NEW RESEARCH

Neural Substrates of Emotion Processing and Cognitive Control Over Emotion in Youth Anxiety: An RDoC-Informed Study Across the Clinical to Nonclinical Continuum of Severity

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Objective: Clinically anxious youth are hypervigilant to emotional stimuli and display difficulty shifting attention from emotional to nonemotional stimuli, suggesting impairments in cognitive control over emotion. However, it is unknown whether the neural substrates of such biases vary across the clinical-to-nonclinical range of anxiety or by age.

Method: Youth aged 7 to 17 years with clinical anxiety (n = 119) or without an anxiety diagnosis (n = 41) matched emotional faces or matched shapes flanked by emotional face distractors during magnetic resonance imaging, probing emotion processing and cognitive control over emotion, respectively. Building from the National Institute of Mental Health Research Domain Criteria (RDoC) framework, clinically anxious youth were sampled across diagnostic categories, and non–clinically affected youth were sampled across minimal-to-subclinical severity.

Results: Across both conditions, anxiety severity was associated with hyperactivation in the right inferior parietal lobe, a substrate of hypervigilance. Brain–anxiety associations were also differentiated by attentional state; anxiety severity was associated with greater left ventrolateral prefrontal cortex activation during emotion processing (face matching) and greater activation in the left posterior superior temporal sulcus and temporoparietal junction (and slower responses) during cognitive control over emotion (shape matching). Age also moderated associations between anxiety and cognitive control over emotion, such that anxiety was associated with greater right thalamus and bilateral posterior cingulate cortex activation for children at younger and mean ages, but not for older youth.

Conclusion: Aberrant function in brain regions implicated in stimulus-driven attention to emotional distractors may contribute to anxiety in youth. Results support the potential utility of attention modulation interventions for anxiety that are tailored to developmental stage.

Clinical Trial Registration Information: Dimensional Brain Behavior Predictors of CBT Outcomes in Pediatric Anxiety; https://clinicaltrials.gov; NCT02810171.

Key words: anxiety; cognitive control; emotion processing; neuroimaging; RDoC; youth

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Preferential attention to threat is an adaptive mechanism for detecting danger but is exaggerated in clinically anxious youth. Across categories of anxiety disorder diagnoses, affected youth display robust attentional biases to emotional stimuli and impaired cognitive control in the presence of emotional distractors.[1] In the present study, youth were asked to modulate attention toward or away from emotional stimuli during functional magnetic resonance imaging scanning, probing emotion processing and cognitive control over emotion, respectively.[2-4] Consistent with the National Institute of Mental Health Research Domain Criteria (RDoC) framework,[5] anxiety was measured dimensionally, across categorical anxiety disorders and the clinical-to-nonclinical spectrum of severity. Given high levels of comorbid anxiety disorders in youth[6] and the relevance of subclinical anxiety symptoms for predicting subsequent impairment,[7] studying the effects of dimensional anxiety on brain circuitry in youth during emotion processing and cognitive control over emotion has strong potential to guide neural targeting for the treatment and prevention of anxiety-related problems.

Anxiety is robustly associated with attentional biases to emotionally salient stimuli, including hypervigilance and

difficulty disengaging attention.[1] Prior work has found that anxious youth and adults exhibit attentional biases to both threatening and happy faces[8] and that anxious youth show elevated startle responses to neutral pictures.[9] Emotionally salient stimuli engage the amygdala and insula,[10,11] but also ventral attention network regions such as the inferior parietal lobe (IPL),[12] such that hyperactivity in these regions likely enhances initial attention to emotionally relevant cues. By contrast, brain regions underlying cognitive control (eg, rostral anterior cingulate cortex [rACC], ventrolateral prefrontal cortex [vlPFC], dorsolateral PFC [dlPFC], and posterior parietal cortex) flexibly modulate thoughts or behavior by constraining attention to task-relevant stimuli.[13] Childhood anxiety is associated with hyperactivity in brain regions implicated in processing emotion,[14] reduced recruitment of cortical networks for cognitive control when emotional stimuli are present,[2,3,14] and abnormal structural and functional connectivity between these networks.[15-18] Together, these results suggest biased attention to emotion and impaired cognitive control over emotion in anxious youth.

Changing one's attentional focus toward emotional stimuli or diverting it engages distinct neural networks and influences the neural substrates of anxiety.[2-4] The Emotional Faces Shifted Attention Task (EFSAT)[4] requires participants to modulate their attentional focus toward or away from emotional stimuli, enabling the examination of brain-behavioral markers of emotion processing and cognitive control over emotion in the same paradigm. In all trials, participants view 3 emotional faces flanked by 3 shapes. Participants are instructed to match faces by their emotional expressions or match shapes, requiring them to ignore the emotional faces. In youth and adults, matching emotional faces engages the amygdala and insula—regions involved in emotion processing, arousal, and salience detection.[2,4,11] By contrast, performing tasks that require participants to ignore emotional distractors (eg, by matching shapes flanked by emotional faces) activates the rACC,[2-4] a brain region that supports cognitive control over emotion,[19] as well as inferior parietal regions[2,4] and the dlPFC (in adults only),[20] which are key nodes of the frontoparietal and ventral attention networks for the implementation of cognitive control and attentional capture, respectively.[13,21]

The few studies that have simultaneously examined emotion processing and cognitive control over emotion in anxious patients vs healthy controls have reported similarities and differences at different ages. Adult patients exhibit hyperactivation in the insula during face matching (fearful, angry, happy),[22] and adult and youth patients exhibit hypoactivation in the rACC and medial PFC during shape matching.[2,3,22] However, previous studies that employed the EFSAT tested only the neural substrates of face matching compared with shape matching without examining correlates of anxiety that are common vs unique to these conditions (ie, relative to a fixation control). Moreover, prior work included relatively small samples of anxious patients (N = 25-37) and focused on categorical differences between clinically anxious and healthy individuals, rather than examining the full continuum of anxiety severity that occurs in youth. Here, we examine whole-brain activation elicited by emotion processing and cognitive control over emotion to probe unique and overlapping neural mechanisms of clinical-to-nonclinical anxiety severity in youth across attentional states.

Developmental stage is a critical consideration in studying attentional biases in youth that is often overlooked in anxiety research. Anxiety disorders often emerge in childhood, and their severity, prevalence, and expression changes through childhood and adolescence.[6] Additionally, the neural substrates underlying anxiety-related biases in emotion and cognitive control processes undergo functional development during this period,[23] which may contribute to discrepancies in pediatric anxiety research. In the present study, we dimensionally assessed behavioral and neural correlates of anxiety in a large sample of youth (N = 160; 7-17 years) spanning the range of the nonclinical–clinical spectrum. We tested the independent and interactive effects of anxiety severity and age on whole-brain neural activation during face matching and shape matching to engage systems underlying emotion processing and cognitive control over emotion, respectively. Both negative (angry and fearful) and positive (happy) facial expressions were considered, given prior work showing that anxious patients display biased responses to both threatening and happy affect in brain regions involved in emotion processing and cognitive control (eg, amygdala and ACC),[2,24-27] including several prior studies using this task.[4,22] Based on previous work using the EFSAT, we hypothesized that anxiety severity would be associated with hyperactivity in bottom-up, emotion processing regions, such as the amygdala, and insula during face matching.[22] Conversely, during shape matching, we predicted that anxiety severity would be associated with reduced activation in regions involved in cognitive control, such as the rACC.[2,3] Due to limited work on age-by-anxiety severity interactions in youth, we remained agnostic of interactive effects.

METHOD

Participants and Procedure

Youth aged 7 to 17 years old with clinical, subclinical, or minimal anxiety symptom severity participated in the first

TABLE 1 Sample Demographic Characteristics and Descriptive Statistics for Study Variables

	Group		
	Full sample (N = 160)	**Clinical anxiety (n = 119)**	**Low anxiety (n = 41)**
Sex, female (%)	73.8	77.3	63.4
Age, y (mean, SD)	12.6 (3.2)	12.4 (3.1)	13.1 (3.5)
PARS (mean, SD)	16.1 (6.6)	19.4 (3.2)	6.4 (3.7)
PARS (range)	0-26	13-26	0-15
Race (%)			
Asian	6.3	5.9	7.3
Black	3.8	3.4	4.9
Multiracial	12.5	10.9	17.1
White	75.0	77.3	68.3
Other/unknown	2.5	2.5	2.4
Ethnicity (%)			
Hispanic/Latino	5.0	5.9	2.4

Note: *PARS = Pediatric Anxiety Rating Scale.*

wave of a pediatric anxiety disorder treatment study at the University of Michigan. Clinically anxious youth met criteria for any anxiety disorder, assessed via the Schedule for Affective Disorders and Schizophrenia for School-Age Children.[28] Youth without any past or current psychiatric diagnosis were also intentionally recruited to sample anxiety symptoms on the full spectrum of "normal" anxiety levels. In contrast to many anxiety studies that recruit only super control participants with minimal or no anxiety symptoms, this study included low anxious youth who did not meet criteria for an anxiety disorder but ranged from subclinical severity to no symptoms. Full inclusion and exclusion criteria are detailed in Supplement 1, available online.

Before receiving treatment, 185 youths (139 clinically anxious youths, 46 low anxious youths) performed the EFSAT while undergoing functional magnetic resonance imaging scanning. There were 25 participants excluded for the following reasons: poor accuracy (<70% overall; n = 10), excessive motion (n = 6), misalignment/poor coverage (n = 7), or insufficient scan data (n = 2) resulting in a final sample of 160 youths (119 clinically anxious youths, 41 low anxious youths) (Table 1). Low anxious and clinically anxious groups did not differ by sex, as shown by χ^2 tests of independence ($\chi^2_{1,\ 160} = 2.37$, $p = .12$. Age and anxiety were uncorrelated in this sample ($r = -0.05$, $p = .54$). All neuroimaging and task-related behavioral data reported are unpublished.

Anxiety Severity

Anxiety symptom severity was dimensionally assessed by master's-level clinicians using the 6-item total score of the Pediatric Anxiety Rating Scale (PARS).[29] The PARS is a 50-item measure of anxiety severity, which is administered by an evaluator and incorporates both parent and child report. Total scores range from 0 to 30, with scores above 13 indicating clinically meaningful anxiety. The PARS has excellent interrater reliability (intraclass correlation coefficient = 0.97) and adequate test-retest reliability (0.55).[29] Cronbach α for the 6 items comprising the total score was .93, indicating excellent internal consistency in the sample. PARS scores ranged from 0 to 26 (clinically anxious: 13-26, low anxious: 0-15), spanning the clinical-to-nonclinical range of severity. The distribution of PARS scores was slightly skewed (−0.77) and bimodal, but all behavioral and neuroimaging results remained significant after Box-Cox transformation (Tables S1 and S2, available online). See Supplement 2 (available online) for an examination of the normality of residual data from significant neuroimaging results.

Emotional Faces Shifting Attention Task

The EFSAT is a validated measure of emotion processing and cognitive control over emotion[2] consisting of 2 conditions in block-related design: face matching and shape matching. In each trial, participants viewed 3 emotional faces in a triangular configuration flanked by 3 shapes in the same field of view (Figure S1, available online). During face matching, participants were instructed to identify the probe face that expressed the same emotion as the target face in the top row. During shape matching, participants selected the probe shape that matched the target shape in the bottom row. The target and congruent probe faces depicted anger, fear, or happiness, and the incongruent probe faces displayed a neutral expression. Participants viewed 3 blocks for each attention state (face matching and shape matching) and emotion (angry, fearful, and happy face stimuli/

distractors), totaling 18 blocks. Each block began with instructions to match faces or match shapes (4 seconds) followed by 4 sequential matching trials (4 seconds each), then a fixation cross (16 seconds). Response time (RT) on correct trials and accuracy were calculated for each condition. Participants were included in analyses if they completed at least 1 block of each emotion in both conditions. Faces were drawn from the stimulus set developed by Gur *et al.*,[30] which includes faces from diverse ethnicities and ages.

Data were initially collected in 1 run (n = 40) lasting 10 minutes 48 seconds. Midway through data collection, the task was divided into 3 runs of 3 minutes 18 seconds to improve scan quality by allowing participants breaks (n = 120). Participants who completed the task in 1 vs multiple runs did not differ in demographic factors (age, sex, race, ethnicity) or motion (mean framewise displacement) (all *p*s > .10). PARS scores were lower among participants who completed the task in 1 block ($_{t53.93} = -2.97$, $p = .004$), but all behavioral and neuroimaging results remained significant when task version (1 block vs 3 blocks) was included as a covariate of no interest (Tables S3 and S4, available online).

Functional Magnetic Resonance Imaging Data Acquisition and Processing

Whole-brain neuroimaging data were collected using a GE 3-Tesla MR750 scanner and 32-channel head coil. Functional data were high spatial and temporal resolution simultaneous multislice scans: repetition time = 800 ms, echo time = 30 ms, flip angle = 52°, field of view = 216 × 216, acquisition matrix 90 × 90, 2.4-mm slice thickness, and 60 axial slices. Functional data were localized to a high-resolution, T1-weighted volumetric scan with the following parameters: repetition time = 2500 ms, echo time = 1.9 ms, flip angle = 8°, slice thickness = 1 mm, 176 slices, field of view = 256 × 256 mm.

Individual echo-planar images were preprocessed and analyzed using SPM12. Raw data were slice time corrected and realigned to the first image acquired. The T1 structural image was then coregistered with the mean functional image. Next, the high-resolution spoiled gradient recalled sequence was coregistered to the T1 structural image and normalized to Montreal Neurological Institute space using high dimensional diffeomorphic anatomical registration through exponentiated lie (DARTEL) algebra, resampling at a 3 × 3 × 3 mm voxel size. Finally, warping was applied to the functional data to bring all subjects into common stereotactic space, and normalized functional data were smoothed with a 6-mm Gaussian kernel. Motion scrubbing was performed using a framewise displacement lever arm of 50 mm, a framewise threshold of 0.9, and a scrub window of zero frames before and after the target frame. Participants with more than 20% of frames exceeding the 0.9-mm threshold were excluded for excessive motion (n = 6). All functional scans were also visually inspected, and participants were excluded for misalignment (n = 2) and poor coverage/data loss (n = 5).

First-level within-subject analyses were performed with a general linear model with 6 regressors of interest (face matching [angry, fearful, and happy faces], shape matching [angry, fearful, and happy face distractors]) and 6 nuisance regressors to correct for motion.

Data Analysis

Main Effects of Emotion Processing and Cognitive Control Over Emotion. To examine the unique effects of emotion processing and cognitive control over emotion on group-level brain activation and to replicate prior work,[2,22] contrast maps were created to examine the main effects of face matching vs shape matching. Data were collapsed across emotional expressions of anger, fear, and happiness, and whole-brain multiple regression analyses were conducted with SPM12. Group-level maps were thresholded at a voxelwise height threshold of $p < .05$ with family-wise error correction. Clusters were considered significant at family-wise error $p < .001$, which corresponds to a cluster extent threshold of $k > 19$ voxels. Main effects analyses were thresholded at a stringent level to enhance specificity in identifying the substrates of face vs shape matching across the sample. Anxiety severity, age, sex, and anxiety-by-age interaction were included in the model as covariates of no interest.

Associations With Anxiety Severity. We examined the independent and interactive effects of anxiety severity and age on participants' accuracy and RT during each condition via multiple linear regression analyses conducted in RStudio version 4.2.2. Within each condition, anxiety severity, and age were tested as independent and interactive predictors of participants' accuracy and RT, controlling for sex.

Contrast maps included all trials within each attention state (face matching and shape matching), collapsed across emotional expressions. Contrasts were modeled against an implicit baseline of fixation (16 seconds/block) and task instructions (4 seconds/block). Whole-brain multiple regression analyses were conducted for each attention state with SPM12. Both models included anxiety severity, age, and anxiety-by-age interaction as dimensional covariates of interest, and sex was included as a covariate of no interest. All variables were mean centered, and the interaction term was created using the product of centered variables to reduce multicollinearity. Group-level maps were thresholded at voxelwise height threshold of $p < .001$,

uncorrected. Significant clusters were thresholded with family-wise error correction at $p < .05$, resulting in a cluster extent threshold of $k > 67$ voxels. In clusters with significant age-by-anxiety interactions, post hoc simple slopes analyses were conducted to assess predictions of brain activation from anxiety symptoms across 3 levels of age (−1 SD, mean, +1 SD). Simple slopes analyses leverage the full dataset to predict the impact of the independent variable (eg, anxiety severity) on the dependent variable (eg, brain activation) at specific levels of the moderator (eg, age), thereby measuring how brain–anxiety associations shift across the age spectrum without segmenting participants into distinct groups. For completeness, a whole-brain independent sample t test was also conducted to examine the effects of anxiety group on brain activation, controlling for children's age and sex (Supplement 3 available online).

RESULTS

Main Effects of Emotion Processing and Cognitive Control Over Emotion

Youth showed high task engagement (mean = 98.5% response rate ± 2.2%) and were accurate at matching faces (mean = 89.6% ± 7.9%) and shapes (mean = 94.3% ± 8.5%). Participants were faster to correctly match shapes (mean = 1,166 ms ± 294) than faces (mean = 1,606 ms ± 362) ($t_{159} = 27.67$, $p < .001$).

Contrast maps tested the main effects of face matching vs shape matching (Figure 1; Table S5, available online). Face matching (vs shape matching) elicited activation in several brain regions involved in emotion processing and emotion regulation, including the bilateral vlPFC, anterior insula, amygdala, and hippocampus. By contrast, shape matching (vs face matching) elicited activation in regions implicated in cognitive control over emotion, including the rACC, bilateral dlPFC, and right posterior parietal cortex, key nodes of the frontoparietal attention network.[13] Finally, both face matching and shape matching activated regions involved in the execution of a matching task, including the middle frontal gyri, precentral and postcentral gyri, and occipital cortex. Post hoc analyses revealed no significant effects of anxiety severity and/or its interaction with age on whole-brain activity or for region-of-interest–based analyses in the rACC for face matching vs shape matching or vice versa, contrasting with prior work (Supplement 4, available online).

Associations With Anxiety Severity

Anxiety severity was positively associated with RTs on correct trials during shape matching ($\beta = 22.64$, SE = 11.18, $t = 2.03$, $p = .044$), but not face matching ($p = .37$), such that more anxious youth were slower to match shapes (Figure 2). Age was inversely associated with RT on correct trials for both conditions; older youth were faster at matching faces ($\beta = -82.45$, SE = 15.50, $t = -5.32$, $p < .001$) and shapes ($\beta = -43.97$, SE = 13.93, $t = -3.16$, $p = .002$). Anxiety severity and age did not interact to predict RT on correct trials for either condition ($ps > .18$). Neither shape-matching accuracy nor face-matching accuracy was predicted by anxiety severity, age, or their interaction ($ps > .20$).

All significant clusters of the multiple regression analyses are presented in Table 2. Anxiety severity was associated with greater engagement of the right IPL for both face matching and shape matching. During face matching, anxiety severity was also associated with greater recruitment of the left vlPFC, extending anteriorly from the region observed as a main effect of this condition. During shape matching, anxiety severity was associated with greater activation in a cluster encompassing the left posterior STS and temporoparietal junction (pSTS/TPJ) and right thalamus.

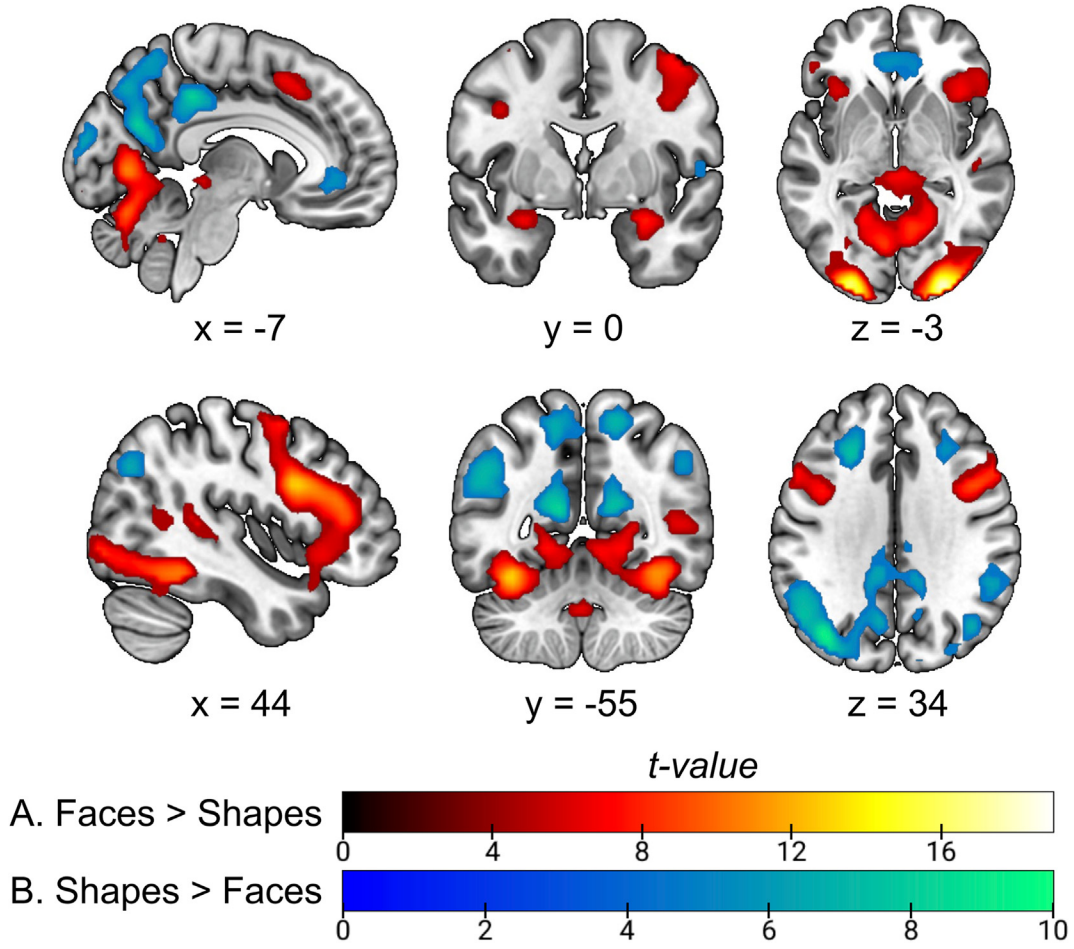
Associations With Age. Main effects of age are fully detailed in Table 2 and Supplement 5, available online. Of note, greater left IPL response was observed with older age, contrasting with the greater right IPL activation observed with greater anxiety.

Anxiety-by-Age Interactions. The shape-matching regression model also revealed an age-by-anxiety severity interaction in the right thalamus and in 2 clusters in the PCC: 1 cluster in the anterior region of the right PCC and 1 bilateral cluster in the posterior PCC (Figure 3). Follow-up simple slopes analyses tested the model-predicted association between anxiety severity and neural activation at younger (−1 SD: 9.4 years), mean (12.6 years), and older (+1 SD: 15.8 years) ages in all 3 clusters. At younger ages, anxiety was positively associated with brain activation in the right thalamus ($\beta = .014$, $p < .001$), right anterior PCC ($\beta = .016$, $p < .001$), and bilateral posterior PCC ($\beta = .036$, $p < .001$). At mean ages, anxiety was also positively associated with activation in the right thalamus ($\beta = .007$, $p < .001$), right anterior PCC ($\beta = .005$, $p = .016$), and bilateral posterior PCC ($\beta = .016$, $p < .001$). However, at older ages, anxiety was not associated with brain activation in any cluster ($ps > .08$) (Figure 3; Table S6, available online). No anxiety severity-by-age interactions emerged during face matching.

DISCUSSION

Anxiety is associated with attentional biases to emotional stimuli and cognitive control deficits in the presence of

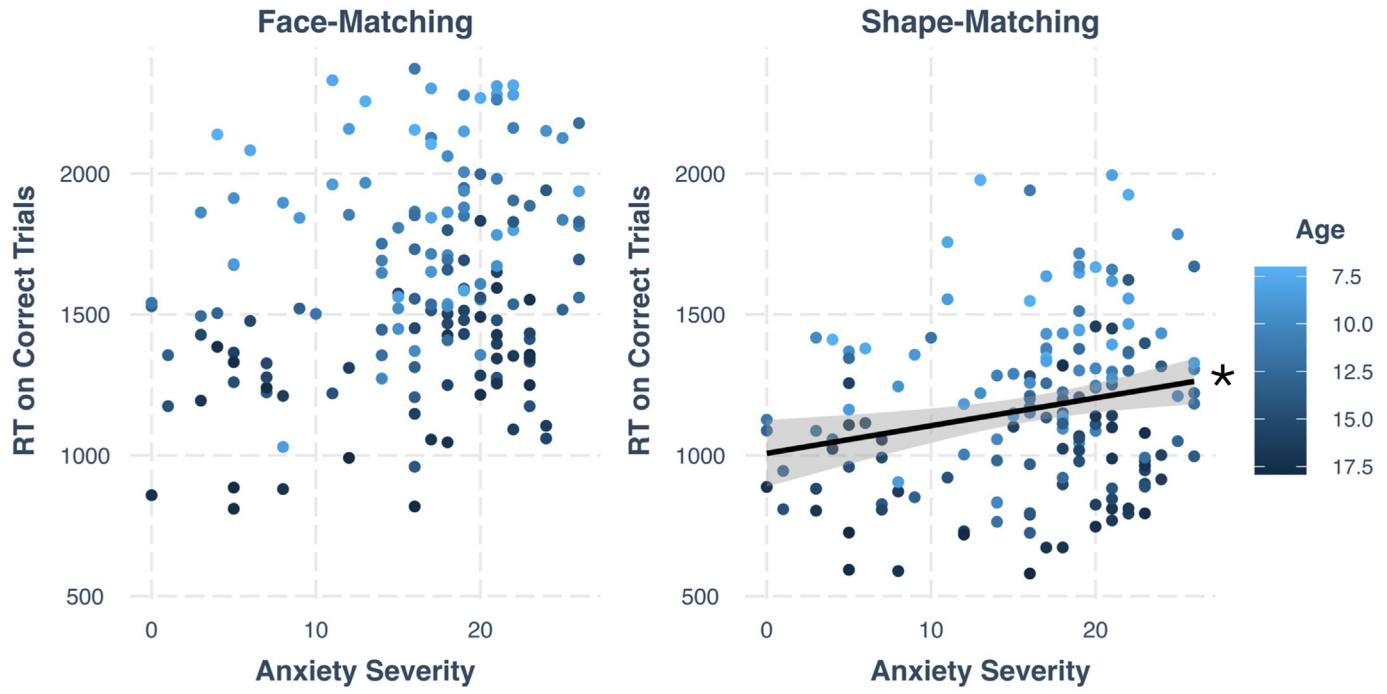
FIGURE 1 Activation Elicited by Face-Matching vs Shape-Matching Blocks of the Emotional Faces Shifting Attention Task Across All Participants



Note: *A. Faces > Shapes = face matching (red-yellow) elicited activation in emotion processing regions, including the bilateral ventrolateral prefrontal cortex, anterior insula, amygdala, and hippocampus; B. Shapes > Faces = shape matching (blue-green) elicited activation in cognitive control regions, including the rostral anterior cingulate cortex, bilateral dorsolateral prefrontal cortex, and right posterior parietal cortex. Please note color figures are available online.*

emotional distractors,[1] but the neural mechanisms underlying these biases across youth development remain poorly understood. In a sample of children and adolescents spanning the nonclinical–clinical spectrum of anxiety, the present study examined the effects of symptom severity and age on brain-behavioral markers of emotion processing (face matching) and cognitive control over emotion (shape matching). Across the whole sample, face matching and shape matching uniquely elicited activation in brain regions involved in emotion processing (eg, amygdala, anterior insula, vlPFC) and cognitive control over emotion (eg, rACC, dlPFC, posterior parietal), respectively, confirming the utility of the EFSAT in probing RDoC constructs relevant to anxiety disorders. Hypothesized associations were not observed between anxiety severity and activity in the amygdala or anterior insula during face matching or with the rACC during shape matching. However, across both conditions, anxiety severity was associated with greater activation of the right IPL. Distinct effects of anxiety for each condition were also observed. During face matching, anxiety severity was associated with greater activity in the left vlPFC, but not with differences in RT. During shape matching, more severe anxiety was associated with greater activation in the left pSTS/TPJ and slower RTs, consistent with prior reports of anxiety-related deficits in cognitive control over emotion[1,13] and demonstrating associated neural substrates. Age also moderated the association between anxiety severity and brain function in the right thalamus and bilateral PCC during shape matching, such that more severe anxiety was associated with greater activation in these regions at younger (−1 SD: 9.4 years) and mean (12.6 years) ages, but not older (+1 SD: 15.8 years) ages.

FIGURE 2 Anxiety Severity Associated With Slower Response Times During Shape Matching



Note: *Anxiety severity was positively associated with response time (RT) on correct shape-matching trials, such that more anxious youth were slower to match shapes (right panel). Anxiety severity was not associated with RT on correct face-matching trials (left panel). Anxiety severity was assessed via the Pediatric Anxiety Rating Scale. Please note color figures are available online. *$p < .05$.*

Neural Substrate for Hypervigilance to Emotion in Youth Anxiety

Across both face-shaping and shape-matching trials, anxiety severity was positively associated with right IPL activation. Interestingly, older age was associated with greater left IPL response. Lateralization of anxiety and age effects in the IPL deserves comment. The IPL is part of the dorsal fronto-parietal attention network and plays a role in volitional attention,[31] such that greater activation may support improved ability to flexibly engage attention, indicated by faster RTs for both conditions, at older ages. However, right-lateralized IPL hyperactivity specifically may contribute to hypervigilance that is common in anxiety.[32–34] For instance, reducing IPL activation via transcranial magnetic stimulation during threat of shock reduced physiological arousal related to fear and anxiety.[35] Thus, greater right IPL activation may relate to hypervigilance to emotional facial affect across attentional states in anxious youth.

Anxiety Differentially Associated With Emotion Processing and Cognitive Control Over Emotion

When participants matched emotional faces, anxiety severity was associated with greater activity in the left vlPFC, but did not relate to task performance. The vlPFC subserves several regulatory functions, including modulating amygdala activity,[36] regulating negative affect,[37] and attentional control.[38] Given that anxiety severity was not associated with RT or accuracy deficits during face matching, left vlPFC engagement may enable more anxious youth to match emotional faces as quickly and as accurately as youth with lower levels of anxiety. These findings align with attentional control theory,[39] which asserts that the effects of emotional stimuli on attentional control are influenced by anxiety severity and cognitive load. If attention to emotion is goal relevant (as during face matching), hypervigilance may contribute to normal or enhanced task performance[39] as well as increased vlPFC engagement.[38]

By contrast, emotional stimuli that distract from task goals (eg, matching shapes) are hypothesized to impair task performance in people with elevated anxiety.[38,39] Supporting this, anxiety severity was associated with slower performance during shape matching and greater activation in the left pSTS/TPJ. The pSTS and TPJ are part of the ventral attention network and are involved in stimulus-driven reorienting to salient distractors[40] via the interruption of top-down attention networks,[21] as well as face processing more broadly.[41] Associations between anxiety

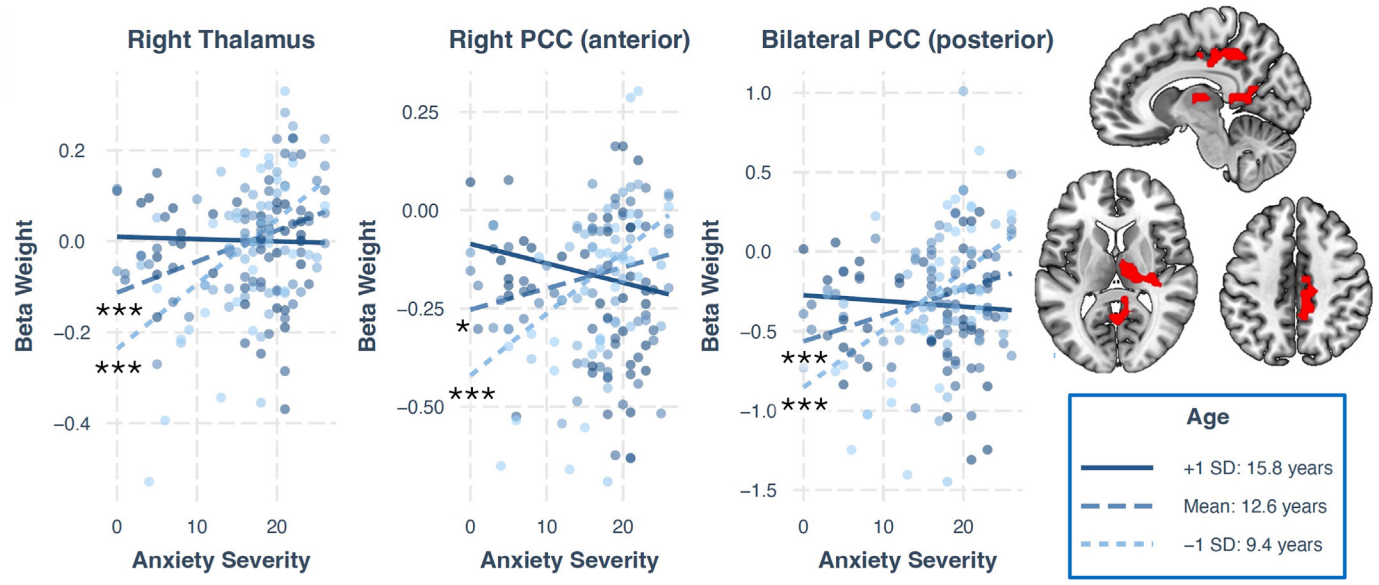
TABLE 2 Brain Activation Associated With Anxiety Severity, Age, and Their Interaction During Face Matching and Shape Matching vs Fixation

Face Matching							Shape Matching						
Region	**Assn**	***z***	***k***	**Peak coordinates**			**Region**	**Assn**	***z***	***k***	**Peak coordinates**		
				x	y	z					x	y	z
Anxiety severity							Anxiety severity						
Left vlPFC	+	4.37	68	−39	47	−10	Left pSTS/TPJ	+	4.27	82	−39	−49	11
Right IPL	+	4.63	95	42	−37	47	**Right IPL**	+	4.16	102	42	−40	50
							Right thalamus	+	4.27	153	9	−16	11
Age							Age						
Left IPL	+	5.33	235	−42	−43	53	**Left IPL**	+	4.65	174	−39	−43	50
Left postcentral gyrus	+	4.19	87	−54	−16	29	**Left postcentral gyrus**	+	4.21	154	−51	−19	29
Left IPS	+	4.97	81	−30	−70	26	Left MT	+	4.51	78	−45	−70	5
Left cerebellum	+	4.15	121	−33	−43	−31	Left cuneus	+	4.71	108	−15	−76	17
Right FG/FFA[a]	+	4.31	72	39	−64	−13	Right FG/IOG[a]	−	4.32	88	21	−91	−7
							Left FG/IOG	−	5.59	127	−21	−94	−7
Right STS	−	5.40	108	51	−10	−7	**Right STS**	−	5.50	77	54	−10	−7
Anxiety × age (not significant)							Anxiety × age						
							Bilateral PCC (posterior)		4.29	94	3	−58	11
							Right PCC (anterior)		3.87	103	15	−25	44
							Right thalamus		4.32	155	30	−22	11

Note: Peak coordinates and descriptive statistics of clusters positively (+) and negatively (−) associated with anxiety severity, age, and their interaction during face matching vs fixation and shape matching vs fixation. Boldface indicates regions that were active across both conditions. Assn = association; FFA = fusiform face area; FG = fusiform gyrus; IOG = inferior occipital gyrus; IPL = inferior parietal lobe; IPS = inferior parietal sulcus; MT = middle temporal visual area; PCC = posterior cingulate cortex; pSTS = posterior superior temporal sulcus; TPJ = temporoparietal junction; vlPFC = ventrolateral prefrontal cortex; STS = superior temporal sulcus.

[a]*Right FFA and FG/IOG were overlapping but spanned different regions and had opposite associations with age during face and shape matching.*

FIGURE 3 Age Moderated the Association Between Anxiety Severity and Activation in the Right Thalamus and Bilateral Posterior Cingulate Cortex During Shape Matching



*Note: Age and anxiety severity interacted to predict brain activation in the right thalamus, right anterior posterior cingulate cortex (PCC), and bilateral posterior PCC during shape-matching trials. Simple slopes plot associations between anxiety severity at the mean age (12.6 years) and 1 SD above (+1 SD; 15.8 years) and below (−1 SD; 9.4 years) the mean age. Please note color figures are available online. ***$p < .001$, **$p < .01$, *$p < .05$.*

severity, slower performance, and pSTS/TPJ hyperactivation during shape matching may indicate that the ventral attention network directed attention to face stimuli, interrupting goal-directed attention to shapes. Supporting this, anxious adults display increased activation in the pSTS and TPJ when viewing emotional distractors.[42] These results may suggest disruptions in cognitive control by the ventral attention network in youth with anxiety, which may lead to more pronounced attention capture by face distractors and slower performance when attention should be directed to shapes. These findings align with research on implicit face emotion training (eg, attention bias modification), which trains attention from emotional to unemotional stimuli to reduce anxiety severity in anxious youth. Future work might test whether the application of neuromodulation to reduce hyperactivation in the ventral attention network could enhance the effects of implicit face emotion training.

Age-Dependent Effects of Anxiety Severity on Cognitive Control Over Emotion

Finally, age moderated the association between anxiety severity and brain activation in the right thalamus and bilateral PCC during shape matching, such that more severe anxiety was associated with greater activation in these regions at younger (−1 SD: 9.4 years) and mean (12.6 years) ages, but not for older youth (+1 SD: 15.8 years). The thalamus is a hub in the automatic processing of emotional stimuli[43] and relays sensory information to prefrontal and cingulate cortices.[44] Adults with anxiety display elevated thalamus activation when viewing or anticipating aversive or emotional stimuli,[45] suggesting the prioritization of threat-related sensory information. In line with this, deep brain stimulation to the thalamus increases attention allocation to threat-related distractors.[46] Thus, elevated thalamic activity at younger and mean ages may suggest hypersensitive sensory gating for emotional stimuli during shape matching, when attention should be directed at shapes. Anxious adolescents were buffered from this effect, possibly due to more developed cognitive control functioning, enabling them to ignore emotional faces. This is supported by findings that older age was associated with faster RTs and less activation in face processing regions during shape matching (Table 2; Supplement 5, available online).

Anxiety severity was also associated with greater activation in the bilateral PCC at younger (−1 SD: 9.4 years) and mean (12.6 years) ages, but not at older (+1 SD: 15.8 years) ages. The PCC is a node in the default mode network (DMN), which is involved in introspective, self-referential thinking.[47] DMN activity is often suppressed during externally focused tasks, when resources should be allocated away from introspection.[47] Youth with psychopathology often fail to show DMN suppression,[48] reflecting disruptions in attention or task engagement.[49] Thus, greater DMN activity in anxious youth during shape matching may hinder the redirection of internally directed thoughts during tasks requiring cognitive control, which is supported by slower RTs in younger and more anxious youth.

With 160 youths, this is the largest sample to date of participants performing the EFSAT. The sample spanned a wide age range (7-17 years), enabling us to examine age as a moderator of the neural substrates of anxiety during emotion processing. In line with the RDoC framework, the study sample included youth with clinical presentations, subclinical presentations, and minimal symptoms, so results represent variations in brain function that were dimensionally associated with anxiety. Additionally, the present study was the first to model face- and shape-matching conditions of the EFSAT against a baseline condition, enabling us to probe unique and overlapping neural mechanisms of emotion processing and cognitive control over emotion in anxiety.

Several limitations and future research considerations should also be noted. First, the cross-sectional study design limited our ability to make inferences about developmental processes. Second, although modeling each condition against a control condition of a fixation cross enabled us to examine common and unique substrates of anxiety across attention states, results may also represent the effects of anxiety on broader processes (eg, matching objects). Third, across all participants, RTs were slower for correct face-matching trials compared with correct shape-matching trials. Faces are more visually complex than shapes, so face matching may have been more challenging than shape matching, possibly requiring participants to engage certain cognitive control functions. Future work should consider using more visually complex nonemotional stimuli as a comparison to equate matching difficulty across emotion processing and cognitive control conditions. Finally, participants in the sample were primarily White and female, constraining our ability to generalize results. Racial/ethnic minority youth are less likely to receive treatment for mental health disorders,[50] but some studies in community samples find elevated rates of subclinical or untreated anxiety symptoms,[51,52] suggesting that dimensional analyses may be especially beneficial for studying anxiety in non-White populations. Future work in this area should recruit diverse samples and employ longitudinal analyses over development to further examine neural mechanisms associated with biased attention to emotional stimuli in youth with anxiety.

In summary, this study examined neural activation engaged by emotion processing (face matching) and cognitive control over emotion (shape matching) in a sample of youth ranging across the clinical-nonclinical

spectrum of anxiety. With more severe anxiety, greater activation in the right IPL (a putative neural substrate of hypervigilance) was observed for both conditions. Unique effects of anxiety on brain and behavior for each condition also emerged. During face matching, more severe anxiety was associated with greater activation in the vlPFC, an emotion regulatory region, possibly preventing anxiety-related slowing of RTs. These findings corroborate prior theory and evidence that avoiding emotional stimuli may not be a beneficial strategy for managing anxiety symptoms. Conversely, during shape matching, which required participants to engage cognitive control to ignore emotional faces, anxiety severity was associated with slower performance and greater activation of the ventral attention network (pSTS/TPJ), suggesting greater stimulus-driven attention to emotional distractors.[40] Additionally, children's age moderated associations between anxiety severity and brain response during shape matching in networks involved in introspection and emotion processing, suggesting that the neural substrates of anxiety may change across development. Findings support that reduction of ventral attention network–mediated attention capture could augment training to improve cognitive control function during emotion processing to prevent and/or treat anxiety in youth and that other brain targets (eg, PCC and thalamus) should be considered at younger ages.

CRediT authorship contribution statement

Dana E. Díaz: Writing – original draft, Formal analysis. **Stefanie R. Russman Block:** Writing – review & editing, Formal analysis, Data curation. **Hannah C. Becker:** Writing – review & editing, Data curation. **K. Luan Phan:** Writing – review & editing, Funding acquisition, Conceptualization. **Christopher S. Monk:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Kate D. Fitzgerald:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

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Data sharing: Deidentified participant data and data dictionary are available upon request from corresponding author.

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