Research Article

ALTERED ACTIVATION OF THE ROSTRAL ANTERIOR CINGULATE CORTEX IN THE CONTEXT OF EMOTIONAL FACE DISTRACTORS IN CHILDREN AND ADOLESCENTS WITH ANXIETY DISORDERS

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Background: ***Pediatric and adult anxiety disorder patients exhibit attention bias to threat and difficulty disengaging attention away from threat. Cognitive frameworks suggest that these patterns are associated with hyperactivation of regions associated with detecting threat, such as the amygdala, and hypoactivation of regions associated with regulating attention, including the lateral prefrontal cortex and rostral anterior cingulate cortex (rACC). The aim of the present study was to examine the neural correlates of these processes in children and adolescents with anxiety disorders.*** **Methods:** ***Participants with an anxiety disorder 7 to 19 years old (n = 34) and typically developing controls (n = 35) underwent fMRI scanning. During scanning, they completed a task with conditions that manipulated whether participants were instructed to match emotional faces (direct emotion processing) or match shapes in the context of emotional face distractors (attentional control).*** **Results:** ***Results revealed a significant difference in rACC activation during shape versus face matching, with controls evidencing greater rACC activation relative to patients.*** **Conclusions:** ***This study identifies abnormalities in rACC activation as a potential neural mediator associated with pediatric anxiety disorders, which can inform frameworks for understanding their development and treatment. Depression and Anxiety 31:870–879, 2014.***
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Key words: ***anxiety; emotion; attention; child; adolescent; anger; neuroimaging; magnetic resonance imaging***

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INTRODUCTION

Children and adults with anxiety disorders exhibit an abnormal pattern of attention to threat, often characterized by an initial attention bias to threat followed by either difficulty in disengaging attention from threat or avoidance of threatening stimuli.[1–6] Understanding the neural correlates of these processes in children and adolescents with anxiety disorders will inform our understanding of the development of anxiety disorders, and could have applications for the design and testing of novel treatments.[7,8]

In explaining how alterations in attention develop in anxiety disorder patients, many frameworks draw on biased competition models, and propose that attention to threat is influenced by competition between "bottom-up" sensory processes involved in detecting threat and "top-down" influences on attention, such as a goal to attend toward nonemotional stimuli.[9–11] Bishop[1] and others have thus suggested that anxiety disorders may be related to overactivation of regions associated with detecting threat, such as the amygdala, and altered top-down control by regions associated with goal-directed attention. Top-down control regions within the Pre-Frontal Cortex (PFC) include the lateral PFC and the rostral Anterior Cingulate Cortex (rACC), which are recruited to regulate attention to threat or resolve conflict between competing stimuli.[12–15] However, the majority of research conducted in pediatric samples to date has focused on the "bottom-up" amygdala-mediated component of threat processing, indicating a need for further investigation of top-down attentional control.

FMRI research in adult Generalized Anxiety Disorder (GAD) or Social Phobia (SP) patients has produced evidence generally consistent with the biased competition model outlined above. Adult anxiety disorder patients demonstrate heightened amygdala activation when performing tasks with threatening stimuli.[16,17] Moreover, adult GAD and SP patients demonstrate reduced rACC activation and reduced rACC-amygdala connectivity while performing tasks with conflicting or distracting emotional stimuli[18–20] and healthy adults with high levels of trait anxiety show reduced rACC and lateral PFC activation during emotional conflict tasks.[12,21]

Emotion processing tasks have also revealed a consistent role for abnormalities in insula activation in adult anxiety disorder patients. The insula is involved in interoception and interpreting changes in bodily states or emotions.[22,23] Research in adults has shown increased insula activation to negative emotional stimuli in anxiety disorder patients and that insula activation relates to anxiety symptom severity.[16,20,24–27] Thus, this region may also play a role in the biased processing of emotional stimuli.

Consistent with the biased competition model and research in adults, several studies have demonstrated increased amygdala activation in pediatric anxiety disorder patients while processing negative emotional stimuli.[28–30] Two studies directly measured attention bias to threat during fMRI scanning in pediatric anxiety disorder patients using the probe detection task, which requires participants to respond to a probe that appears after faces are presented. The latency to respond to the probe after it appears in the place of a threatening face is used to measure attention bias to threat. When pediatric GAD patients performed this task during fMRI scanning and faces were presented for 500 ms, patients demonstrated an attention bias away from threatening faces and increased right vlPFC activity compared to controls.[31] When the faces were presented briefly (17 ms) and then masked, pediatric GAD patients demonstrated increased amygdala activation and weaker amygdala connectivity with the right vlPFC relative to controls.[32] These results are consistent with heightened rapid threat detection mediated by the amygdala as proposed in biased competition frameworks. However, conclusions that can be drawn regarding activation of prefrontal regions in the presence of emotional distractors are limited because none of the tasks described required participants to perform a cognitive task while simultaneously being presented with emotional face distractors.

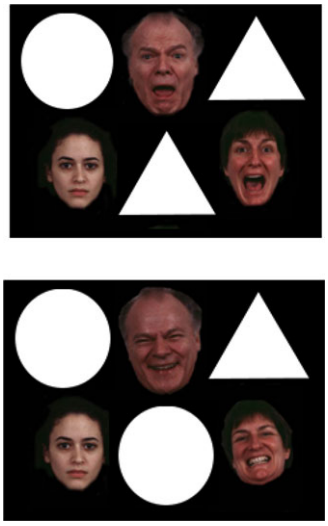

Figure 1. Example trials of the Emotional Faces Shifting Attention Task (EFSAT). Example trials for the fear (top) and happy (bottom) conditions. Trials were presented in block format and participants were instructed at the beginning of each block to either match faces or match shapes for that block. The match faces condition requires attending to the emotional faces whereas the match shapes condition requires performing the shape-matching task in the context of emotional face distractors.

The goal of the present paper was to address this gap by examining neural activation in pediatric anxiety disorder patients under two conditions: during direct emotion processing (a face matching task) and while performing a relatively simple task in the presence of emotional face distractors that are irrelevant to task performance (a shape matching task; Fig. 1). When healthy adult participants perform this task, matching faces (relative to

shapes) results in increased activation in face processing and limbic regions such as the amygdala whereas matching shapes (relative to faces) is associated with greater rACC activation.[15] Moreover, adult patients with SP evidence greater insula activation during face matching and reduced rACC activation during shape matching relative to controls.[20]

We hypothesized that during the shape-matching condition, the condition with irrelevant but potentially distracting Emotional Faces, pediatric anxiety disorder patients would demonstrate reduced rACC activation relative to controls. Second, we hypothesized that pediatric anxiety disorder patients would evidence increased amygdala and insula activation to Threatening Faces (vs. Happy Faces) in the shape-matching condition and face-matching condition.

MATERIALS AND METHODS

PARTICIPANTS

Participants with anxiety disorders were recruited through university psychiatry outpatient clinics and the community and controls were recruited via fliers and postings throughout the community. Participants under 18 provided informed assent and their parents provided written informed consent; participants 18 years and older provided written informed consent. All procedures were approved by the University of Michigan Institutional Review Board. Primary diagnosis was based on structured clinical interview with the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL)[33] for patients 17 years and younger and with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-IV)[34] for patients 18 years and older. Structured clinical interview was also used to confirm a lack of psychiatric diagnosis within the control group. In line with previous work,[28–31] we included participants with GAD, SP, and/or Separation Anxiety Disorder (SAD) because these disorders are highly comorbid during development.[35] None of the anxiety disorder patients were currently taking psychotropic medications or undergoing psychotherapy treatment.

Forty-four participants with a primary GAD, SP, or SAD diagnosis and 47 controls performed the Emotional Faces Shifting Attention Task (EFSAT)[15,20] during fMRI scanning. One control dropped out during scanning, 18 participants were removed for >3 mm maximum movement from the reference image or >3 mm maximum Euclidean distance for volume-to-volume translation or rotation (nine patients and nine controls), two controls were removed for accuracy (<60%), and one patient was removed for signal dropout in the images, leaving 34 anxiety disorder patients and 35 controls between 7 and 19 years old available for analysis (Table 1). The excluded patients did not differ from the included patients in age or anxiety symptoms. Excluded control participants were younger ($M = 11.02$, $SD = 3.3$) than included control participants ($M = 15.2$, $SD = 3.9$), $t(44) = -3.2$, $P = .002$. Of the participants in the final sample, 25 patients and 16 controls are overlapping with the sample reported on in a paper with a different task.[36] Three patients and 13 controls were 18–19 years old and thus could be considered young adults. In order to examine results with an approach comparable to prior work on adolescents, we also reran analyses restricting the sample to participants aged 7–17 years old.

PROCEDURE

A trial of the EFSAT consists of three faces in a triangular configuration, with one on the top row and two on the bottom, and three shapes in an upside-down triangular configuration (Fig. 1). During the faces condition, participants were instructed to identify which faces out of the two on the bottom row matched the emotion of the target face on the top row. During the shapes condition, participants were instructed to match one of the two shapes on the top row with the target shape on the bottom row.

Participants completed two runs of the EFSAT. There were a total of 18 faces blocks and 18 shapes blocks with six each of the following conditions: Angry Faces, Fear Faces, and Happy Faces (blocks in which participants were instructed to match faces for faces that were angry, fearful, or happy, respectively) and Angry Shapes, Fear Shapes, and Happy Shapes (blocks in which participants were instructed to match shapes and the unrelated distractor faces were angry, fearful or happy, respectively). The order of conditions was counterbalanced across participants. Each block was 20 s long and began with a 4 s instruction screen instructing participants to either match faces or shapes for that block and then four trials of the task lasting 4 s each. Participants responded with a button box. Accuracy and Response Times (RT) were recorded.

fMRI Data Acquisition. MRI images were acquired on a 3.0 Tesla GE Signa. A high-resolution T1-weighted Spoiled-Gradient Echo (SPGR) image (TR = 9 ms, TE = 1.8 ms, flip angle = 15°, slice thickness = 1.2 mm, 124 slices, FOV = 256 × 256 mm) was acquired for anatomical reference and T2*-weighted BOLD images were acquired using a reverse spiral sequence (TR = 2,000 ms; TE = 30 ms; slice thickness = 3 mm, 43 slices collected parallel to the AC-PC line; 64 × 64 matrix; 220 × 220 mm field of view; flip angle = 90°) for the functional data.

Measures. Anxiety symptoms were measured with the Multidimensional Anxiety Scale for Children (MASC)[37] and the Liebowitz Social Anxiety Scale Child-Adolescent version (LSAS).[38]

ANALYSES

Behavioral Data Analysis. Mean accuracy and RT were obtained for each condition. Group differences in behavior were examined using repeated-measures ANOVA in SPSS v20 and significant interactions were followed up with paired samples *t*-tests. These analyses were also rerun controlling for age, given the wide age range of the sample. Behavioral data were missing for one control.

fMRI Data Analysis. Data underwent a standard preprocessing procedure in SPM8. Large spikes in the k-space data were filtered out and data were reconstructed into images using field map correction to decrease distortions. Functional images were slice-timing corrected and realigned to the first volume of the first run. Coregistration was done in two steps. First, the T1-overlay was coregistered to the realigned functional images. Then the high resolution T1 was coregistered to the (coregistered) T1-overlay. The high resolution T1 was then segmented using Voxel-Based Morphometry (VBM8) and normalized to a template in Montreal Neurological Institute (MNI) space using DARTEL[39] and the resulting deformation field was applied to the time-series data. Finally, images were smoothed with a 6 mm full width at half maximum Gaussian kernel. Condition effects were modeled at the individual subject level using the general linear model and the six movement parameters from the realignment procedure were entered as nuisance covariates. Voxel size for the processed images was 2 × 2 × 2.

Main Effect of Task. Before examining group differences, a one-sample *t*-test was used to examine main effects of task condition across all participants in SPM8. Based on regions of interest from our hypotheses, we tested whether Faces > Shapes elicited greater bilateral amygdala and insula activation and if Shapes > Faces was associated with greater rACC activation. In order to test significance, Family-Wise Error (FWE) correction was applied within Regions of Interest (ROIs). The amygdala and insula ROIs were defined anatomically

TABLE 1. Participant characteristics

	Anxiety disorder group (M, SD) $n = 34$	Control group (M, SD) $n = 35$	Group difference
Age	13.84 (3.3)	15.20 (3.9)	$t(67) = 1.58$, $P = .12$
Gender (percent female)	65%	49%	$X^2(1, N = 69) = 1.83$, $P = .18$
MASC total scores	60.5 (18.1)	32.7 (12.3)	**$t(67) = -7.49$, $P < .001$**
LSAS total scores	62.7 (32.5)	9.5 (9.1)	**$t(46) = -6.59$, $P < .001$**

Note: Bold indicates a significant group difference. MASC, Multidimensional Anxiety Scale for Children; LSAS, Leibowitz Social Anxiety Scale. LSAS scores were only collected for a subset of participants and were not collected in 18 controls and three anxiety disorder patients.

using the Wake Forest University Pickatlas (WFU Pickatlas).[40] In order to obtain an ROI for the rACC, the Anterior Cingulate Region was intersected with the medial frontal region defined by the Automated Anatomical Labeling atlas in order to define a region encompassing the rostral portion of the ACC. This ROI consisted of 591 voxels. Whole-brain results for these contrasts were also examined at $P < .05$ FWE whole-brain corrected with cluster threshold of 10. Of note, in order to maximize power to detect a signal while minimizing the amount of time that participants remained in the scanner, we did not include a sensorimotor control condition. Thus, the effects of one condition are interpreted relative to the other condition (e.g., a difference in BOLD signal for the Faces>Shapes contrast could be driven by greater activation in the faces condition or greater deactivation in the shapes condition).

Group Differences in Amygdala, Insula, and rACC Activation. A two-sample *t*-test was used to examine overall differences in activation between the two conditions between the groups, first collapsing across all emotion types (All Faces vs. All Shapes). Because of the wide age range in this sample and a significant group difference in reaction times during the task (Table 2), age and mean reaction times were entered as nuisance covariates in any second-level analyses conducted in SPM8. Group differences were tested using the amygdala, insula, and rACC ROIs described above. Additionally, a whole-brain analysis at $P < .001$ uncorrected with a cluster threshold of 10 was conducted.

Emotion-specific effects were examined in two ways. First, we examined the following contrasts: Angry Faces versus Angry Shapes, Fearful Faces versus Fearful Shapes, and Happy Faces versus Happy Shapes, in order to determine whether group differences observed in the main analysis (Faces vs. Shapes) were present for each type of emotional stimulus. Second, we examined our threat-related hypotheses by testing the following contrasts: Angry Faces versus Happy Faces, Fearful Faces versus Happy Faces, Angry Shapes versus Happy Shapes, Fearful Shapes versus Happy Shapes. Because we conducted seven comparisons to examine emotion-specific effects, we set the significance threshold at $P < .007$ (.05/7).

Relation between Anxiety, Age, and Activation. Additional analyses were conducted in order to examine whether the effects observed from primary analyses were associated with anxiety symptoms or age. MASC and LSAS total scores were entered as regressors onto the contrast of Faces versus Shapes in SPM8 within the patient group in order to examine the relation between anxiety symptoms and activation during the task. A group × age interaction was conducted in SPM8 in order to test age-related effects. We tested for an interaction with both a linear effect of age as well as a quadratic effect of age, by entering the squared age term as a covariate in SPM8.

RESULTS

GROUP DIFFERENCES IN BEHAVIOR

There was no group difference in accuracy for the EFSAT, although it approached significance, $F(1, 66) = 3.14$, $P = .08$. There was a condition × emotion interaction, $F(2, 65) = 10.07$, $P < .001$. This was due to lower accuracy on face matching, particularly for Angry Faces (Table 2). Paired samples *t*-tests indicated that participants evidenced lower accuracy for Angry Face matching relative to Fearful Face matching, $t(67) = -4.08$, $P < .001$, and Happy Face matching, $t(67) = -3.23$, $P = .002$. There was a group difference in RT, $F(1,66) = 4.65$, $P = .04$, due to the anxiety disorder group being slower to respond overall. There was also a condition x emotion interaction, $F(2, 65) = 7.52$, $P = .001$, with

TABLE 2. Behavioral results for EFSAT by group and condition

	Anxiety disorder group accuracy (M, SD)	Control group accuracy (M,SD)	Anxiety disorder group RT (M,SD)	Control group RT (M, SD)
EFSAT				
Angry face	73.8% (15.3)	78.7% (14.1)	1692.1 (311.2)	1545.3 (400.9)
Fearful face	84.4% (14.7)	84.9% (15.0)	1593.6 (341.2)	1420.9 (400.4)
Happy face	79.7% (18.9)	86.0% (15.1)	1536.9 (273.9)	1394.9 (383.4)
Angry shape	87.9% (10.9)	89.8% (9.4)	1249.2 (279.2)	1060.5 (299.3)
Fearful Shape	85.2% (15.4)	87.7% (12.8)	1207.7 (283.9)	1054.5 (307.5)
Happy shape	85.0% (15.5)	91.1% (11.7)	1178.2 (298.8)	1053.9 (315.6)
All conditions	82.7% (9.2)	86.4% (8.0)	1409.6 (268.7)	1257.2 (315.9)

Note: RT, reaction time in ms.

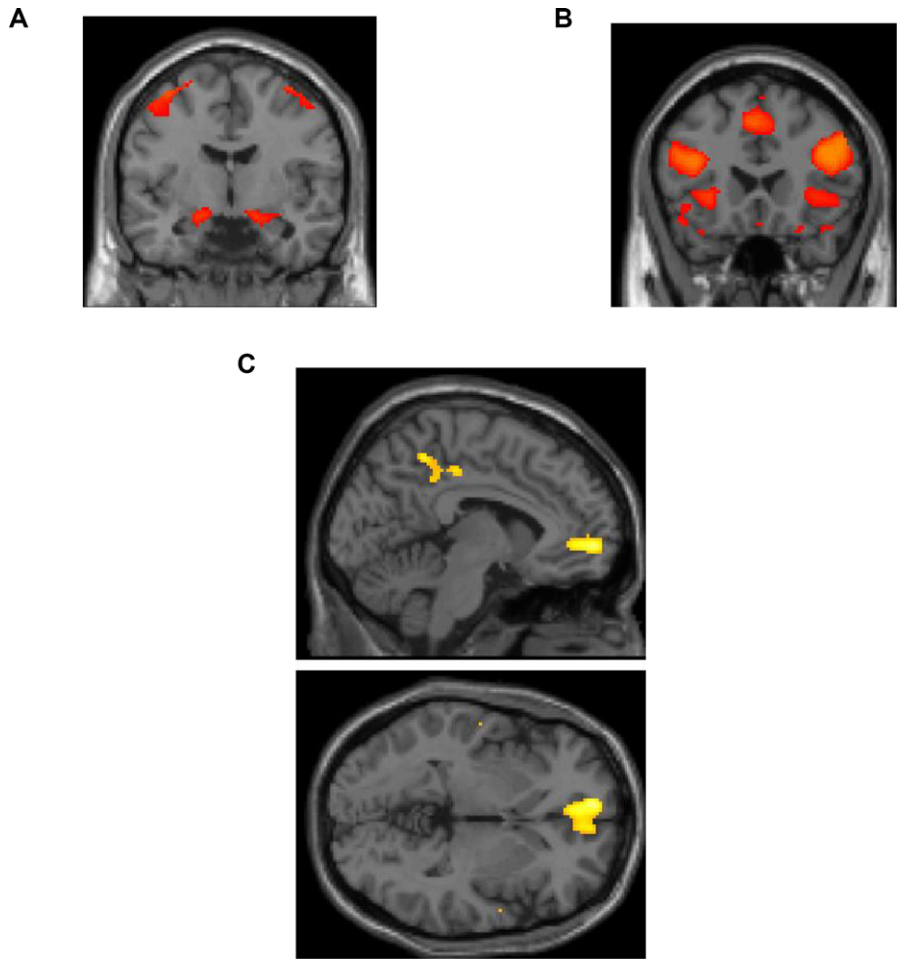

Figure 2. Activation associated with face matching and shape matching during the Emotional Faces Shifting Attention Task. Face matching (Faces>Shapes) is associated with greater bilateral amygdala activation (A) and bilateral insula activation (B) whereas shape matching (Shapes>Faces) is associated with greater rostral anterior cingulate cortex activation (C) across all participants. All figures are thresholded at $P < .001$ uncorrected.

a similar pattern as for accuracy (Table 2). Participants evidenced slower reaction times for angry face matching relative to Fearful Face matching, $t(67) = 3.97$, $P < .001$, and Happy Face matching $t(67) = 5.65$, $P < .001$. They also evidenced slower reaction times for matching shapes with Angry Face distractors relative to matching shapes with Happy Face distractors $t(67) = 2.14$, $P = .04$.

When performing these analyses with age entered as a covariate, the group differences and emotion interactions were no longer significant. Controlling for age, there was a main effect of condition for accuracy, $F(1, 65) = 4.56$, $P = .04$, and for RT, $F(1, 65) = 32.2$, $P < .001$, indicating that across both groups participants were faster and more accurate while matching shapes relative to faces. There were also main effects of age on accuracy, $F(1, 65) = 45.4$, $P < .001$, and RT, $F(1, 65) = 75.6$, $P < .001$, due to younger participants evidencing lower accuracy and slower RTs in both groups.

MAIN EFFECT OF TASK

As predicted, when combining across the groups, Faces > Shapes was associated with activation of the bilateral amygdala, left amygdala: $t(66) = 4.80$, $P < .001$, $z = 4.43$, size = 58 voxels, xyz = (−18, −6, −14), and right amygdala: $t(66) = 4.56$, $P = .001$, $z = 4.24$, size = 65 voxels, (18, −6, −16), as well as the bilateral insula, left insula: $t(66) = 4.92$, $P = .002$, $z = 4.53$ size = 131 voxels, xyz = (−30, 22, −2), and right insula: $t(66) = 4.59$, $P = .007$, $z = 4.26$, size = 143 voxels, xyz = (36, 28, −2). Additionally, Shapes > Faces was associated with rACC activation, $t(66) = 4.89$, $P < .001$, $z = 4.50$, size = 108 voxels, (−6, 56, −2; Fig. 2). Whole-brain results for these analyses are presented in Table 3. These main effects of task were still significant when limiting the sample to participants 17 and younger: Faces > Shapes, left amygdala: $t(50) = 4.09$, $P = .007$ and right amygdala: $t(50) = 4.07$, $P = .007$, left insula: $t(50) = 4.69$, $P = .008$ and right insula: $t(50) = 4.02$, $P = .05$; Shapes > Faces, rACC: $t(50) = 4.46$, $P = .003$.

TABLE 3. Whole-brain activation table for main effects of condition (face matching and shape matching) within all participants

Effect	Statistic	Number of voxels	Coordinates	Region
Face matching vs. shape matching	$t(66) = 15.38$, $P < .001$	9,156	(−26, −94, −2)	Middle occipital gyrus
	$t(66) = 8.85$, $P < .001$	1,194	(42, 14, 26)	Right inferior frontal gyrus
	$t(66) = 7.42$, $P < .001$	635	(−40, 12, 28)	Left inferior frontal gyrus
	$t(66) = 6.21$, $P = .001$	203	(−4, 12, 50)	Left medial frontal gyrus
	$t(66) = 5.68$, $P = .007$	22	(−36, −10, 64)	Left precentral gyrus
Shape matching vs. face matching	$t(66) = 6.06$, $P = .002$	104	(58, −42, 36)	Right supramarginal gyrus
	$t(66) = 5.94$, $P = .003$	45	(−58, −34, 42)	Left inferior parietal lobule
	$t(66) = 5.87$, $P = .006$	54	(2, −28, 44)	Posterior cingulate
	$t(66) = 5.41$, $P = .017$	26	(−48, −60, 38)	Left angular gyrus

Note: *P*-values are family-wise error whole-brain corrected.

GROUP DIFFERENCES IN AMYGDALA, INSULA, AND RACC ACTIVATION

Examining overall group differences collapsing across the three emotion types, there was a group difference in rACC activation for Shapes > Faces. As hypothesized, controls evidenced greater rACC activation while matching shapes (in the context of emotional face distractors) relative to the anxiety disorder group, $t(65) = 3.63$, $P = .022$, $z = 3.45$, size = 16 voxels, xyz = (8, 56, −2; Fig. 3). When limiting the sample to participants 17 and younger, results were in the same direction although they no longer reached significance ($P = .13$), which may reflect the decrease in sample size. No other regions outside of the rACC were significantly different between the groups within ROIs or for the whole-brain analysis at $P < .001$ uncorrected.

Further analyses were then conducted in order to explore emotion-specific effects. The first analysis revealed that there was a difference in rACC activation during Angry Shape versus Angry Face matching in controls relative to anxiety disorder patients, $t(65) = 3.84$, $P = .011$, $z = 3.63$, size = 23 voxels, xyz = (−2, 58, −2), suggesting that group differences were driven by the Angry Face conditions (Fig. 4). However, this effect was not significant when controlling for multiple comparisons.

In the second analysis, we compared activation across emotions within each task condition. This analysis revealed a group difference in rACC activation during Angry Face versus Happy Face matching, $t(65) = 3.42$, $P = .031$, $z = 3.27$, size = 4 voxels, xyz = (6, 56, −6), reflecting the finding that controls evidenced deactivation within this region during Angry Face > Happy Face matching, whereas the anxiety disorder group did not. However, this was not significant when corrected for multiple comparisons. No other emotion-specific effects were significant within the three ROIs for face or shape matching.

Finally, post hoc analyses were performed in order to examine whether rACC activation for the contrast of shape versus face matching related to behavioral performance in either condition. Mean contrast values were extracted from the functionally activated cluster of the rACC and examined in SPSS. Analyses indicated that rACC activation was not related to accuracy for face or shape matching within either group. However, in controls, rACC activation was related to RT for face matching, $r = .37$, $P = .03$ (Fig. 5).

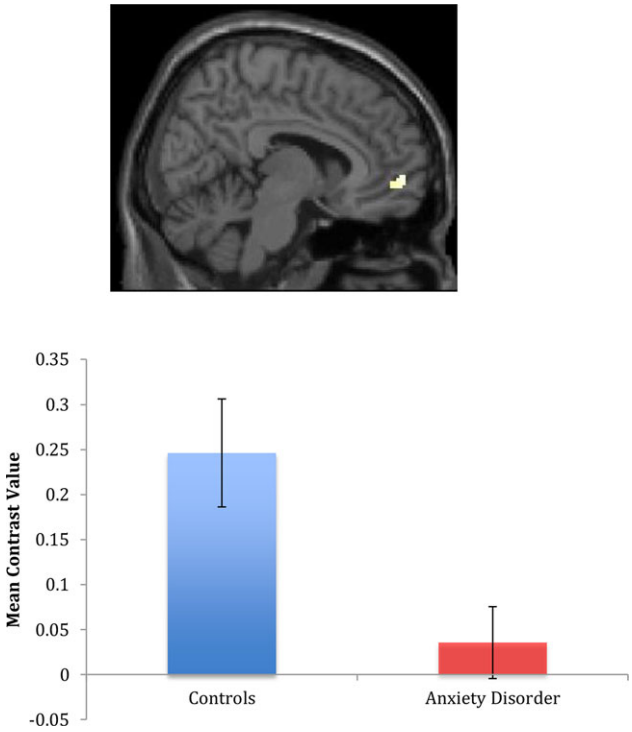

Figure 3. Controls evidence greater rostral anterior cingulate cortex (rACC) activation during shape matching relative to the anxiety disorder group. SPM figure demonstrates the contrast of Controls > Anxiety Disorder Group for the contrast of Shapes > Faces. Graph shows mean contrast values extracted from a functional mask of the rACC defined by all voxels activated for the contrast of Shapes > Faces. Error bars represent one standard error above and below mean.

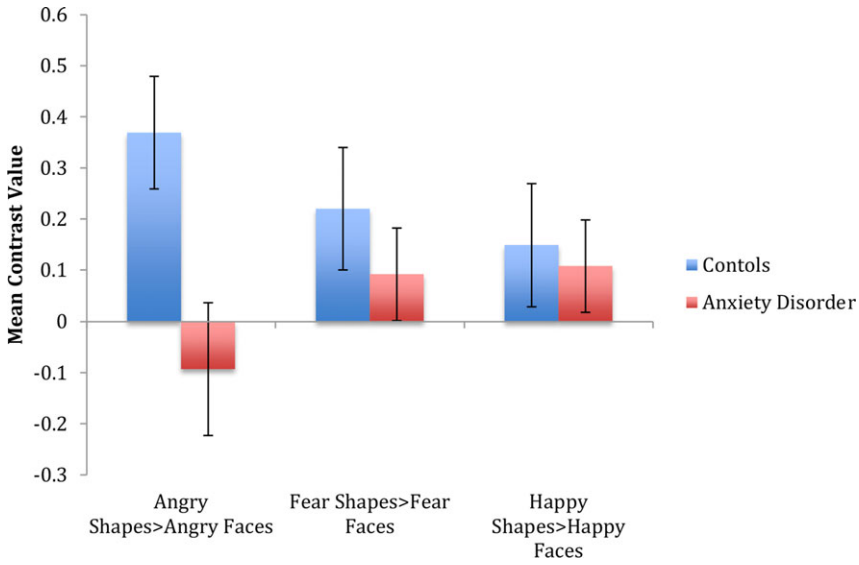

Figure 4. Rostral anterior cingulate cortex activation to shape matching versus face matching by group and emotion. Contrast values are extracted from the functional rACC mask for Shapes > Faces by emotion type (angry, fear, and happy). Error bars represent 1 standard error above and below mean.

RELATION BETWEEN ANXIETY, AGE, AND ACTIVATION

We did not find a significant relation between MASC or LSAS scores and amygdala, insula, or rACC activation within the anxiety disorder group or interactions with the linear or quadratic effect of age on activation during the task.

DISCUSSION

The goal of this paper was to examine neural activation in pediatric anxiety disorder patients during direct emotion processing and a shape-matching condition performed in the context of emotional face distractors. Results demonstrated that pediatric anxiety disorder

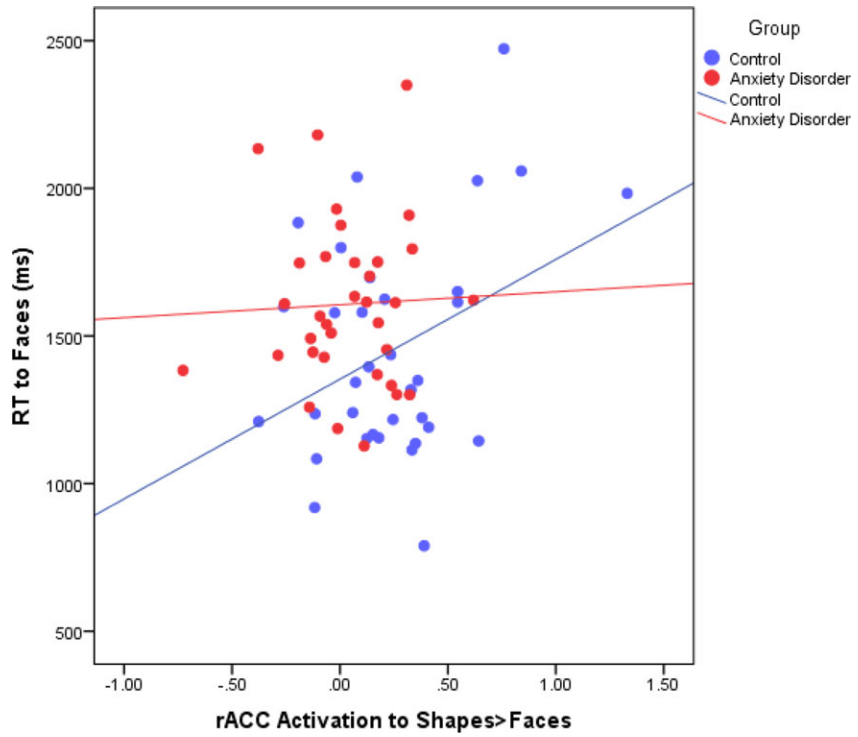

Figure 5. Association between rostral anterior cingulate cortex activation to shapes > faces and reaction time to faces. Contrast values are extracted from the functional rACC mask. RT = reaction time.

patients evidenced reduced rACC activation relative to controls for shape matching. In addition, there was a trend indicating that rACC activation was dependent on the emotional content of face stimuli. However, there was no support for the hypothesis that differences in amygdala and insula activation to negative emotional faces would be observed. This is the first study to our knowledge to use a task with both direct emotion processing and emotional face distractors in pediatric anxiety disorder patients. Given the previously established role of the rACC in goal-directed attention, reduced rACC activation during shape matching may play a role in difficulty disengaging attention from threat in anxiety disorder patients.

The present study provides preliminary evidence of emotional modulation of behavior and rACC activation during direct emotion processing and during a condition with emotional face distractors in child and adolescent participants. The behavioral results indicated that Angry Faces were the most difficult emotion type in both tasks. Participants in both groups were slower and less accurate when matching Angry Faces relative to fearful or Happy Faces. Additionally, they were slower at matching shapes in the context of angry emotional face distractors relative to happy face distractors. Post hoc analyses suggested that the difference between groups in rACC activation for shape versus face matching was strongest for the angry condition. Therefore, controls may be modulating rACC activation based on the emotional content of the face distractors (increasing rACC activation when face distractors are angry) whereas the anxiety disorder patients fail to evidence this modulation.

However, the pattern of results observed also point to an alternative potential interpretation of the group difference in rACC activation. When examining the main effect of condition for shape matching versus face matching, rACC activation was observed alongside activation of the posterior cingulate cortex (Table 3, Fig. 2). Thus, this pattern of activation for shape matching versus face matching could potentially be the result of deactivation of the default mode network during the more difficult face matching task. The default mode network, sometimes referred to as a "task negative network" consists of a distributed set of regions including the medial PFC, the posterior cingulate, and the precuneus and is often deactivated during the performance of difficult tasks.[41–43] Thus, the observed group difference in rACC activation could be driven by a difference in task-induced deactivation during the more difficult face-matching condition rather than a difference in activation during shape matching. In support of this possibility, a significant effect of emotion was observed in the rACC for face matching, with controls evidencing a significant deactivation of the rACC for angry relative to happy face matching, whereas anxiety disorder patients did not evidence this effect. This also concurs with the finding that rACC activation to shape versus face matching was related to reaction times for face matching within the control group, which could indicate that controls who had more difficulty with face matching (i.e., displayed longer reaction times) showed greater differential default mode network activity between the face and shape matching conditions, whereas patients with similarly long reaction times in the face matching condition did not show this differential effect.

In this case, the group difference in rACC activation would indicate that shape matching was associated with greater default mode network activation in controls, suggesting the shape-matching task was easier for controls relative to the anxiety disorder group. Therefore, these results still support the hypothesis that performing the shape-matching task in the presence of emotional distractors is more difficult for anxiety disorder patients, but point to different mechanisms that could contribute to anxiety. On the one hand, if controls exhibit greater rACC activation during the shape matching condition relative to patients, then differences regulating attention in anxiety disorder patients may be due to failure to recruit this region in order to resolve emotional conflict. On the other hand, anxiety disorder patients may be expending more cognitive effort to perform shape matching (consistent with the default mode network interpretation), suggesting it may take more effort on the part of patients to overcome bottom-up influences on attention to perform the shape matching task. Future research with a baseline comparison condition, such as fixation, will be necessary in order to determine whether these results are due to rACC activation during the shape matching condition or deactivation during face matching.

Similar to the findings of the study conducted in adult anxiety disorder patients,[20] we found no difference in amygdala activation between the anxiety disorder and control groups. Additionally, we did not observe the hypothesized difference in insula activation between groups. It is possible that if anxiety disorder patients had more difficulty regulating their attention in general that they were more likely to attend to emotional faces in both conditions (when matching faces and when matching shapes). In this case, if amygdala and insula activation were generally high across both task conditions, this may have made it more difficult to detect a difference in activation between the two conditions in the anxiety disorder group.

There are several limitations to note. As mentioned, the lack of a baseline condition prevents the detection of activation that may occur during both the face-matching and shape-matching conditions but does not differ between them. Additionally, the lack of a baseline condition precludes a definitive test of whether the group difference in rACC activation represents deactivation to the face matching task or activation to shape matching. Second, due to the blocked design, we were unable to remove incorrect trials or control for differences in reaction time at the trial level. Future research with mixed or event-related designs could help to supplement the results found here and address some of these limitations.

CONCLUSIONS

This study provides novel evidence of altered rACC function in pediatric anxiety disorder patients relative to controls. This may be indicative of altered attentional control or increased difficulty performing the shape matching task in the context of emotional face distractors for pediatric anxiety disorder patients. These results have implications for furthering our understanding of the development and treatment of pediatric anxiety disorders. Prospective research will be necessary in order to determine how alterations in rACC function develop and whether they play a causal role in the development of altered attention to threat. Treatment studies could be used to test whether these disturbances can be modified through cognitive or pharmacological intervention. Regulating attention in the presence of threatening stimuli appears to be a particular challenge for pediatric anxiety disorder patients; understanding the neural mediators of this process may shed light on how to overcome it.

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