalence and expression of pediatric

anxiety disorders (Kessler et al., 2012; MacKinaw-Koons & Vasey, 2000). However, given that girls display particularly elevated rates of anxiety (Kessler et al., 2005; Merikangas & Avenevoli, 2002; Ost, 1987), there are likely alternative sources of impairment. The uncinate fasciculus, which connects ventral regions of the prefrontal cortex with the amygdala via direct projections through the insula (Von Der Heide et al., 2013), may be one of multiple pathways that can contribute to the development of anxiety when disrupted. Impairment in other prefrontal-limbic pathways, like the cingulum, may instead underlie anxiety symptoms in girls.

This study had important strengths that should be noted. First, our diffusion data was acquired with 64 directions and a smaller isotropic voxel size (1.7 mm^3) than most developmental studies of white matter microstructure in anxiety. These methods allow for more precise registration of standard regions of interest to native diffusion space, especially for smaller tracts like the uncinate fasciculus. Second, sample size was modest; while post-hoc analyses indicated we were powered to detect the observed cingulum effects, a replication is nonetheless advised given recent reports showing that reported brain-behavior effects in small studies are sometimes inflated (Marek et al., 2022). We also reaffirm the assertion in such reports that small-sample neuroimaging studies have an important place in building an evidence base linking brain and behavior, particularly using newer scan parameters and in well-characterized under-represented samples (Michalska et al., under revised review). Nonetheless, effect sizes should be interpreted with caution and warrant replication in larger-scale consortia. Third, our sample consisted of Latina girls -- a demographic group that is not well-represented in research, even

though Latinx children are one of the largest and fastest-growing ethnic groups in the United States (Colby & Ortman, 2015). Despite these strengths, several limitations and future research considerations should also be considered. First, this was a cross-sectional study and the girls in our sample were primarily in early and middle stages of pubertal development due to our initial recruitment of only premenstrual children. Thus, we are limited in our ability to make inferences about developmental processes. Further, it is difficult to disentangle the effects of age and pubertal status, given that they are inherently confounded in all youth samples. Puberty and brain development occur alongside, and are influenced by, the accumulation of experiences with age (see e.g., Koenen et al., 2013; Romans et al., 2003; L. Zhang et al., 2019). Thus, increasing exposure to certain stimuli or situations with age may underlie maturational changes in brain structure in any developmental study. However, our finding that age and pubertal timing did not moderate the association between anxiety and FA, even though they were correlated with pubertal stage, indicates that the observed interactive effects were largely driven by pubertal stage. Future studies should include later pubertal stages and, if possible, longitudinally track children's anxiety symptoms and white matter microstructure throughout puberty and into adulthood. In addition, including measures of hormonal concentration may help address the mechanism by which pubertal development influences cingulum microstructure and why sex differences emerge in the association between anxiety and uncinate fasciculus FA. Finally, anxiety in childhood in minoritized youth may be an index of other psychosocial stressors that were not measured in the present analyses. Factors like acculturative stress and low treatment engagement may

contribute to the elevated levels of anxiety in our community sample of children. Future research might continue to examine how psychosocial stressors may mediate the relationship between anxiety symptoms and white matter microstructure among ethnic minority youth (e.g., Fani et al., 2021).

In summary, the current study examined the influence of anxiety and pubertal stage on white matter microstructure in a sample of preadolescent Latina girls. Our results suggest that anxiety contributes to disruptions in cingulum white matter microstructure, and that this relationship varies as a function of pubertal stage. Anxiety-related microstructural vulnerability in white matter regions implicated in cognition and emotion regulation may represent a critical biomarker to be targeted in future intervention work, especially among preadolescent girls who are at an elevated risk for anxiety.

Chapter 3: Trait social anxiety and induced social anticipation predict threat biases in the perception of ambiguously fearful but not angry facial affect

Abstract

Social anxiety influences emotion processing via hypervigilance toward threat-relevant signals and interpretive biases. However, less is known about its effect on perceptual processes, partly because most prior studies are correlational and cannot directionally test associations between social anxiety and threat biases in perception. Current research also suffers from important limitations including homogeneous demographic samples (i.e., white, upper-middle-class, treatment-seeking) and insensitive analytic methods that confound threat sensitivity and threat bias. In an ethnically-diverse sample of young adults with elevated social anxiety symptoms, we tested associations between trait social anxiety and biases in the perception of ambiguous facial affect morphed between happy and fearful or angry emotional expressions. We further tested whether threat biases could be induced by experimentally manipulating participants' anticipatory anxiety via a social threat. Preliminary evidence suggests that socially anxious young adults may display biases in the perception of ambiguously fearful affect, and such biases may also be induced by short-term fluctuations in social anticipatory anxiety. Future work should test whether interventions that reduce the perceptual salience of fear cues ameliorate anxiety or increase engagement in social settings.

Introduction

Social anxiety disorders are the second most common type of anxiety disorder (Wittchen et al., 2011), characterized by elevated anxiety around social situations (Clark, 1995; Hinrichsen & Clark, 2003) and an increased tendency to identify ambiguous emotions as threatening (Cooney et al., 2006; Maoz et al., 2016; Yoon et al., 2014). Social anxiety may influence emotion processing via altered attention to threat-relevant signals (Cisler & Koster, 2010; Mueller et al., 2009; Pishyar et al., 2004; Taylor et al., 2016) and interpretive biases (Amin et al., 1998; Constans et al., 1999; D. Roth et al., 2001; Stopa & Clark, 2000) but less is known about its effect on perceptual processes. Further, many studies on threat biases in social anxiety are correlational and thus unable to directionally test whether anxiety changes emotion perception or if biased emotion perception leads to anxiety. In the present study, participants rated the emotion of facial affect morphed between safe (happy) and threatening (fearful, angry) expressions, and judgments were used to quantify their threat biases. We tested whether participants' threat biases were influenced by trait social anxiety symptoms and whether threat biases could be induced by experimentally manipulating participants' anxiety via a social threat. Because anxiety-induced threat biases may be prevalent among groups experiencing elevated stress levels, like minoritized communities, the present study included an ethnically diverse sample of young adults ranging in social anxiety symptoms. By testing perceptual representations of ambiguous facial affect, the approach outlined may reveal new targets for the prevention and treatment of social anxiety disorder.

Individuals with elevated social anxiety have an increased tendency to classify ambiguous facial expressions as negative (Maoz et al., 2016; Reeb-Sutherland et al., 2015; Richards et al., 2002). Even though this bias has been well documented behaviorally, the mechanistic sources remain poorly understood, specifically whether aberrations in perception precede cognitive decisions. Research suggests that attentional (Cisler & Koster, 2010; Mueller et al., 2009; Pishyar et al., 2004; Taylor et al., 2016) and interpretive biases (Amin et al., 1998; Constans et al., 1999; D. Roth et al., 2001; Stopa & Clark, 2000) contribute to the development of anxiety. However, differences in perception may also contribute to these downstream biases in emotion processing. For instance, people with elevated anxiety display enhanced unconscious processing of subliminal fearful facial affect (Li, Zinbarg, et al., 2008) and other threat cues (Mathews & MacLeod, 1986), suggesting biases in emotion perception can arise prior to conscious cognition. Anxiety may influence sensory systems to prioritize threat-relevant stimuli, which may influence perceptual representations of threat. When viewing the emotions of others, people with social anxiety display elevated neural responses in the amygdala (K. Blair et al., 2008; Brühl et al., 2014; Etkin & Wager, 2007; Stein et al., 2002), a core brain structure in threat processing that is responsible for emotional arousal and salience detection (Etkin, 2010, 2012). Socially anxious people also display elevated visual cortical engagement (e.g., fusiform gyrus, primary visual cortex) for social stimuli (Brühl et al., 2014; Etkin & Wager, 2007; Gentili et al., 2016; Straube et al., 2005) and increased functional connectivity between these regions and the amygdala (Brühl et al., 2014), suggesting that perceptual enhancements may stem from amygdalar feedback to visual

cortex (Pourtois et al., 2013). Here, we aim to test perceptual sources of threat biases in socially anxious young adults. To reduce the influence of top-down, interpretive biases on participants' emotion ratings, stimuli were presented rapidly (200ms) and were backward-masked to interrupt stimulus processing (Liss, 1968). Thus, participants were constrained to rely on their initial response to the brief exposure to make emotion judgments.

Although there are well-documented influences of social anxiety on the identification of emotional facial affect (Machado-de-Sousa et al., 2010), the underlying mechanisms are not yet clear. Some researchers argue that socially anxious individuals display greater sensitivity to threat cues, which manifests as a heightened ability to detect an emotion with smaller displays (Joormann & Gotlib, 2006) and/or as greater accuracy at labeling threat (Cui et al., 2021; Yoon et al., 2014). Others observe reduced sensitivity (Gilboa-Schechtman et al., 2008; Montagne et al., 2006) and reduced accuracy (Simonian et al., 2001) in social anxiety. Differences across studies may stem partially from variations in task design (reviewed in Azoulay et al., 2020). Many studies on facial emotion processing in social anxiety test accuracy in identifying full-intensity emotional expressions or emotions that are morphed on a continuum with neutral facial affect. However, these studies are unable to disambiguate whether differences in emotion identification reflect a heightened ability to accurately detect threat at low levels (i.e., threat sensitivity) or a bias toward choosing threat over ambiguous or safe alternatives (i.e., threat bias). Instead, we use an approach that has effectively probed biases in threat perception (Maoz et al., 2016; Pollak & Kistler, 2002; Reeb-Sutherland et al., 2015), in

which ambiguous faces are created by sequentially morphing two different emotional expressions (e.g., happy to fearful). This is believed to elicit a stronger bias than conventional morphing (i.e., neutral to fearful) because these stimuli generate a conflict in classifying the emotional expression. Further, because both ends of the spectrum are full-intensity emotional expressions, this precludes the possibility that the differences that emerge are indicative of an overall greater sensitivity to emotional cues. In the present study, faces were morphed across two emotion spectra spanning from safety cues to threat cues: happiness to fear and happiness to anger. Anger and fear were chosen because they represent distinct forms of threat. Fearful faces signal the presence of an indirect or undetermined source of danger, whereas angry faces represent a more direct threat, like an aggressor. By testing both fear and anger, our findings will inform whether previously reported negativity biases in anxiety are global (Gilboa-Schechtman et al., 2008), or exhibit unique signatures for fear (Doty et al., 2013; Richards et al., 2002) vs anger (Bradley et al., 1998; Heim-Dreger et al., 2006).

Because anxiety research is inherently correlational, it is difficult to determine if threat biases are induced by anxiety, contribute to elevations in anxiety, or whether a third variable underlies both phenomena. Although anxiety diagnoses cannot ethically be experimentally manipulated, researchers have attempted to probe directional associations by inducing state anxiety among anxious and/or healthy participants (Chavanne & Robinson, 2021; Richards et al., 1992). In the present study, we induced anticipatory anxiety via a novel social threat manipulation adapted from prior work (Eisenbarth et al., 2016) and tested subsequent changes in participants' threat biases. We chose to elicit

anticipatory anxiety because the anticipation of social situations is a central symptom of social anxiety and contributes to the emergence and maintenance of the disorder (Clark, 1995; Hinrichsen & Clark, 2003). Inducing anticipatory anxiety causes momentary behavioral, physiological, and neural changes that resemble those experienced in people with social anxiety. Specifically, anticipation of and exposure to social threat reliably increases subjective anxiety and physiological reactivity, core symptoms of social anxiety (Kemeny, 2003; Kudielka, Hellhammer, & Kirschbaum, 2007; Leitenberg, 2013; Somerville et al., 2013). Further, social threat anticipation induces functional changes in the neural circuitry thought to contribute to social anxiety (Burklund et al., 2017; Fehlner et al., 2020; Gianaros et al., 2008; Somerville et al., 2013; Wager et al., 2009). For instance, among youth and adults, social evaluation led to increased arousal, increased medial prefrontal cortex activity, and increased connectivity between the medial prefrontal cortex and the striatum (Somerville et al., 2013). Thus, social anxiety symptoms could be attributed to overactivation of threat response elicited by repeated anticipatory anxiety in social settings.

Understanding how momentary elevations in anticipatory anxiety contribute to threat biases may have important implications for populations that are exposed to chronic stress, including minoritized groups. Repeated activation of threat response from frequent exposure to stressors is linked to the development of anxiety disorders (Adamec et al., 2001; McEwen, 2000). For example, people employed in jobs that expose them to frequent negative interactions with customers may feel anxious about meeting new people and choose to limit social interactions during their leisure, contributing to greater

social anxiety symptoms. People with anxiety also display psychophysiological characteristics that resemble those elicited by chronic stress (Dieleman et al., 2014). Thus, the long-term effects of chronically elevated threat response in people with social anxiety may lead to the development of threat biases. Many Latinx communities disproportionately face social, acculturative, and socioeconomic stressors (Pérez et al., 2008; Torres et al., 2012), which can increase their risk for developing anxiety disorders (Mendoza et al., 2017). Some studies find that Latinx groups report more anxiety symptoms than other ethnic groups and are at higher risk for experiencing health disparities that create barriers to treatment (Alegria et al., 2006; Lewis-Fernandez et al., 2005; Pina & Silverman, 2004; Varela et al., 2008). Similarly, following the COVID-19 pandemic, Asian people report experiencing more discrimination and greater levels of stress, anxiety, and depression than white people (Chae et al., 2021; Hahm et al., 2021; Lee & Waters, 2021; C. Wu et al., 2021). Although minoritized groups experience elevated stress and anxiety, research on threat biases in social anxiety includes primarily white samples from advantaged socioeconomic backgrounds. This gap in the literature indicates a critical need to understand the correlates of social anxiety in underrepresented communities. Our work examines how social anxiety and induced anticipatory anxiety are associated with threat biases in emotion processing in an ethnically-diverse sample of young adults with a large proportion of Latinx and Asian descent.

The present study seeks to advance our understanding of the etiology of threat biases in young adults ranging in social anxiety symptoms. Participants judged the emotion of faces blended between threatening (fear/anger) and safe (happy) expressions

before and after exposure to a social threat manipulation or a control manipulation. Signal detection theoretic metrics were employed to quantify threat biases – the tendency to choose threat over ambiguous or safe alternatives. Our first aim tested whether trait social anxiety symptoms predicted threat biases in the perception of ambiguous facial affect. We hypothesized that social anxiety symptoms would be associated with increased threat bias. Given previous work finding that socially anxious adults display biases in the perception of both fearful (Richards et al., 2002) and angry (Joormann & Gotlib, 2006) facial affect, we were agnostic to the specificity of emotion. Our second aim tested whether inducing anticipatory anxiety via a social threat manipulation led to changes in the identification of ambiguous facial affect. We hypothesized that participants exposed to the social stressor would display greater increases in threat biases relative to participants in the control condition. Finding that experimentally inducing anticipatory anxiety leads to greater threat biases would provide fundamental insight into the etiology of social anxiety and may reveal new targets for its treatment. For example, finding that biased face perception mediates impaired capacity for threat/safety discrimination would suggest perceptual training may be an effective augmentation strategy for exposure-based cognitive behavior therapy.

Methods

Participants and Procedure

Participants were undergraduate students recruited from the University of California, Riverside Psychology Department to participate in a two-part study for course credit. In part 1, participants completed an online survey during which they reported

demographic characteristics, social anxiety symptoms, and other mental health outcomes not included in the current analyses. In part 2, participants completed two blocks of an in-laboratory explicit emotion identification task punctuated by a social threat or control manipulation. Eighty-nine participants completed parts 1 and 2 of the study. Six participants were removed from all analyses due to poor accuracy on block 1 of the emotion identification task (see 'Emotion Identification Task'), resulting in a final sample of 83 participants. See Table 3.1 for demographic information. Skin conductance data was collected in part 2 but is not assessed in the present analyses.

Table 3.1. Sample demographic characteristics and descriptive statistics for study variables.

Characteristic (*N* = 83)	**Descriptive Statistics**
Age	
Mean (SD)	20.2 (2.7)
Range	17-36
Sex	
Female	59
Male	20
Non-binary	4
Ethnicity	
Asian	37
Hispanic/Latinx	15
White	10
Black	2
Other/mixed ethnicity	19
LSAS – fear (*N* = 82)	
Mean (SD)	33.6 (13.1)
Range	4-61
LSAS – avoidance (*N* = 82)	
Mean (SD)	28.9 (11.8)
Range	4-61

Note. LSAS = Liebowitz Social Anxiety Scale.

Measures

Social Anxiety

Participants' social anxiety symptoms were assessed via the Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987) on Qualtrics within 3 months prior to participation in the emotion identification task at Part 2 (17.1 days $\pm$ 16.9). The LSAS has two subscales, one measuring anxiety/fear and one measuring avoidance. Each subscale is comprised of the same 24 items that relate to social interactions (e.g., "Talking to people in authority.") and/or performing (e.g., "Acting, performing, or giving a talk in front of an audience."). For each item, participants rated their fear of the situation (0 = none to 3 = severe) and avoidance frequency (0 = never to 3 = usually). This scale possesses strong psychometric properties (Beard et al., 2011; Fresco et al., 2001). Each subscale on the LSAS ranges from 0 to 72, summing to a maximum total score of 144. Participants in our study displayed elevated levels of social anxiety. Total scores ranged from 14 to 119 (M = 62.4 $\pm$ 23.6). Clinicians distinguish between two types of social anxiety disorder: nongeneralized social anxiety, a subtype encompassing individuals whose fears reactions are restricted to specific situations, such as fear of public speaking, and generalized social anxiety, a subtype referring to individuals whose fears are more severe and evident in most social situations (Mennin et al., 2002). Research in populations with clinical social anxiety has defined 30 as a cutoff for nongeneralized social anxiety, and 60 as a cutoff for generalized social anxiety. In our sample, 87.8% of participants met the cutoff for the nongeneralized social anxiety subtype and 57.3% met the cutoff for the generalized social anxiety subtype. Participants'

scores on the fear subscale ranged from 4 to 61 ($M = 33.6 \pm 13.1$) and scores on the avoidance subscale ranged from 4 to 61 ($M = 28.9 \pm 11.8$). One participant was excluded from analyses involving the LSAS because they did not complete the measure.

Emotion Identification Task

Participants completed two blocks of a previously validated face emotion identification task (Hopkins et al., 2021), during which they are shown face stimuli and asked to identify the emotion displayed (happiness, sadness, fear, or anger) via arrow keys. An ethnically diverse (i.e., white, Asian, African American) set of eight people posing happy, angry, and fearful facial expressions (Tottenham et al., 2009) was morphed along two emotion spectra (happiness-fear; happiness-anger) in steps of 7%, totaling to 15 morphs per face identity in each emotion spectrum. Four of the face identities were presented in block 1 and four were presented in block 2 and the order of presentation was counterbalanced across participants (version 1, version 2). Based on prior work using a similar paradigm (Maoz et al., 2016; Stoddard et al., 2016), each trial consisted of a black fixation cross against a white background (1000 ms), stimulus presentation (200 ms), a visual noise mask (200 ms), and response screen (2000 ms). Stimuli were backward masked to interrupt stimulus processing (Liss, 1968) and reduce the influence of interpretive biases. The stimulus presentation duration was selected to minimize processing demands while ensuring relatively rapid response selection. Each stimulus was presented three times per block for a total of 360 trials per each of the two 20-minute blocks. Each block was composed of three sub-blocks, in which all morphs of each of the four face identities were displayed once in randomized order. Because the goal of the

proposed project is to evaluate a potential perceptual locus for threat bias, all stimuli were equated across low-level features (e.g., luminance, contrast) using the SHINE Matlab toolbox (Willenbockel et al., 2010) to ensure that such nuisance variables do not affect results. A social threat or control manipulation was administered between blocks. Prior to the start of the task, participants completed ten practice trials with faces of full-intensity emotional expressions. Practice stimuli did not include any face identities that were used in the task.

Participants who did not meet 70% accuracy on the full-intensity emotional expressions (100% happy, 100% fearful, 100% angry) during block 1 of the emotion identification task were excluded from all analyses ($N = 6$; mean LSAS total = 44.3). If participants met the accuracy criteria at block 1, they were not removed for poor accuracy during block 2 because eliciting state anxiety reduces emotion labeling accuracy (Dyer et al., 2022). Seven participants were not shown the correct faces in block 2 due to a technical error and were removed from all analyses using data collected during or after block 2, but were retained in analyses that only used data collected in block 1. Thus, analyses involving block 2 had a final sample of 76 participants.

Social Threat and Control Manipulations

Between blocks 1 and 2, participants underwent a social threat manipulation or a control manipulation. Participants were randomized into either condition prior to participation in part 2 of the study. Participants in the social threat condition were told that they would be required to give a 7-minute speech on the topic of science, politics, or government. Specifically, participants watched a recorded video in which they were

informed by an experimenter that they would give their speech to a panel of experts in psychology, bioengineering, and political science immediately after they completed block 2. This task was adapted from a previously validated paradigm (Eisenbarth et al., 2016) because the anticipation of public speaking under a social evaluative threat reliably induces threat responses (Kemeny, 2003; Kudielka, Hellhammer, & Kirschbaum, 2007). Participants were not informed about the speech until they completed block 1 to ensure that anticipatory anxiety was only elicited in block 2. In block 2 of the emotion identification task, participants in the social threat manipulation condition received notifications every 5 minutes stating the length of time left before they were to give their speech (i.e., "You have 15 minutes until you give your speech").

Participants in the control condition were told that they would write a short journal entry about their day at the end of block 2. To minimize feelings of anxiety, instructions stated that no one would read the journal entry, but that they would reflect on the process of writing it. In block 2 of the emotion identification task, participants in the control condition viewed notifications every 5 minutes stating the length of time left before the task was finished (i.e., "the task will end in 15 minutes").

At the end of the experiment, before they were informed of the deception, participants self-reported on a 1-5 Likert scale how nervous they were about the thought of giving a speech or writing a journal entry.

State Anxiety

State anxiety symptoms were measured via self-report before, during, and after the emotion identification task on the 20-item state anxiety subscale of the State-Trait

Anxiety Inventory (STAI-State; Spielberger et al., 1972). The STAI-State assesses state feelings of anxiety by asking participants to indicate how they feel "right now…at this moment." Participants responded to all items on a three-point Likert scale and each subscale was summed to a total score ranging from 20 to 60. The STAI-State was measured three times: at baseline (immediately before the emotion identification task), mid-task (immediately following the social threat or control manipulation, prior to block 2), and post-task (immediately after block 2 of the emotion identification task).

Data Analysis

Efficacy of Social Threat Manipulation

We first tested the efficacy of the social threat manipulation, the speech preparation task, and whether it elicited changes in state anxiety relative to the control task, the journal entry. To measure whether anticipatory state anxiety was increased in the social threat condition relative to the control condition, we calculated task-related changes in state anxiety. We subtracted baseline state anxiety from mid-task state anxiety, and post-task state anxiety.

Linear regressions tested the effect of experimental condition and social anxiety symptoms on post-task ratings of self-reported nervousness about the manipulation, controlling for task version. The LSAS fear and avoidance subscales were tested as social anxiety measures in two separate models. Fear and avoidance subscales were tested separately because data were collected in person following the COVID-19 pandemic. Thus, participants might avoid social activities as a precaution to prevent illness rather than as a result of social anxiety. Bonferroni corrections were conducted for multiple

comparisons at $p < 0.025$. To assess whether elevations in anticipatory state anxiety resulting from the social threat manipulation were uniquely relevant to social anxiety, an exploratory post hoc analyses tested the same model with trait anxiety predicting post-task nervousness ratings.

Threat Thresholds and Labeling Accuracy

Behavioral responses pre- (block 1) and post-manipulation (block 2) were used to quantify threat biases toward fear and anger judgments via participants' threat threshold (i.e., the facial expression at which a participant's judgment switches from predominantly happy to predominantly fearful or angry). Biases that were specific to the perception of ambiguously fearful or angry facial affect were termed fear thresholds or anger thresholds, respectively. Block 1 and 2 threat thresholds were calculated as the point of subjective equality via psychometric function fit to participants' emotion ratings. Within each emotion spectrum, the percent of trials an individual chose fear or anger was plotted against the morph level (0% to 100% fear/anger), and a Logistic function with a fixed guess rate (γ =.01) and lapse rate (λ =.01) was fitted to the response percentages. Lower threat thresholds signify a greater tendency to label a face as fearful or anger rather than happy, indicating greater threat biases.

First, we tested whether social anxiety was associated with baseline threat biases in the perception of facial affect. We tested whether threat thresholds at block 1 (prior to the social threat or control manipulation) were correlated with the fear and avoidance subscales of the LSAS. We conducted Bonferroni corrections for multiple comparisons across the two LSAS subscales (fear, avoidance) and two emotion spectra (happy-fearful,

happy-angry), $p < 0.0125$. We did not observe any sex differences in LSAS fear or avoidance subscales (ps > .21), emotion identification accuracy (ps > .18), or threat thresholds (ps > .14) so gender was not included as a covariate in any subsequent analyses.

Next, we tested whether the social threat manipulation elicited changes in threat biases relative to the control condition. Independent samples t-tests measured whether changes in state anxiety differed by experimental manipulation. We conducted two repeated measures ANCOVAs to examine whether inducing anticipatory anxiety via a social threat manipulation changed participants' 1) emotion identification accuracy and, 2) threat thresholds. The first model tested changes in participants' accuracy on the full-intensity emotional expressions (100% angry, fearful, and happy). This model included emotion (happy, angry, fearful) and task block as within-subject factors, experimental manipulation (control, social threat) as a between-subjects factor, and task version as a covariate. In the second model testing changes in participants' threat thresholds, emotion spectra (happy-angry, happy-fearful) and task block were included as within-subject factors, experimental manipulation (control, social threat) was a between-subjects factor, and task version (counterbalanced sets of stimuli across blocks 1 and 2) was a covariate.

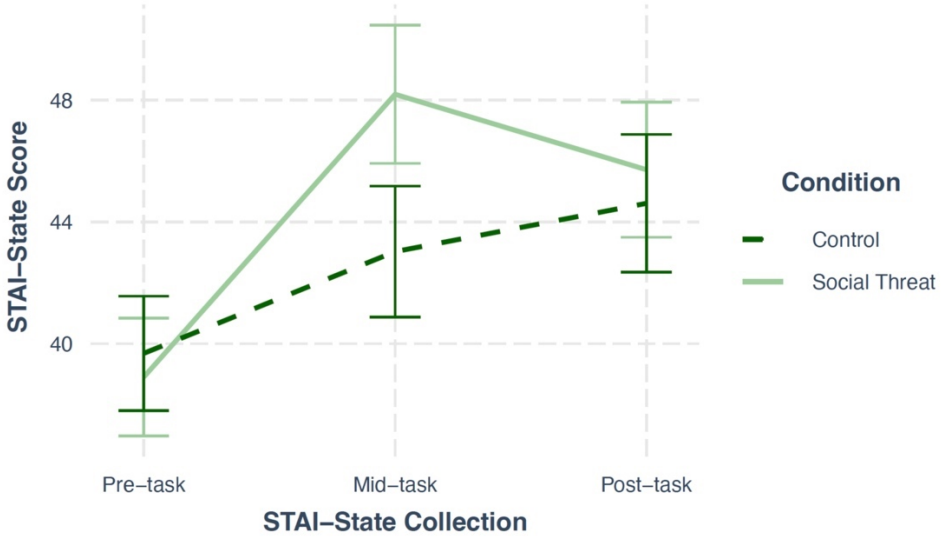
Finally, we conducted a third ANCOVA to probe whether increases in anticipatory state anxiety across both experimental conditions influenced participants' threat thresholds. In this model, emotion spectra (happy-angry, happy-fearful) and task block were within-subject factors, change in state anxiety from baseline to mid-task was a continuous between-subjects factor, and task version was a covariate.

Results

Efficacy of Social Threat Manipulation

To examine whether the social threat manipulation induced greater increases in anticipatory state anxiety relative to the control condition, we conducted an independent samples t-test on the change in state anxiety from baseline to mid-task (measured directly after the manipulation) in each condition. We observed that participants in the social threat condition experienced greater increases in state anxiety from baseline to mid-task relative to participants in the control condition, $t(81) = 2.84$, $p = .006$ (Figure 3.1). However, state anxiety was no longer elevated for participants in the social threat condition relative to the control condition at the end of block 2 (i.e., post-task state anxiety), $t(74) = 0.64$, $p = .52$. Post-hoc t-tests revealed that state anxiety decreased from mid-task to post-task for participants in the social threat manipulation condition, $t(41) = 2.09$, $p = .042$, but not the control condition, $t(40) = -1.72$, $p = .09$.

Figure 3.1. State anxiety by measurement time and condition.



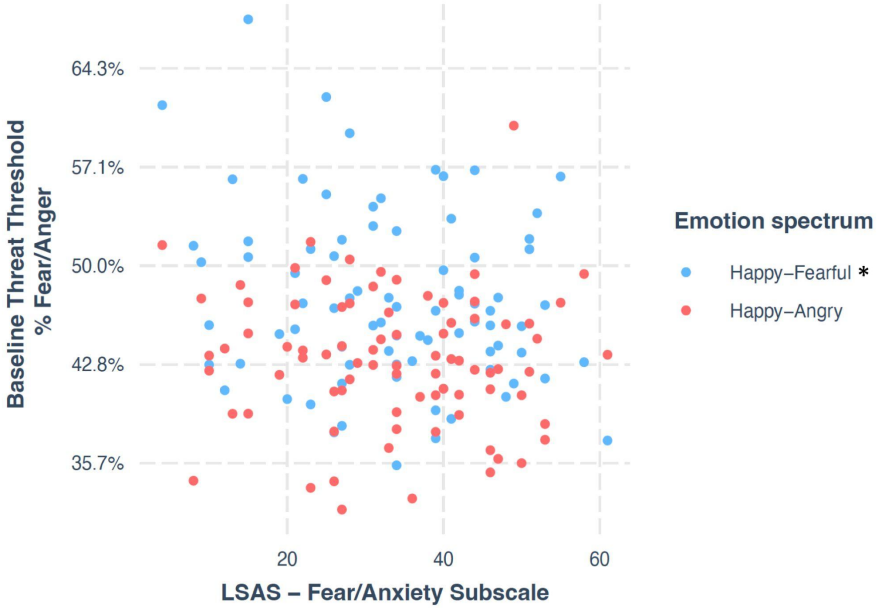
Note. Participants in the social threat condition experienced greater increases in state anxiety (STAI-State) from pre-task to mid-task (directly after the manipulation) relative to participants in the control condition, $t(81) = 2.84$, $p = .006$. STAI = State-Trait Anxiety Inventory.

Next, a linear regression tested whether 1) the social threat manipulation made participants more nervous than the control task, and 2) whether socially anxious participants were more nervous across either condition. A linear regression revealed that post-task ratings of self-reported nervousness about the manipulation was predicted by experimental condition, $\beta = 1.55$, $p < .001$, and LSAS fear subscale score, $\beta = .02$, $p = .041$, controlling for task version. As predicted, participants in the social threat condition were more nervous than participants in the control condition. Nervousness was also positively associated with scores on the LSAS fear subscale, across both conditions. However, this association did not hold with Bonferroni correction. In the remaining three models, only experimental condition predicted nervousness, $ps < .001$. Nervousness was not significantly associated with avoidance of social situations or trait anxiety, $ps > .15$.

Threat Thresholds and Labeling Accuracy

To address our first aim, whether trait social anxiety was associated with threat biases in emotion perception, correlations tested the association between participants' fear and avoidance of social situations on the LSAS and baseline threat biases in emotion perception. The LSAS fear subscale was inversely correlated with participants' fear thresholds in block 1, r = -.22, p = .05. That is, participants with a greater fear of social situations displayed lower baseline fear thresholds, indicating a greater tendency to categorize ambiguous facial affect as fearful relative to happy (Figure 3.2). However, this association did not hold for Bonferroni correction. The LSAS avoidance subscale was not correlated with block 1 fear thresholds, r = -.04, p = .70. Neither LSAS subscale was associated with block 1 anger thresholds, ps > .58.

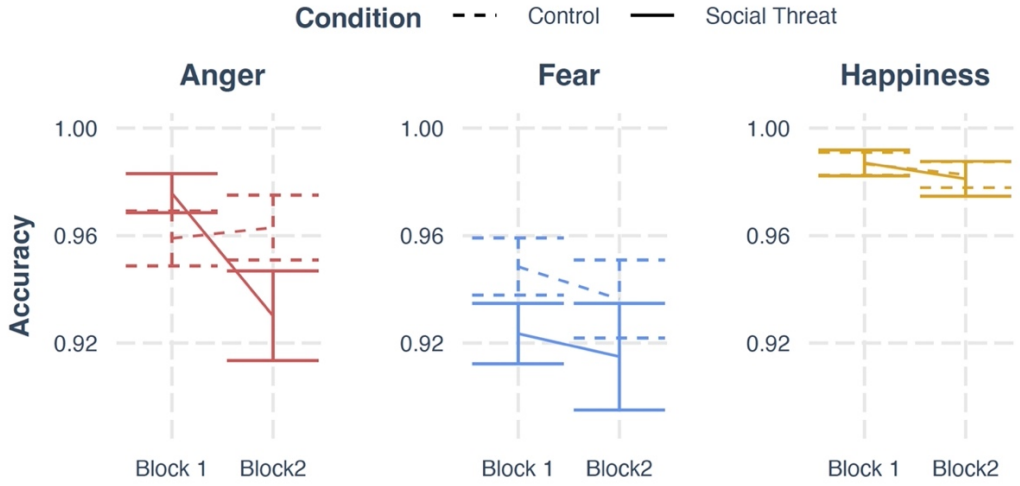
Figure 3.2. Associations between fear of social situations and threat thresholds at block 1.



Note. Fear of social situations was measured via the Liebowitz Social Anxiety Scale (LSAS) fear/anxiety subscale. Threat thresholds were calculated as the point of subjective equality via psychometric functions fit to the percent of trials participants labeled as fearful (blue) or angry (red). *p < .05.

Second, we tested the effects of the social threat manipulation on participants' accuracy in categorizing full-intensity emotional expressions via a repeated measures ANCOVA. Emotion (happy, angry, fearful) and task block were within-subject factors, experimental manipulation (control, social threat) was a between-subjects factor, and task version (counterbalanced sets of stimuli across blocks 1 and 2) was a covariate. We observed a three-way interaction between task block, emotion, and condition, $F(1.76, 146) = 3.87$, $p = .028$. Experimental manipulation impacted changes in anger accuracy from block 1 to block 2, $t(74) = 2.78$, $p = .007$. Participants in the social threat manipulation condition displayed reductions in anger accuracy following the social threat manipulation, whereas participants in the control condition demonstrated increased accuracy during block 2 relative to block 1 (Figure 3.3). The experimental manipulation did not influence changes in accuracy labeling fearful faces, $t(74) = .156$, $p = .88$, or happy faces, $t(74) = .24$, $p = .81$. The ANCOVA also revealed a three-way interaction between task block, emotion, and task version, $F(1.76, 146) = 8.92$, $p < .001$. No other main effects or interactions emerged. All analyses were Greenhouse-Geisser corrected.

Figure 3.3. Accuracy labeling full-intensity facial affect before (Block 1) and after (Block 2) the social threat or control manipulation.

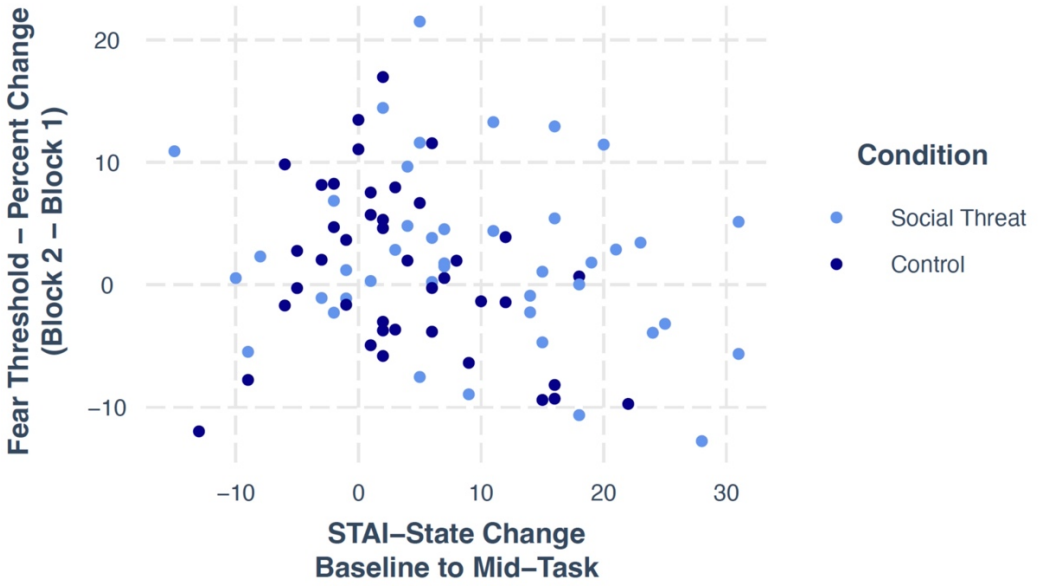


Next, we probed the effects of the social threat manipulation on participants' threat thresholds with a second repeated measures ANCOVA. Emotion spectra (happy-angry, happy-fearful) and task block were within-subject factors, experimental manipulation (control, social threat) was a between-subjects factor, and task version was a covariate. Contrary to our hypotheses, experimental condition did not interact with task block. We observed a significant main effect of experimental condition, $F(1, 73) = 4.48$, $p = .038$. People in the social threat condition had higher threat thresholds than those in the control condition across both blocks, $t(74) = 2.06$, $p = .043$, indicating that they had pre-existing reduced threat biases that were maintained throughout the experiment. We also observed a three-way interaction between emotion, task block, and task version, $F(1, 73) = 19.21$, $p < .001$. No other main effects or interactions emerged.

Lastly, we examined whether elevations in state anxiety following the social threat or control manipulation predicted changes in threat thresholds, regardless of experimental condition. Again, a repeated measures ANCOVA was conducted with

emotion spectra (happy-angry, happy-fearful) and task block were within-subject factors, and task version was a covariate. The continuous between-subjects variable was the change in participants' state anxiety from baseline to mid-task. We observed a significant three-way interaction between emotion, task block, and change in state anxiety, $F(1, 73) = 4.66$, $p = .034$, such that change in state anxiety was inversely associated with participants' changes in fear thresholds, $r = -.28$, $p = .015$, but not anger thresholds, $r = .10$, $p = .38$. That is, participants who experienced greater increases in state anxiety following either the social threat or control manipulation displayed greater reductions in fear thresholds (i.e., greater increases in fear biases) in block 2 relative to block 1 (Figure 3.4). We also observed a main effect of emotion on threat thresholds, $F(1, 73) = 5.61$, $p = .020$, such that participants displayed lower threat thresholds for anger relative to fear, $t(75) = 5.56$, $p < .001$. We also observed a three-way interaction between emotion, task block, and task version, $F(1, 73) = 15.99$, $p < .001$. No other main effects or interactions emerged (ps > .059).

Figure 3.4. Changes in state anxiety from baseline to mid-task are associated with changes in fear thresholds for participants in the social threat and control conditions.



Note. STAI-State = State-Trait Anxiety Inventory - State Anxiety subscale

Discussion

Social anxiety disorders are characterized by an increased tendency to identify ambiguous emotions as threatening (Cooney et al., 2006; Maoz et al., 2016; Yoon et al., 2014), though less is known about whether such differences are indicative of enhanced sensitivity to threat or of a bias toward threat selection over equally prominent alternatives. In a diverse sample of young adults ranging in social anxiety symptoms, we examined baseline associations between social anxiety and threat biases in the perception of ambiguously fearful and angry facial affect. We further tested whether experimentally inducing anxiety via a social threat manipulation led to changes in emotion perception. Three key findings emerged. First, greater trait fear of social situations was positively associated with baseline threat biases for fearful but not angry facial affect, prior to multiple comparison corrections. Second, contrary to our hypotheses, the social threat

manipulation did not elicit greater changes in threat biases than the control manipulation. However, situational elevation in state anxiety following the social threat or control manipulation was associated with increased biases in perceiving fearful but not angry faces. Third, participants in the social threat condition were less accurate in categorizing full-intensity anger expressions following the manipulation, whereas participants in the control condition displayed increased accuracy. No such differences emerged for happy or fearful faces.

In line with hypotheses, the LSAS fear subscale was inversely correlated with baseline threat thresholds for ambiguously fearful but not angry facial affect, prior to multiple comparison corrections. In other words, socially anxious people tended to label ambiguous faces as fearful when faces displayed a lower proportion of fear and a higher proportion of happiness, compared to participants with low social anxiety. Using emotional faces that displayed conflicting emotional expressions enabled us to find that socially anxious participants prioritized of fear cues over happiness cues. This precludes the possibility that social anxiety is associated with greater overall sensitivity to emotional facial affect and instead suggests a bias toward fear detection. Given mixed research finding threat biases in social anxiety are specific to fear (Doty et al., 2013; Richards et al., 2002), to anger (Bradley et al., 1998; Heim-Dreger et al., 2006), or are global (Gilboa-Schechtman et al., 2008), we were agnostic as to the effect of emotion. We observed that labeling biases were specific to fear cues and did not extend to angry facial affect. Whereas anger is thought to signal a direct threat cue, fear may signal more indirect threat or danger in the environment (e.g., LeDoux, 1996). People with social

anxiety tend to perceive social situations as threatening. Prioritizing others' fear cues over safe or neutral cues may enable socially anxious individuals to detect and avoid fear-inducing situations. For example, if someone looks fearful at a party, it may be because they are in an uncomfortable conversation -- a cue for others to avoid the same discomfort. In this case, enhanced sensory prioritization of fear cues might be more relevant for socially anxious people than a direct threat cue like anger or a safety cue. Interestingly, these biases in fear perception were not elicited for people who were high on the avoidance subscale of the LSAS. The present study was conducted in person following the COVID-19 pandemic and health concerns likely contributed to participants' avoidance of social situations. Thus, the LSAS avoidance subscale may have not uniquely captured individual differences in trait social anxiety.

The present study employed a novel social threat manipulation to elicit state anxiety and experimentally test whether anticipation of a social stressor induced threat biases. The social threat manipulation elicited short-term increases in anticipatory state anxiety; participants in the social threat condition displayed larger increases in state anxiety from baseline immediately following the manipulation compared to participants in the control condition. Preparing a speech under social evaluative threat robustly increases subjective anxiety and engages the sympathetic nervous system (Allen et al., 2014; Kudielka et al., 2007). However, most studies examine the influence of social evaluative stress during speech production or the subsequent recovery period. Fewer studies probe correlates of anticipation of social evaluation, which is a key feature of social anxiety disorders (Clark & Wells, 1995; Rapee & Heimberg, 1997) and may be

more relevant for examining biases in emotion processing. Whereas biases in emotion perception experienced during or after a social interaction can influence performance or memory, biases that emerge during the anticipation of social evaluation can cause people to avoid social interaction altogether. Avoidance of social situations may contribute to further increases in social anxiety by reducing opportunities to habituate or reappraise fears and further reinforcing threat biases (Stirling et al., 2006). Of note, elevations in state anxiety induced by the social threat manipulation did not persist throughout the second block of emotion labeling. Future work should test whether anticipation of a social threat influences biological indices of arousal, and if so, for how long.

Our second aim tested whether anticipatory anxiety induced via a social threat manipulation led to changes in participants' emotion perception. Contrary to our hypotheses, experimental condition did not influence changes in participants' threat thresholds from block 1 to block 2. However, across both conditions, participants who experienced elevations in mid-task anticipatory state anxiety displayed greater fear biases in the second emotion identification block, relative to the first. In other words, momentary elevations in anticipatory state anxiety led to changes in the perception of ambiguously fearful affect that replicated those observed in social anxiety. This suggests that feeling negative anticipation about social situations may be a key feature underlying biased perception of facial affect in social anxiety. In some cases, it might be adaptive for state feelings of social anticipation to cause people to prioritize threat cues more than cues to safety. For instance, in a high-pressure situation like a job interview, it may be beneficial to be highly attuned to subtle indications of displeasure so that one can adjust

their behavior accordingly. However, frequently feeling anticipatory anxiety is maladaptive and can interfere with daily functioning across a variety of settings. Future work should delve further into the distinct and overlapping correlates of social anxiety and anticipatory state anxiety. For instance, neuroimaging studies might test whether inducing anticipatory anxiety in socially anxious and non-anxious populations leads to changes neural activation elicited by threat stimuli.

If inducing anticipatory anxiety is sufficient to influence threat perception, is suggests that threat biases in anxiety may be modified by treatment. For instance, if these processes are reciprocal, then reducing the perceptual salience of fear cues relative to safe or ambiguous features might lead to downstream differences in interpreting social situations. Threat biases in the perception of ambiguous emotional stimuli might be targeted via training on threat-safety discrimination (Ginat-Frolich et al., 2017, 2019) or attentional bias modification (MacLeod & Clarke, 2015; Schmidt et al., 2009). Preliminary evidence suggests that modifying attention to or perception of threat-relevant stimuli can reduce feelings of anxiety (Schmidt et al., 2009) and limit avoidance of feared stimuli (Ginat-Frolich et al., 2019), indicating a possible augmentation strategy for exposure-based cognitive behavioral therapy.

Finally, we observed that participants in the social threat condition displayed reduced accuracy in labeling full-intensity anger expressions following the manipulation, whereas participants in the control condition displayed increased accuracy. Preliminary research has found that inducing state anxiety leads to global decrements in emotion recognition accuracy among healthy participants (Attwood et al., 2017; Dyer et al.,

2022). In the present study, however, impairments induced by the social threat manipulation were specific to the identification of full-intensity anger. Methodological differences in how state anxiety was induced might underlie discrepant results. Previous studies induced anxiety via inhalation of carbon dioxide-enriched air (Attwood et al., 2017; Dyer et al., 2022), which replicates symptoms of generalized anxiety disorder (Bailey et al., 2005). By contrast, in our sample, state anxiety was elicited via anticipation of a social-evaluative threat, which was designed to replicate social anxiety symptoms specifically. We also observed that, prior to multiple comparison correction, fear of social situations was uniquely predictive of post-task ratings of nervousness about the manipulation, whereas trait anxiety was not. This suggests that the anxiety induced by the social threat manipulation may be especially relevant for socially anxious participants and may replicate their symptoms more closely compared to people with elevated trait anxiety. Here, we observed that social anxiety and induced anxiety were associated threat biases that were specific to fear. This may lead to hypervigilance to fearful affect at the expense of categorizing other forms of threat (e.g., anger). Future work should test whether decrements in labeling threat affect following a social threat induction are specific to anger or expand to other negative emotions like sadness and disgust.

The present study provides preliminary evidence that biases in fear perception contribute to the onset and/or maintenance of social anxiety disorder in young adults. This study was bolstered by several strengths. First, we employed a novel experimental manipulation that was successful in eliciting short-term elevations in anticipatory social anxiety. Second, because stimuli were combined between two conflicting emotional

expressions, we successfully targeted biases in threat perception, rather than elevations in threat sensitivity. Finally, our sample consisted of young adults with elevated social anxiety, with a majority from Latinx and Asian backgrounds – groups that are commonly underrepresented in research. Several limitations of the study should also be noted. Contrary to our hypotheses, experimental condition did not influence subsequent increases in participants' threat biases. One reason for this may be that, although the social threat manipulation induced short-term increases in anticipatory state anxiety, elevations were not maintained throughout the entirety of the second block. Decreases in state anxiety may have been due to boredom or task fatigue. Future work should test physiological indices of arousal following a social evaluative stressor using measures like skin conductance response to better understand its impact on anticipatory state anxiety. Alternatively, it is possible that the control task also increased anticipatory state anxiety, reducing differences between conditions. Unexpectedly, participants in the control condition displayed mid-task and post-task increases in state anxiety from baseline. Participants in our sample reported elevated levels of depression and anxiety, so asking them about their day may have led to rumination about mistakes or stress about upcoming tasks. Given that anticipatory state anxiety was associated with threat biases when data was collapsed across conditions, this is a likely possibility. Future work should test other control tasks that do not require self-reflection and may be less arousing. A second complication in the present study was that the task version participants were assigned to (i.e., which faces participants saw first) significantly influenced emotion judgments. Participants saw a new set of faces following the social threat or control manipulation to

ensure that previous face judgments would not bias those following the manipulation. Faces were matched by ethnicity and gender across both versions to reduce the effects of the task version. However, differences in actors' displays of emotion may have contributed to significant differences in emotion judgments across versions. Larger sample sizes may be necessary to find significant effects of condition after controlling for version effects.

In sum, socially anxious young adults may display biases in the perception of ambiguously fearful affect, and such biases may also be induced by short-term fluctuations in social anticipatory anxiety. Accurate identification of other people's emotional expressions provides us with important cues to the emotional state of our interaction partners. Misinterpreting ambiguous emotional expressions or giving greater salience to fear cues could contribute to the onset and/or maintenance of social anxiety in several ways. For one, misunderstanding social cues could lead to impaired communication between interaction partners and uncomfortable social interactions. Perceiving others' expressions as threatening may cause socially anxious people to further avoid social situations, reducing opportunities to habituate or reappraise fears. Future work should test whether interventions that reduce the perceptual salience of fear cues effectively improve social skills or ameliorate anxiety.

General Discussion

The goal of this dissertation was to examine the behavioral and neurodevelopmental correlates of biases in threat perception in youth with anxiety, and

how such associations are influenced by anticipatory state anxiety. Existing developmental research on threat biases in anxiety suffers from important limitations. For instance, there is mixed evidence as to the contribution of prefrontal regions to impaired regulatory control in anxiety, and how it interacts with pubertal development. Additionally, perceptual sources of threat biases in anxiety are not well understood because existing correlational studies cannot directionally test associations. Finally, most pediatric anxiety research is composed of homogenous samples of white, upper-middle-class, treatment-seeking youth, raising important questions about whether extant models of threat bias in anxiety are generalizable to minoritized populations. Results from this dissertation offered two major contributions to the literature. First, functional and structural evidence for impaired prefrontal regulation of hypersensitive arousal networks in trait anxiety was observed in Chapters 1 and 2. I contend that compounding anxiety-related differences in prefrontal function during childhood may lead to structural change in adolescence or adulthood, and this progression may be influenced by pubertal changes in neurodevelopment. Second, Chapters 1 and 3 revealed that fluctuations in anticipatory state anxiety influence the perception of ambiguously fearful facial affect and may exert dissociable impacts on high- versus low-trait-anxious children. I discuss the implications of these findings for culturally sensitive pediatric anxiety research and treatment. Finally, I conclude by enumerating limitations and opportunities for future directions.

Impaired Prefrontal Regulation of Hypersensitive Arousal Networks in Anxiety

Anxiety is associated with biases in threat perception and regulation, but less is known about the direction of prefrontal engagement and how it interacts with

developmental mechanisms. This dissertation provides evidence supporting that biased fear perception in anxiety is subserved by increased sensitivity to threat in arousal networks and reduced regulatory control over these networks. In Chapter 1, trait anxiety was associated with differences in brain function during implicit fear processing; trait-anxious preadolescent girls displayed increased insula sensitivity and reduced activation in the IFG, a prefrontal region that enables task control and emotion regulation in the face of task-irrelevant emotional distractors (Aron et al., 2004; Dolcos et al., 2006; Morawetz et al., 2017; Winecoff et al., 2011). In Chapter 2, structural brain analyses that were conducted in a subset of participants from Chapter 1 revealed that anxiety symptoms predicted reduced white matter integrity in the cingulum. The cingulum connects medial temporal, arousal networks with prefrontal brain regions involved in emotion regulation. Together, these chapters provide evidence that impaired connectivity between arousal and regulatory nodes (Chapter 2) and prefrontal dysfunction during fear processing (Chapter 1) may contribute to the development of anxiety in preadolescent girls. Notably, trait anxiety did not influence how quickly or accurately girls labeled the gender of fearful faces. However, in a separate sample of young adults, Chapter 3 revealed socially anxious participants displayed behavioral threat biases that were specific to ambiguously fearful facial affect, supporting explicit labeling biases in anxiety.

The findings of this dissertation contribute to a mixed literature in pediatric anxiety research, in which some studies find that anxious children display reduced prefrontal response when viewing threat-relevant stimuli (Bishop, Duncan, Brett, et al., 2004; Mujica-Parodi et al., 2009) and others find increased engagement (Fales et al.,

2010; J. M. Fitzgerald et al., 2017). Associations between anxiety and prefrontal activation to negative emotional affect may be influenced by task instructions. In implicit face emotion processing, children passively view emotional face stimuli or are instructed to attend to non-emotional features of the face, such as gender (as in Chapter 1). In explicit face emotion processing, children are instructed to attend to the emotion of the face by detecting, classifying, or labeling emotional cues (as in Chapter 3), or evaluating their emotional responses to them. Some research has found that, during *explicit* emotion processing, left IFG activity is increased for anxious participants (Fales et al., 2010; J. M. Fitzgerald et al., 2017). The left IFG plays a role in generating inner speech (Geva et al., 2011; Morin & Hamper, 2012), which may be employed to explicitly categorize emotional stimuli (Kohn et al., 2014). Thus, hyperactivation of this region during explicit emotion labeling may suggest that anxious children have more difficulty identifying emotions and rely more on inner dialogue to do so. Conversely, in line with previous work utilizing *implicit* emotion processing paradigms (Mujica-Parodi et al., 2009), Chapter 1 revealed that anxiety severity was associated with reduced activation in the left IFG. These results suggest that anxious children display impaired executive function and/or regulation when performing tasks in the face of emotional distractors. Alterations in the ability to engage with or disengage from task-irrelevant negative information may contribute to an interruption of daily functioning and the maintenance of anxiety symptoms (MacLeod et al., 1986), making it a potential treatment target for future interventions (Mogg & Bradley, 2018).

Differences in the valence of the association between pediatric anxiety and prefrontal engagement across studies may also be due to variability in dispositional or demographic characteristics across samples. For instance, associations between prefrontal activation and anxiety symptom severity may be moderated by anxiety diagnosis. A study by Monk et al. (2006) found that during implicit threat processing, youth with generalized anxiety disorder displayed elevated inferior frontal (vlPFC) activation compared to controls. But paradoxically, among anxious youth, increased vlPFC activation was associated with *reduced* symptom severity. This suggests that enhanced inferior frontal activation may help anxious youth regulate responses to anxiety-inducing stimuli by inhibiting hyperactive responses in salience-processing regions (e.g., amygdala, insula), effectively reducing anxiety symptoms. By contrast, non-anxious participants tend to display less aversive responses to pictures of negative facial affect, and thus, may not need to engage regulatory regions. Although the girls in Chapters 1 and 2 were not seeking treatment for anxiety upon enrollment, over 80% of participants in both studies met or surpassed the threshold for clinically-significant levels of self-reported anxiety on the SCARED, indicating that the sample was more anxious than most community samples. Perceptions of mental illness vary across cultures and influence rates of treatment. Latinx youth seek treatment for mental health issues significantly less than non-Latinx whites (Gudiño et al., 2009; Kataoka et al., 2002), even though they display elevated rates of anxiety compared to other racial and ethnic groups (Glover et al., 1999; McLaughlin et al., 2007; Pina & Silverman, 2004; Potochnick & Perreira, 2010; Varela et al., 2008). Thus, researchers should consider culturally-relevant values

and beliefs when employing diagnostic boundaries for anxiety in diverse populations (Kapke & Gerdes, 2016).

This dissertation may also inform the developmental process of impaired prefrontal regulation over salience-processing regions like the amygdala and insula, whereby chronic compounding functional differences in childhood lead to subsequent structural change in adolescence or adulthood. In Chapter 1, anxiety was associated with aberrant function in the insula and IFG, regions that are connected by the uncinate fasciculus (Briggs et al., 2019). Anxiety is associated with reduced white matter integrity in the uncinate fasciculus in adolescence (Liao et al., 2014) and adulthood (Baur et al., 2011; Phan et al., 2009; Tromp et al., 2012; Wang et al., 2016), but decrements are not yet present in anxious girls (Aggarwal et al., 2022; Tromp, Williams, et al., 2019), as replicated in Chapter 2. This suggests the possibility that repeated impaired prefrontal control over aberrant insula activity in childhood may contribute to subsequent reductions in structural connectivity between these regions in adolescence or adulthood. In offering this interpretation, it is important to acknowledge the cross-sectional nature of the present work. Other studies provide some support for this idea using twin-design methods. For example, a monozygotic twin study in adolescents revealed that anxiety symptoms predicted decreased white matter integrity in the uncinate fasciculus (Adluru et al., 2017). This supports the hypothesis that, after controlling for shared genetic and environmental factors, the experience of anxiety symptoms can contribute to reduced uncinate fasciculus white matter integrity during adolescence. Importantly, if this is true, then training participants to downregulate emotional arousal by engaging prefrontal regions could

prevent diminished white matter integrity in the uncinate fasciculus in adolescence and adulthood. Several studies have observed experience-dependent changes in white matter integrity (Jäncke et al., 2009; Mackey et al., 2012; Scholz et al., 2009), bolstering feasibility.

In contrast with intact uncinate fasciculus integrity, Chapter 2 revealed that anxious girls displayed reduced cingulum integrity, and this association was especially strong for pre-pubertal girls. White matter microstructure of the cingulum and uncinate fasciculus exhibit protracted development throughout adolescence and into adulthood (Lebel et al., 2008, 2012) and may be influenced by pubertal development (Asato et al., 2010; Chahal et al., 2018). Puberty spurs changes in the valence of functional connectivity between the amygdala and anterior cingulate cortex (ACC), regions that are connected by the cingulum, with adolescents and adults exhibiting negative connectivity and children exhibiting positive connectivity (Gee et al., 2013a; M. Wu et al., 2016). Negative amygdala-ACC functional connectivity suggests effective prefrontal regulation over the amygdala (i.e., activation of the ACC coupled with reduced amygdala activation), whereas positive or no connectivity might suggest ineffective or underdeveloped regulation. Amygdala-ACC functional connectivity becomes more negative with age in healthy youth (Gee et al., 2013a; Jalbrzikowski et al., 2017; Kujawa et al., 2016a), indexing developing regulatory skills. Importantly, the opposite pattern is observed in anxious youth (Kujawa et al., 2016a). Thus, girls without anxiety may experience increases in cingulum integrity through middle childhood and early adolescence, as they develop regulatory skills. For anxious girls, developments in

cingulum microstructural integrity may be delayed, or decrements may persist throughout adolescence and adulthood. Longitudinal research that jointly and prospectively measures functional and structural connectivity between prefrontal regions and salience-processing networks is necessary to further probe the interactive influences of anxiety and pubertal development.

Fluctuations in Anticipatory State Anxiety Influence Fear Perception

Studies examining pathological anxiety often neglect to probe short-term fluctuations in anticipatory anxiety, which can be induced by the research environment, vary systematically across demographic groups, and influence results. The results of this dissertation suggest that transient fluctuations in anticipatory state anxiety influence the perception of fearful facial affect, which may have important implications for research considerations and anxiety treatment, discussed below. In Chapter 3, young adults who experienced greater elevations in anticipatory state anxiety following a social threat or control manipulation were subsequently more likely to perceive ambiguous faces as fearful. Anticipatory state anxiety was also associated with differences in neural response to fearful faces in Chapter 1, whereby children with elevated pre-scan state anxiety displayed less fear-intensity modulation in brain regions critical to emotion perception (Adolphs, 2002). In other words, state-anxious children displayed reduced responsiveness to changes in fear intensity in perceptual regions relative to non-anxious children. Although Chapters 1 and 3 may seem contradictory at first, both support the possibility that state anxiety is associated with an increased tendency to perceive ambiguous or low-intensity facial affect as fearful. State anxiety can facilitate threat detection via perceptual

enhancements (Li, Howard, et al., 2008; Phelps et al., 2006), enabling the identification of threat at lower levels of intensity (Muris et al., 2003). Because all stimuli presented in Chapter 1 displayed some degree of fear, state-anxious children may have detected fear even at low levels of intensity. This may have led to state-anxious children displaying more consistent levels of activation in the IOG/FG across all stimuli. By contrast, children with low state anxiety may have only detected fear at moderate or high levels of intensity, thus displaying more modulated responses as fear intensity increased. Together these results may suggest that perceptual overgeneralization across fear intensity levels may contribute to behavioral threat biases elicited by elevated anticipatory state anxiety.

Biases in fear perception in anxiety may result from amygdalar influences on visual cortices. The amygdala can influence visual perception through both bottom-up and top-down mechanisms (see Sussman et al., 2016 for a comprehensive review). The amygdala receives crude, low-spatial frequency information about threat cues via a subcortical pathway from the superior colliculi and pulvinar that bypasses detailed visual processing (Day-Brown et al., 2010). Through this pathway, the amygdala can rapidly process threat stimuli (Méndez-Bértolo et al., 2016) and boost subsequent sensory processing via re-entrant feedback signals to visual cortices (Ohman, 2005; Vuilleumier, 2005; Vuilleumier & Pourtois, 2007). This pathway is hypothesized to explain why people can detect and process threat cues more quickly than safety cues (Eastwood et al., 2001; Ohman et al., 2001; Schupp et al., 2004). Supporting bottom-up processing, research has found that the amygdala is activated by unconsciously processed fearful faces (J. S. Morris et al., 1998; Whalen et al., 1998), relies more on low spatial frequency

information (Vuilleumier et al., 2003), and responds faster than visual cortices when processing fearful affect (Méndez-Bértolo et al., 2016). Threatening stimuli elicit greater amygdala activation in clinical anxiety, trait anxiety, and state anxiety, relative to non-anxious participants (Bishop, Duncan, & Lawrence, 2004; Calder et al., 2011; Dickie & Armony, 2008; Etkin et al., 2004; Etkin & Wager, 2007; Günther et al., 2020; Killgore & Yurgelun-Todd, 2005; Larson et al., 2005; K. M. Thomas et al., 2001). Anxious people also display elevated visual cortical engagement for feared stimuli (Brühl et al., 2014; Etkin & Wager, 2007; Frick et al., 2013; Gentili et al., 2016; Straube et al., 2005) and increased functional connectivity between visual regions and the amygdala (Brühl et al., 2014; Frick et al., 2013), suggesting that perceptual enhancements may stem from amygdalar feedback to the visual cortex (Pourtois et al., 2013).

There are several possible reasons why anxiety-related differences in visual cortical engagement were elicited without corresponding differences in amygdala activation in Study 1. First, the sample was fairly modest, which may have limited the power to detect amygdala differences. In addition, other bottom-up mechanisms may have contributed to differences in perceptual processing. Studies suggest that the right TPJ and inferior frontal cortex make up the ventral network, which drives bottom-up orienting to salient sensory information that is outside the focus of processing (Corbetta & Shulman, 2002). In Chapter 1, children were instructed to label the gender of fearful faces so emotional facial cues were task-irrelevant. State anxiety moderated the association between trait anxiety and right TPJ activity, such that state anxiety and TPJ activity were inversely associated among high trait-anxious children and positively

associated among low trait-anxious children. Thus, in low trait-anxious children, state anxiety may drive bottom-up stimulus-driven attention via the right TPJ, enabling the perceptual prioritization of threat stimuli. State anxiety appears to have the opposite effect for trait-anxious children, demonstrating a potentially atypical response to threats.

Together, Chapters 1 and 3 revealed that transient fluctuations in anticipatory anxiety influence the perception of ambiguously fearful facial affect. Importantly, this suggests that threat biases in anxiety may be modified by treating perceptual biases. As discussed in Chapter 3, threat biases in the perception of ambiguous emotional stimuli might be targeted via training on threat-safety discrimination (Ginat-Frolich et al., 2017, 2019) or attentional bias modification (MacLeod & Clarke, 2015; Schmidt et al., 2009). Preliminary evidence suggests that modifying attention to or perception of threat-relevant stimuli can reduce feelings of anxiety (Schmidt et al., 2009) and limit avoidance of feared stimuli (Ginat-Frolich et al., 2019). Thus, training anxious people to reduce the perceptual salience of threat cues relative to safe or neutral features of ambiguous images during times of arousal might reduce interpretive biases or ameliorate anticipatory anxiety.

Methodological Considerations for Culturally Sensitive Research

Results of this dissertation inform culturally sensitive research practices in several ways. Elevated rates of anxiety were observed in community samples of preadolescent Latina girls (Chapters 1 and 2) and ethnically-diverse young adults, with a large proportion from Asian and Latinx descent (Chapter 3). This is in line with work finding elevated rates of anxiety in Latinx samples (Glover et al., 1999; McLaughlin et al., 2007;

Pina & Silverman, 2004; Potochnick & Perreira, 2010; Varela et al., 2008) and among Asian populations following the COVID-19 pandemic (Chae et al., 2021; Hahm et al., 2021; Lee & Waters, 2021; C. Wu et al., 2021). Many Latinx and Asian people report experiencing discrimination or acculturative stressors (Chae et al., 2021; Hahm et al., 2021; Pérez et al., 2008; Torres et al., 2012), which may contribute to elevated risk for anxiety disorders among children (Mendoza et al., 2017). Despite reporting increased rates of anxiety, Latinx and Asian youth are less likely to utilize mental health services than white youth (Anyon et al., 2014; Flores et al., 2010; Lipson et al., 2018; Lopez et al., 2008; Yeh et al., 2003). Structural barriers like financial costs, logistical issues, language barriers, or availability of services may contribute to underutilization (Radez et al., 2021). In addition, cultural values that are shared across Latinx and Asian populations may contribute to stigmatization and reduce help-seeking behaviors (Zhou et al., 2021), though these values might be largely protective otherwise.

Elevated risk for anxiety and reduced treatment-seeking may contribute to greater rates of anxiety in community samples of Latinx and Asian youth, relative to other demographic groups. In studies that aim to examine "healthy controls," the effects of systematic differences in anxiety across demographic groups may be misattributed to cultural factors. Conversely, low rates of treatment-seeking may contribute to the underrepresentation of Asian and Latinx youth in pediatric anxiety research. To increase diversity in research, pediatric researchers should consider recruiting outside of clinics and avoid using stigmatizing language on recruitment materials. The results of this dissertation also revealed that anticipatory state anxiety elicited by research participation

led to changes in participants' neural (Chapter 1) and behavioral responses (Chapter 3) to threat-relevant stimuli. Because minoritized groups are underrepresented in research and, for historic reasons, often display greater mistrust in medical, academic, and scientific institutions than white participants (Loue & Sajatovic, 2008; Preloran et al., 2001; Yancey et al., 2006), there may be systematic differences in state anxiety across demographic groups that lead to inaccurate interpretations of results. Because the samples in this dissertation included few (Chapter 3) or no white youth (Chapters 1 and 2), it was not possible to test associations between race-ethnicity and anticipatory anxiety. However, given the extensive effects of anticipatory anxiety on study results, this is an important consideration for future research.

Limitations and Future Directions

Several limitations of this dissertation and avenues for future research should be considered. First, and arguably most importantly, all studies in this dissertation were cross-sectional, limiting inferences about developmental processes. I hypothesize that similar mechanisms underlie anxiety-related differences across all three Chapters, but may be subserved by different mechanisms across pubertal development. However, longitudinal research is necessary (and currently ongoing) to track developmental changes in the association between white matter integrity, brain function, and threat biases in anxiety. Similarly, a second limitation of this dissertation is that brain structure, brain function, and behavioral threat biases were tested in separate chapters and samples. Thus, relationships between these variables were inferred but not tested directly. To address this, we plan to conduct the experiment in Chapter 3 in the MRI scanner. In doing

so, all three measures can be obtained simultaneously, enabling the examination of neural correlates of explicit threat biases. This will also allow us to test whether perceptual biases that resulted from elevations in anticipatory state anxiety in Chapters 1 (neural activation) and 3 (behavioral biases) are directly related. We also plan to employ functional connectivity analyses to directly test impairments in prefrontal control over arousal and salience-processing networks. Finally, although this dissertation was strengthened by its measurement of self-report and brain structure and function, analyses would be greatly improved with the addition of physiological assessments like electrodermal activity. Whereas self-reported anxiety is subject to response biases, physiological data provide an objective means of monitoring emotional arousal, can reveal non-conscious or automatic physiological responses, and can be tracked throughout the entirety of the experiment. Further, physiological indicators of arousal are not always concordant with self-report (Michalska & Glenn, under revised review) and can provide unique information not captured via other assessments. Finally, physiological arousal has been found to influence hemodynamic responses in the early visual cortex, even in the absence of visual stimulation (Burlingham et al., 2022; Z. N. Roth et al., 2020). Thus, variations in physiological reactivity might predict activity in perceptual networks, even if differences in amygdala activation don't emerge or are undetectable.

Conclusions

In closing, childhood anxiety is associated with impaired prefrontal regulation of hypersensitive arousal networks (Chapters 1 and 2), and these networks may be influenced by pubertal development (Chapter 2). Further, when youth view ambiguously

fearful facial affect, fluctuations in anticipatory state anxiety influence perceptual brain networks (Chapter 1) and emotion judgments (Chapter 3) and may moderate the effects of trait anxiety on brain activity (Chapter 1). Together, these findings inform culturally sensitive research on perceptual biases in childhood anxiety and encourage the development of novel treatments.

Appendix A

Supplemental Results

Exploratory analyses were conducted to ensure that significant effects of puberty were not driven by age or pubertal timing, the relative measure of pubertal stage compared to peers.

Age Effects

Anxiety symptoms and age were tested as independent and interactive predictors of ROI FA, controlling for ROI volume. Each informant type (child-report, parent-report) and ROI (cingulum, uncinate fasciculus) was tested in four separate models. A main effect of ROI volume emerged in all four models, $ps < .024$. A main effect of age on cingulum microstructure emerged in the model with child-reported anxiety symptoms, $p = .033$, but did not hold after Bonferroni correction. No other main effects or interactions emerged in any of the models, $ps > .08$, suggesting that the effects of parent-reported anxiety and pubertal stage on cingulum FA were not due to age differences.

Pubertal Stage Effects

To examine the influence of pubertal timing on cingulum FA, we regressed age onto pubertal stage and calculated standardized residual pubertal stage scores. Anxiety symptoms and pubertal timing scores were tested as independent and interactive predictors of ROI FA, controlling for ROI volume. Again, each informant type (child-report, parent-report) and ROI (cingulum, uncinate fasciculus) was tested in four separate models. A main effect of ROI volume emerged in all four models, $ps < .022$. No other significant effects emerged in any of the four models, $ps > 0.14$. This suggests that

individual differences in pubertal timing do not underlie variations in cingulum or uncinate fasciculus microstructure in our sample.

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