Published in final edited form as:

Prog Neuropsychopharmacol Biol Psychiatry. 2018 June 08; 84(Pt A): 250–256. doi:10.1016/j.pnpbp.2018.03.013.

Anterior Cingulate Activation to Implicit Threat Before and After Treatment for Pediatric Anxiety Disorders

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Abstract

Background—Research suggests that individuals with anxiety have difficulty ignoring threat distractors when completing tasks with competing stimuli. Studies examining the neural correlates of these emotional processing difficulties in youth anxiety highlight reduced recruitment of regions associated with goal-directed attention, such as the anterior cingulate cortex (ACC). In the current study, we examined neural activation during an emotional conflict task in youth with anxiety disorders before and after treatment.

Methods—Twenty-five youth (ages 9–19 years) with generalized, separation, and/or social anxiety disorder and 25 healthy controls underwent 2 functional magnetic resonance imaging scans approximately 13 weeks apart. At each scan, participants completed a task in which they matched shapes in the context of emotional distractors (happy and threatening faces). Between

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Author Contributions: All authors contributed to study design and revised and approved the final manuscript. K.B. processed/analyzed data and drafted the manuscript. A.K. and B.H. contributed to data analysis and manuscript preparation. K.L.P. designed study and contributed to data analysis/approach and manuscript preparation.

Conflict of Interest: None

Ethical Statement: The University of Michigan and University of Illinois at Chicago Institutional Review Boards approved the study, and informed consent was obtained from all parents and participants age 18 or older, with assent obtained from participants under age 18. Further, we complied with the American Psychological Association's ethical standards in the treatment of our sample.

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scans, anxious youth were treated with the selective serotonin reuptake inhibitor (SSRI) sertraline or cognitive behavior therapy (CBT).

Results—Prior to treatment, anxious youth exhibited reduced activation of the medial prefrontal cortex, encompassing the rostral ACC, when matching shapes in the context of threat distractors relative to healthy controls. Activation in this region increased in anxious youth after treatment, but remained unchanged in the healthy control group. Increases in rostral ACC activation were related to greater reductions in social anxiety and avoidance symptoms following treatment.

Conclusions—Effective treatments for pediatric anxiety may enhance rostral ACC response during attempts to filter out threat-relevant stimuli. These findings highlight rostral ACC activity during implicit emotion processing as a possible mechanism of CBT and SSRI treatment change among youth with anxiety disorders.

Keywords

pediatric anxiety; treatment; neuroimaging; attention; emotion processing

1. Introduction

Pediatric anxiety disorders, one of the most common classes of psychological disorders in youth (Costello *et al.* 2003), are characterized by a tendency to disproportionately allocate attentional resources toward threat-relevant stimuli (for a review, see Puliafico & Kendall, 2006). Specifically, there is accumulating evidence from behavioral studies that children, adolescents, and adults with anxiety have difficulty ignoring threat distractors when completing tasks with conflicting or competing stimuli (Bogels & Mansell, 2004; Derryberry & Reed, 2002; Moriya & Tanno, 2008; Puliafico & Kendall, 2006). Given this, attempts have been made to uncover the neural correlates of these emotion processing patterns in order to inform understanding of the development and treatment of anxiety disorders.

Researchers have consistently demonstrated that individuals with anxiety exhibit enhanced engagement of regions associated with the detection of threat, such as the amygdala, and altered top-down control by regions associated with goal-directed attention, such as the medial prefrontal cortex (mPFC), including the rostral and dorsal anterior cingulate cortex (ACC) (for a review, see Bishop, 2007). The rostral ACC in particular has been identified as an important region for regulating attention to threat and resolving conflict between competing stimuli (Etkin *et al.* 2006; Kanske & Kotz, 2010). Notably, there is increasing evidence that adults with anxiety exhibit less activation in the rostral ACC while performing tasks that require participants to shift their attention away from emotional stimuli (Klumpp *et al.* 2011; Wheaton *et al.* 2014). Moreover, using an emotional conflict task developed in our lab, we have previously shown that when participants are instructed to match shapes in the context of emotional face distractors, both youth (Swartz *et al.* 2014) and adults (Klumpp *et al.* 2013) with anxiety disorders exhibit less rostral ACC activation compared to healthy controls.

Despite previous studies highlighting this differential neural response during implicit emotion processing among anxious patients, few attempts have been made to investigate the influence of anxiety treatment on these neural responses. Two of the most common and efficacious treatments for anxiety disorders in youth are cognitive behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) (Birmaher *et al.* 2003; Compton *et al.* 2004; Scott *et al.* 2005; Walkup *et al.* 2008). Although improving attention for threat-relevant stimuli is not a direct target of these treatments, there is some evidence from behavioral studies suggesting that biases in attention for threatening stimuli improve with treatment (Pishyar *et al.* 2008) and that the therapeutic effects of anxiety treatment are mediated by early changes in attentional bias (Reinecke *et al.* 2013). Moreover, a recent study from our laboratory showing that anxious youth who recruit less dorsal ACC during an emotional conflict task (i.e., matching shapes in the context of emotional face distractors) have greater reductions in anxiety symptoms following CBT and SSRI treatment (Burkhouse *et al.* 2016).

Together, these previous findings suggest that youth with anxiety who have preexisting deficits in implicit emotion processing (i.e., failure to inhibit emotional stimuli or recruit rostral/dorsal ACC during attempts to filter out emotional stimuli) may benefit the most from anxiety treatment, potentially due to having more to gain in treatment. However, few attempts have been made to examine whether altered neural engagement during implicit emotion processing improves pre-to-post treatment among youth with anxiety disorders, and whether changes in neural responses correspond to changes in anxiety symptoms. In fact, only one small (N = 14) functional magnetic resonance imaging (fMRI) study to date has been conducted to investigate the neural correlates of treatment in youth with anxiety. Maslowsky and colleagues (2010) found that anxious youth had an increase in activation of the ventrolateral prefrontal cortex, a region implicated in the regulation of emotion (Ochsner *et al.* 2004; Phan *et al.* 2005), when processing threatening faces in a probe detection task.

Extending these previous findings, the current study is the first to examine changes in neural activation during an emotional conflict task pre-to-post treatment among children and adolescents with anxiety. This two-site study was modeled after the Child/Adolescent Anxiety Multimodal Study (Compton *et al.* 2010) in that it included youth across a large span of development (7-19 years) with primary diagnoses of generalized anxiety disorder (GAD), separation anxiety disorder, and/or social anxiety disorder (SAD) treated with either sertraline (i.e., SSRI) or psychotherapy (i.e., CBT). Given our previous finding that less dorsal ACC activation during an emotional conflict task (i.e., when instructed to match shapes in the context of emotional face distractors) predicted better treatment response in anxious youth (Burkhouse *et al.* 2016), we expected that this region would increase from pre-to-post treatment among anxious youth, but remain stable among healthy control children and adolescents. We also predicted that similar effects would emerge for the rostral portion of the ACC given our previously described finding highlighting a deficit in this region in anxious, relative to healthy control, youth (Swartz *et al.* 2015). Based on behavioral findings (Pishyar *et al.* 2008; Reinecke *et al.* 2013), we expected that our findings would be observed for implicit processing of threatening faces (i.e., matching shapes in the context of angry and fearful face distractors). We also explored whether effects emerged for the processing of non-threatening facial expressions (i.e., happy faces). Lastly, exploratory

analyses were conducted to determine whether changes in ACC activation during implicit emotion processing were related to clinical response to treatment (i.e., change in symptoms of anxiety following treatment).

2. Method

2.1. Participants

Participants were youth between the ages of 7 and 19 who participated in a pediatric anxiety treatment study at the University of Michigan (UM) and University of Illinois at Chicago (UIC). Healthy control and treatment-seeking children and adolescents with a primary diagnosis of GAD, SAD, or separation anxiety disorder were eligible to participate. Exclusion criteria in the study included history of bipolar disorder, schizophrenia, intellectual disability, pervasive development disorders, current substance use disorders, severe depression, or suicidal ideation. Participants were not taking psychotropic medications or in psychotherapy for at least 4 weeks prior to the initial assessment. The Schedule of Affective Disorders and Schizophrenia for School-Age Children (Kaufman *et al.* 1997) diagnostic interview was used to assess for diagnoses by Master's or Doctoral level clinicians (see Kujawa *et al.* 2015 for more details).

A total of 60 participants (29 anxious youth, 31 healthy control youth) completed the fMRI Emotional Faces Shifting Attention Task (EFSAT) at baseline and post-treatment (approximately 13 weeks apart; anxious youth $M = 13.24$, $SD = 1.72$, Range = 12-18, control youth $M = 14.14$, $SD = 1.94$, Range = 12-22).¹ Data from 6 participants (4 healthy control, 2 anxious) were excluded for movement during the fMRI (> 3 mm in any one direction across each functional run) and 4 participants were excluded for low accuracy on the task (< 40%), leaving a total sample of 50 youth (25 anxious, 25 healthy control) with pre- and post-treatment fMRI data and clinical measures. The number of subjects excluded due to poor behavioral performance or movement during the scan did not differ based on study site or patient group (lowest $p = .45$). The final included sample was 59.5% female; 73.0% Caucasian, 8.1% African American, 5.4% Asian, and 13.5% multiracial; 10.8% identified as Hispanic/Latino. Youth included in this study ranged in age from 9-19 ($M = 15.52$, $SD = 2.74$). The UM and UIC Institutional Review Boards approved the study, and informed consent was obtained from all parents and participants age 18 or older, with assent obtained from participants under age 18.

Of the 50 participants with pre- and post-treatment fMRI and clinical measures, 25 had a primary diagnosis of GAD ($n = 13$), social anxiety disorder ($n = 11$), or separation anxiety disorder ($n = 1$), and 25 had no lifetime history of any DSM-IV Axis-I psychological disorder. Among the anxious youth, 17 had a current diagnosis of GAD, 16 had a current diagnosis of social anxiety disorder, and 2 had a current diagnosis of separation anxiety disorder. Youth in the anxiety group were eligible to participate if they had current comorbid psychopathologies: panic disorder ($n = 3$), obsessive-compulsive disorder ($n = 1$), specific phobia ($n = 5$), depression ($n = 2$), and ADHD ($n = 3$).

¹Baseline fMRI data during the Emotional Conflict Task have been previously reported in Burkhouse *et al.* 2017 and Swartz *et al.* 2014.

2.2. Treatment

At UM, anxious participants were offered and self-selected treatment with SSRI or CBT. At UIC, participants were randomly assigned to receive either an SSRI or CBT. SSRI treatment consisted of 12 weeks of sertraline prescribed by a child psychiatrist during medication management sessions, beginning with a dose of 25 mg/day and using a flexible-dosing design increasing on subsequent visits up to 200 mg/day based on tolerability and treatment response. CBT was delivered through weekly 60-minute sessions ($M = 15.44$, $SD = 0.53$, $Range = 14-16$) by a Master's or Doctoral level therapist using an established manualized CBT intervention (i.e., Coping Cat, C.A.T Project) for pediatric anxiety (Kendall *et al.* 2002, 2006). The Coping Cat program combines behavioral strategies (e.g., modeling, relaxation, *in vivo* exposure tasks, and contingency management) with cognitive strategies (e.g., problem-solving, appraisal of personal abilities and perceived threat) to help youth cope with anxiety.

2.3. Clinical Measures

To assess overall severity of anxiety symptoms, participants were administered the Pediatric Anxiety Rating Scale (PARS, Research Units, 2002) by trained research assistants trained by masters- and doctoral- level clinicians. Internal consistency for PARS total scores was excellent (Cronbach's $\alpha = 0.95$). Participants were also administered the Liebowitz Social Anxiety Scale for Children and Adolescents (LSAS-CA, Masia-Warner *et al.* 2003). The LSAS-CA is a 24-item scale of social anxiety symptoms. Two LSAS-CA subscales were created: total anxiety and total avoidance. Finally, participants also completed the Multidimensional Anxiety Scale for Children (MASC; March *et al.* 1997). The MASC is a 39-item scale of anxiety symptoms. Three subscales were created: physical symptoms, harm avoidance, and social anxiety. Healthy control and anxious youth completed the anxiety symptom measures at baseline, and anxious youth completed the measures following treatment.

2.4. Emotional Conflict Task

The emotional faces shifting attention task previously described (EFSAT; Klumpp *et al.* 2012, 2013, 2015; Swartz *et al.* 2014) consists of three faces in a triangular configuration, and three shapes in an upside-down triangular configuration (Figure 1). During the faces condition, participants were instructed to identify which face on the bottom row matched the emotion of the target face on the top. During the shapes condition, participants were instructed to match shapes on the top row with the target shape on the bottom. Participants completed two runs, for a total of 18 faces blocks and 18 shapes blocks with six blocks of each condition: match angry faces, fear faces, and happy faces, and match shapes with angry faces, fear faces, and happy faces as distractors. Each block began with a 4s cue to either 'match faces' or 'match shapes' followed by the four sequential matching trials, each lasting 4s. Accuracy and response time (RT) were calculated for each condition.

2.5. fMRI Data Acquisition and Processing

MRI data were collected on 3 Tesla GE scanners with 8-channel head coils at both sites. At UM, functional data were collected with a gradient-echo reverse spiral acquisition with the

following parameters: repetition time (TR) = 2s, echo time (TE) = 30ms, flip angle = 90°, = field of view (FOV) = 22 × 22 cm, acquisition matrix 64 × 64, 3-mm slice thickness, and 43 axial slices. At UIC, functional data were acquired using gradient-echo echo-planar imaging (EPI) sequence with the following parameters: TR = 2s, TE = minFull [~25ms], flip angle = 90°, FOV = 22 × 22 cm, acquisition matrix 64 × 64, 3-mm slice thickness, and 44 axial slices.

Functional images were preprocessed in SPM8 (Wellcome Trust Centre for Neuroimaging, <http://www.fil.ion.ucl.ac.uk/spm/>) for slice timing correction, image normalization, resampling at a 2 × 2 × 2 mm³ voxel size, and 8-mm Gaussian smoothing kernel.² Condition effects were modeled at the individual subject level using the general linear model and the nuisance regressors for 6 motion parameters were included to correct for motion artifacts. For each participant, contrast images of brain activity were generated for second-level analysis. Consistent with previous studies using the EFSAT task (Burkhouse *et al.* 2016; Klumpp *et al.* 2012, 2013, 2015; Swartz *et al.* 2014) and because the emotional conflict task does not include a fixation (baseline) condition, the SPM contrast of interest for the current study was Matching Shapes versus Matching Faces. As processing of *both* angry and fearful faces has been shown to be altered in individuals with anxiety disorders, we collapsed across these face types to evaluate implicit processing during threatening (Match Shapes[threat] > Match Faces[threat] contrast) and non-threatening (Match Shapes[happy] > Match Faces[happy] contrast) conditions.

2.6. Data Analysis

2.6.1. Behavioral analysis—To examine the influence of emotion (threatening versus happy), condition (shapes versus faces), and time (scan 1, scan 2) on accuracy and RT, a mixed-design ANOVA was conducted. Emotion, condition, and time served as within-subjects variables, anxiety group served as a between-subjects variable, and accuracy or RT served as the dependent variable.

2.6.2. fMRI analysis—To examine changes in activation, a flexible factorial analysis of variance (ANOVA) using Group (anxiety, healthy control) and Time (pre-treatment/scan 1, post-treatment/scan 2) as between- and within-subjects factors, respectively, was conducted in SPM8 to test for main effects of Group and Time, as well as for Group × Time interactions. The primary effect of interest for the fMRI analysis was the Match Shapes[threat] > Match Faces[threat] contrast. To examine the specificity of this effect to threatening stimuli, we also performed parallel analyses on the Match Shapes[happy] > Match Faces[happy] contrast. To maximize power in our whole-brain fMRI analyses, the initial search to test these main and interaction effects combined participants from both the SSRI and CBT groups. To correct for multiple comparisons, joint height and extent thresholds were determined within a mask covering the entire brain except the cerebellum due to limited coverage (created with MARINA, Walter *et al.* 2003) via Monte Carlo

²Framewise displacement (FD) utilizing FSL (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki>) was also examined on all participants to control for additional motion artifacts. Healthy controls ($M = 0.06$ mm, $SD = 0.02$ mm) and anxious youth ($M = 0.07$ mm, $SD = 0.05$ mm) did not differ in FD values. One participant had one run in which their FD value exceeded standard threshold (0.30 mm). Excluding this subject from analyses did not change the pattern or significance of findings described below.

simulations (10,000 iterations) and applied to second-level statistical results for a corrected $p < .05$ [December 16, 2015, updated release; 10,000 iterations; http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html; (Eklund, Nichols, & Knutsson, 2016)]. Minimum cluster size for significant effects was 70 voxels (volume=560 mm³) at uncorrected $p < .001$. To interpret results, parameter estimates of peak activation (β weights, arbitrary units [a.u.]) were extracted from individual activity maps for each participant using MarsBar (Brett *et al.* 2002) and submitted to post hoc t -tests for ANOVA findings, and examination of associations between ANOVA findings and symptom severity in the Statistical Package for the Social Sciences (SPSS) (Chicago, IL version 18).

3. Results

3.1. Participant Characteristics

Participant characteristics separated by diagnostic and treatment groups are presented in Tables 1 and 2, respectively. Among youth with anxiety disorders, anxiety severity decreased following treatment (i.e., PARS, $t(24) = 11.57$, $p < 0.001$, mean difference = 12.60), as did social anxiety [i.e., LSAS – anxiety, $t(24) = 8.66$, $p < 0.001$, mean difference = 22.40; MASC – social anxiety, $t(24) = 5.18$, $p < 0.001$, mean difference = 7.80], avoidance [i.e., LSAS – avoidance, $t(24) = 7.78$, $p < 0.001$, mean difference = 20.52; MASC – harm avoidance, $t(24) = 3.83$, $p < 0.01$, mean difference = 4.75], and physical [MASC – physical symptoms $t(24) = 5.99$, $p < 0.001$, mean difference = 10.13] symptoms. With regard to treatment response, 79.5% of the sample responded to treatment and 64.0% showed evidence of remission, as indicated by at least a 35% and 50% decrease in PARS, respectively (Caporino *et al.* 2013). Study sites (UIC, UM) did not significantly differ on rates of diagnostic group (anxious vs. healthy control), treatment modality (CBT vs. SSRI), anxiety symptom severity (PARS, LSAS), age, sex, race, or primary diagnoses (p s $> .06$).

3.2. Behavioral Performance

Results from the ANOVA for accuracy revealed a main effect of condition, $F(1,48) = 9.23$, $p < .01$, $\eta^2 = .16$, such that participants displayed greater accuracy when matching shapes ($M = 88.32$, $SE = 1.51$) versus faces ($M = 84.97$, $SE = 1.70$). Results revealed no other significant main effects or interactions with group for accuracy (lowest $p = .13$). When examining RT data for correct trials, results revealed main effects of condition, $F(1,48) = 316.94$, $p < .001$, $\eta^2 = .87$, emotion, $F(1,48) = 27.52$, $p < .001$, $\eta^2 = .36$, and time, $F(1,48) = 4.69$, $p = .04$, $\eta^2 = .09$. Specifically, participants were faster at matching shapes ($M = 1066.94$, $SE = 26.63$) versus faces ($M = 1380.27$, $SE = 29.83$), happy ($M = 1192.17$, $SE = 27.90$) versus threatening ($M = 1255.04$, $SE = 27.15$) faces, and faces and shapes at time 2 ($M = 1203.86$, $SE = 30.25$) versus time 1 ($M = 1243.35$, $SE = 26.35$). Results also revealed a significant condition $\times$ emotion $\times$ time interaction, $F(1,48) = 8.29$, $p < .01$, $\eta^2 = .15$. Post hoc analyses revealed that youth became slower at matching shapes in the context of threatening face distractors from time 1 ($M = 1018.65$, $SE = 30.42$) to time 2 ($M = 1125.95$, $SE = 29.48$). Results indicated no significant main effect or interactions with group for RT (lowest $p = .16$).

3.3. fMRI Results

3.3.1. Treatment effects—We first examined changes in brain activation during implicit threat processing between Time 1 and Time 2 among the anxious and healthy youth. Results from the SPM ANOVA revealed no main effect of group or time during the Match Shapes[threat] > Match Faces[threat] contrast; however, there was a significant Group $\times$ Time interaction in the mPFC/rostral portion of the ACC [MNI coordinates 6, 54, -2, BA = 10, 32, volume=1032 mm³, $F(1,48) = 20.03$, $p < .001$ see Figure 2a]. Follow-up inspection of the extracted BOLD signal (β weights) from the rostral ACC revealed that pre-treatment activation during implicit threat processing significantly increased after treatment among anxious youth ($t(24) = 3.17$, $p < 0.01$, mean difference = 0.87, Figure 2b), whereas rostral ACC activation between Scan 1 and Scan 2 did not significantly change in the healthy control group ($t(24) = 0.39$, $p = 0.70$, mean difference = -0.14). Notably, this finding was maintained when controlling for study site ($p < .05$) and post hoc tests revealed comparable effects across treatments and study sites for change in rostral ACC from pre-to-post treatment among the anxious youth (CBT t -value = .52, SSRI t -value = .56, UIC t -value = .62, UM t -value = .41). Importantly, rostral ACC activation during implicit threat processing was greater in the healthy control versus anxious youth at pre-treatment ($t(48) = 1.92$, $p < 0.05$, mean difference = 0.67, t -value = .27); however, the groups did not differ significantly at Scan 2 ($t(48) = 0.88$, $p = 0.39$, mean difference = 0.34, t -value = .13). Finally, to examine the specificity of increases in rostral ACC activation for implicit threat processing, we analyzed the change in activation from Time 1 to Time 2 during the Match Shapes[Happy] > Match Faces[Happy] contrast. However, whole brain analyses revealed no significant regions for the main effects or interactions.

3.3.2. Correlation between Brain Changes and Symptom Severity—Finally, analyses were conducted to determine whether change in rostral ACC activation during implicit threat processing related to change in symptoms of anxiety pre-to-post treatment. Partial correlational analyses between treatment change (PreTx - PostTx) in anxiety scores (i.e., PARS, LSAS-anxiety, LSAS-avoidance) and rostral ACC change (PreTx - PostTx) were conducted controlling for study site. Rostral ACC change was not significantly related to change in anxiety symptom severity (PARS: $p = .07$, $r = -.32$) or physical symptoms (MASC - physical: $p = .42$, $r = -.19$). However, results revealed significant negative relations between rostral ACC change and social anxiety symptom change (LSAS - social anxiety: $p < .01$, $r = -.58$; MASC - social anxiety: $p < .01$, $r = -.57$), and between rostral ACC change and avoidance symptom change (LSAS - avoidance: $p < .01$, $r = -.57$; MASC - harm avoidance: $p = .03$, $r = -.49$). Specifically, greater pre-to-post treatment increases in rostral ACC activation during implicit threat processing were related to greater pre-to-post treatment decreases in social anxiety and avoidance symptoms (LSAS findings displayed in Figure 3). Changes in anxiety symptoms were unrelated to changes in accuracy or RT when matching shapes in the context of threatening face distractors pre-to-post treatment (lowest $p = .30$).

4. Discussion

In the current study, we investigated neural activation during an emotional conflict task before and after CBT and SSRI treatment among anxious youth. As expected based on previous findings (Swartz *et al.* 2015), prior to receiving treatment, anxious youth exhibited reduced activation of the mPFC, encompassing the rostral ACC, when matching shapes in the context of threatening face distractors relative to healthy controls. Consistent with our primary hypothesis, we found that activation in this region significantly increased in anxious youth after CBT and SSRI treatment, whereas rostral ACC activation remained relatively stable in the healthy control group. These findings appeared to be specific to implicit processing of threatening faces, and were not significant for the contrast of matching shapes in the context of happy face distractors versus matching happy faces. Therefore, CBT and SSRI treatment for anxious youth may enhance rostral ACC response during implicit regulation of threatening stimuli.

Findings from the present study also revealed that change in rostral ACC activation when anxious youth were required to direct their attention away from threatening stimuli correlated with change in social anxiety and avoidance symptoms, such that increases in rostral ACC activation were related to a greater reduction in symptoms following treatment. This finding provides some initial insight into the possible neural mechanisms implicated in CBT and SSRI treatment for children and adolescents with anxiety disorders. Specifically, while previous behavioral studies suggest therapeutic response for anxiety is associated with enhanced implicit emotion regulation (e.g., emotional Stroop, dot-probe detection) after completing CBT (Pishyar *et al.* 2008; Reinecke *et al.* 2013), no studies have directly tested whether changes in brain activation during an emotional conflict task correspond to treatment gains in anxious youth or adults. Thus, it is possible that enhanced recruitment of the rostral ACC may constitute one manner in which these treatments reduce youth anxiety symptoms, particularly social anxiety and avoidance.

As previously highlighted, the rostral ACC has been previously shown to be implicated in conflict monitoring and attempts to filter out competing, or distracting, stimuli in the environment (Etkin *et al.* 2006), and both youth (Swartz *et al.* 2015) and adults (Klumpp *et al.* 2011, 2013; Wheaton *et al.* 2014) with anxiety exhibit less activation of this region during emotional conflict tasks. Although the current study found that CBT and SSRI treatment successfully increases this region during implicit threat processing among anxious youth, the precise mechanisms in which these treatments target brain function is not well understood. Researchers have suggested that both CBT and SSRIs influence limbic and prefrontal circuitry, but their proximal mechanisms of action may differ (for a review, see DeRubeis *et al.* 2008). That is, CBT may more directly target regions involved in cognitive control given its focus on cognitive interventions (e.g., cognitive restructuring) and exposures to negative stimuli, whereas SSRIs may work to indirectly improve implicit emotion processing by first acting on limbic regions involved in automatic emotional reactions. In the current study, we were underpowered to examine differences by type of treatment; however, post hoc tests revealed comparable effect sizes across the two treatments. Nonetheless, it will be important for future studies to include larger samples in order to evaluate distinct effects of SSRI treatment and CBT on brain function.

The current study benefited from several strengths, including being the first study to examine changes in neural activation during an emotional conflict task pre-to-post treatment among anxious youth. Only one other study to date has been conducted to examine changes in brain function in relation to anxiety treatment and it focused on bottom-up versus top-down emotion processing. As previously discussed, ventrolateral prefrontal cortex activation increased during processing of threatening faces among anxious youth following treatment with SSRIs and CBT (Maslowsky *et al.* 2010). Thus, together these findings provide preliminary evidence that activation in brain regions involved in implicit emotion regulation can be increased with treatment for youth anxiety disorders. Although longitudinal studies are needed to determine the long-term stability of these neural effects following treatment, the current findings raise the possibility of a brain assay (i.e., rostral ACC activation) that can track treatment effects for youth anxiety and/or serve as a potential treatment target. Specifically, future mechanistically-based interventions aimed at enhancing rostral ACC activation (i.e., cognitive training, transcranial magnetic stimulation to enhance cognitive restructuring, increasing cognitive mediated functioning via a pharmacological enhancer) may prove to be most useful in reducing anxiety symptoms for youth who demonstrate deficits in filtering out threat-relevant stimuli prior to beginning treatment.

There were limitations to the current study, which provide important avenues for future research. First, given the sample size of the current study, we were unable to examine moderators (i.e., age, sex, treatment type) of changes in brain activation. Second, the study sample is heterogeneous with regard to primary diagnoses. Although we were unable to examine if primary diagnoses of SAD and GAD moderated the effects, exploratory analyses indicated that change in rostral ACC activation during implicit threat processing corresponded to change in social anxiety symptoms following treatment. However, given that we did not have a symptom measure of worry or generalized anxiety symptoms, future studies with proper statistical power are needed to determine if these effects are specific to SAD or are also demonstrated in other anxiety diagnostic groups. These future studies should also explore how psychiatric comorbidity (e.g., major depression, ADHD) impact the pattern of findings. Third, the study was completed across two sites. Although our findings were maintained when controlling for study site, nonspecific factors from each site, such as patient preference versus random assignment, may have contributed to the findings. In addition, the interview-based measure of anxiety (i.e., PARS) was conducted by research assistants not blinded to treatment. While similar effects were observed across interview and self-report measures of anxiety, future studies should utilize independent raters (i.e., blinded to treatment) to assess change in anxiety symptoms. Fourth, no studies to date have evaluated the psychometric properties of the emotional conflict task. In order for the current findings to be effectively translated to intervention efforts, it will be essential to evaluate the reliability (i.e., test-retest, internal consistency) of key neural regions (e.g., ACC, amygdala) elicited by the task. Finally, due to the lack of treatment control condition, we cannot definitively conclude that group differences in ACC change are due to treatment versus diagnostic status. One possibility is that the rostral ACC may change in anxious youth as a function of course of symptoms or other factors not related to treatment. Thus, future studies would benefit from the inclusion of a treatment control condition to rule out this possibility.

5. Conclusion

In summary, findings from the current study suggest that CBT and SSRI treatment for anxious youth appears to enhance rostral ACC response during implicit processing of threatening stimuli. The results also suggest that change in rostral ACC activation corresponds to change in social anxiety and avoidance symptoms among youth. If replicated, the current and previous findings (Burkhouse *et al.* 2016) highlight ACC activity during implicit emotion processing as both a mechanism and predictor of treatment change and may be used to guide treatment selection for children and adolescents with anxiety disorders.

Acknowledgments

We would like to thank James Swain, M.D., Ph.D., Gregory Hanna, M.D., Elizabeth Koschmann, Ph.D., David Simpson, Ph.D., L.C.S.W., and Sucheta Connolly, M.D. for their help in providing therapeutic services for the current study.

Financial Support: This work was supported by National Institute of Mental Health Grant [R01-MH086517] to C.S.M. and K.L.P. KLB is supported by National Institute of Mental Health Grant [K23-MH113793].

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Highlights

- Neural correlates of threat processing in anxious youth at pre and post treatment
- Activation of the rostral ACC increased in anxious youth after treatment
- Activation in this region remained unchanged in the healthy control group
- Increases in rostral ACC activation were related to greater reductions in anxiety
- Youth anxiety treatments increase rostral ACC response during threat processing

Figure 1.

Schematic of exemplar 'Match Faces' and 'Match Shapes' blocks in the Emotional Faces Shifting Attention Task (EFSAT). 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.

Figure 2.

A) Whole brain analysis (corrected at $p < .05$) depicting a significant Group $\times$ Time interaction in the mPFC/rostral ACC during the Match Shapes [Threat] > Match Faces[Threat] contrast. B) Bar graph depicts extracted BOLD signal change [β weights, arbitrary units (a.u.)] from rostral ACC showing activation during implicit threat processing is greater in healthy control than the anxious group at pre-treatment, and is increased by treatment among the anxious youth.

Figure 3.

Association between change (pre minus post) in rostral ACC activation (mean blood-oxygen-level-dependent parameter estimates; a.u. = arbitrary units) during implicit threat processing and change (pre minus post) in social anxiety symptoms using the Liebowitz Social Anxiety Scale and avoidance symptoms using the Liebowitz Avoidance Scale.

Table 1

Baseline characteristics of the sample separated by diagnostic group.

	Anxious Youth (<i>n</i> = 25)	Control Youth (<i>n</i> = 25)	Statistic
	M(SD)	M(SD)	<i>t</i>
Age	15.28 (2.65)	15.92 (2.81)	0.62
PARS	22.80 (4.13)	2.21 (3.34)	-19.56**
LSAS-Anxiety	34.32 (15.74)	6.04 (5.71)	-8.39**
LSAS-Avoidance	31.12 (16.46)	4.50 (5.03)	-7.71**
MASC-Physical Symptoms	16.25 (8.23)	3.96 (4.54)	-6.51**
MASC-Harm Avoidance	17.42 (4.70)	13.88 (4.84)	-2.17*
MASC-Social Anxiety	16.67 (6.99)	6.36 (4.30)	-6.24**
	N (%)	N (%)	χ^2
Female	16 (64%)	17 (70.8%)	0.37
Caucasian	16 (64%)	16 (66.7%)	0.09
Study Site (UIC)	13 (52%)	16 (64%)	0.74

*Note:** = $p < .05$;** = $p < .001$;

PARS = pediatric anxiety rating scale; LSAS = Liebowitz social anxiety scale-children and adolescent version; MASC = multidimensional anxiety scale for children.

Table 2

Characteristics of the sample separated by treatment group.

	CBT (<i>n</i> = 9)	SSRI (<i>n</i> = 16)	Statistic
	M(SD)	M(SD)	<i>t</i>
Age	14.56 (2.70)	15.69 (2.63)	0.32
Pre PARS	22.11 (2.80)	23.19 (4.76)	0.54
Post PARS	10.11 (5.71)	10.31 (5.49)	0.95
Pre LSAS-Anxiety	35.44 (11.84)	33.69 (17.90)	-0.80
Post LSAS-Anxiety	11.11 (8.04)	12.38 (13.76)	0.80
Pre LSAS-Avoidance	31.78 (12.47)	30.75 (18.71)	-0.89
Post LSAS-Avoidance	10.11 (8.07)	10.88 (12.63)	0.87
Pre MASC-Physical Symptoms	13.88 (7.86)	17.44 (8.40)	0.99
Post MASC-Physical Symptoms	5.25 (5.73)	5.81 (5.55)	0.18
Pre MASC-Harm Avoidance	17.75 (6.34)	17.25 (3.87)	-0.24
Post MASC-Harm Avoidance	14.25 (1.41)	11.25 (7.23)	-1.01
Pre MASC-Social Anxiety	15.50 (6.21)	17.25 (7.45)	0.57
Post MASC-Social Anxiety	9.50 (9.26)	7.63 (7.22)	-0.96
	N (%)	N (%)	χ^2
Female	7 (77.8%)	9 (56.3%)	0.37
Caucasian	6 (66.7%)	10 (62.5%)	0.09
Study Site (UIC)	3 (33.0%)	10 (62%)	0.74
Primary GAD	6 (66.7%)	7 (43.8%)	1.21
Primary Social Anxiety	3 (33.3%)	8 (50.0%)	0.65
Primary Separation Anxiety	0 (0 %)	1 (6.2%)	0.59

*Note.**
= $p < .05$;**
= $p < .001$;

CBT = cognitive behavioral therapy; SSRI = selective serotonin reuptake inhibitor; Pre = pre-treatment; Post = post-treatment; PARS = pediatric anxiety rating scale; LSAS = Liebowitz social anxiety scale-children and adolescent version; MASC = multidimensional anxiety scale for children; GAD = generalized anxiety disorder.