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Childhood trauma moderates inhibitory control and anterior cingulate cortex activation during stress.

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Abstract

Objective: The anterior cingulate cortex (ACC) is a critical for both stress and inhibitory control processes and has been implicated in childhood trauma. This prospective study tested the hypothesis that early trauma moderates the association between inhibitory control during late childhood and ACC stress reactivity during adolescence.

Method—Sixty-four adolescents were stratified into higher-or lower-childhood-trauma groups. Inhibitory control was indicated by fewer errors on a Stroop Color-Word task. Personalized stress cues during functional magnetic resonance imaging assessed neural correlates of stress in adolescents.

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Results: Using *a priori*-defined anterior (rCZa) and posterior rostral cingulate zones of the ACC, associated with Stroop Color-Word task performance in prior meta-analyses, Stroop errors correlated inversely with activation in the rCZa during stress-cue exposure (r=−.23, p=.04). Childhood trauma moderated the association between Stroop errors and rCZa stress reactivity (interaction=−1.26, p=.02, 95%CI=−2.33, −.20), where Stroop errors were inversely associated with brain activation among those with higher childhood trauma (simple slopes=−.83, p=.007, 95%CI=−1.40, −.25). Low stress-related rCZa activation inversely (R^2=.19, b=−.43, p=.001, 95%CI=−4.11, −1.06) and Stroop errors directly (R^2=.09, b=.27, p=.048, 95%CI=.02, 5.8) associated with baseline subjective anxiety while controlling for childhood trauma.

Conclusions—This is the first study to demonstrate a moderating role of childhood trauma on the relationship between inhibitory control and stress-related ACC activation. Childhood trauma may portend neurodevelopmental changes that impede recruitment of control-associated ACC-functioning during distress, which may relate to dysregulation of stress-induced affective responses. Further work is needed to elucidate relationships between childhood trauma and addictive behaviors precipitated by stress.

Keywords

Trauma; Inhibitory Control; Anterior Cingulate Cortex; Stress; Anxiety

1 INTRODUCTION

Whereas inhibitory control and affective stress responses have been investigated separately in previous studies, there is substantial overlap in the functioning of frontal cortical regions underlying both processes and their contributions to the risk of substance use and addiction disorders (Li and Sinha, 2008). The ACC, in particular, has been widely implicated in integrating input from various sources and facilitating both cognitive abilities and affective responses (Bush et al., 2000). Exposure to stress stimuli increased activation in the ACC and elicited greater feelings of anxiety, which may contribute to reward-seeking behaviors including consumption towards addictive substances (Sinha et al., 2005). Separately, ACC function has been linked to inhibitory control abilities (Cieslik et al., 2015; Li et al., 2006). Indeed, several meta-analytic studies of brain activations associated with performance of the Stroop Word-Color and other inhibitory control tasks showed that the ACC had among the highest concordance and convergent activity across multiple fMRI studies (Cieslik et al., 2015; Laird et al., 2005; Neumann et al., 2005). However, the relationship between inhibitory abilities and engagement of inhibitory control regions when encountering stressful situations remains incompletely understood. As the ACC is critical for both inhibitory control and processing stressful stimuli, and is associated with the resolution of emotional stress (Bush et al., 2000), this study examines the combined relationship between inhibitory control, ACC stress reactivity and childhood trauma in a single model.

Childhood trauma is associated with dysregulation of the hypothalamic-pituitary-adrenocortical stress response system, which may alter individuals' brain physiology and functioning and may predispose exposed individuals to psychiatric vulnerabilities later in life (Teicher et al., 2016). Severe and long-lasting consequences to early experiences of trauma may include neuronal loss and reduced cortical thickness within the ACC (Kelly et

al., 2013; Teicher et al., 2003), and cognitive deficits in inhibitory control in adolescence (Marshall et al., 2016). In parallel, traumatic life events have been associated with smaller volumes in the ACC (Ansell et al., 2012). Individuals with post-traumatic stress disorder have demonstrated reduced rostral-ACC activation during emotion processing and poorer behavioral inhibition in those who also experienced childhood trauma (Shin et al., 2001; Stevens et al., 2016). Furthermore, childhood trauma is associated with depression, anxiety and addictive disorders (Hovens et al., 2015; Lotzin et al., 2016). In addition, maltreatment-related changes in brain areas associated with self-regulation under distressing situations have been implicated in addiction psychopathology and may in part underlie a heightened risk for addictive behaviors in those who have experienced childhood abuse (Puetz and McCrory, 2015).

Early maltreatment and traumatic experiences may contribute to greater sensitivity to stressful situations through persistent changes in the functioning of brain regions that process stress and emotion. Prior studies have suggested that childhood trauma may have pervasive effects on neural circuits that facilitate inhibitory control and processing of stress stimuli and anxiety (Elsey et al., 2015). However, the impact of childhood trauma on ACC stress reactivity among individuals with varying levels of inhibitory control during childhood remains an important research gap. Assessment of this relationship may provide insight into how childhood inhibitory control relates to stress-related neural circuitry in trauma-exposed adolescents.

1.1 Study Overview

The current study examined the relationship between childhood trauma, inhibitory control on the Stroop Word-Color task during childhood, and stress-related ACC activation during adolescence, with a specific focus on stress cue reactivity in ACC regions of interest (ROIs) defined *a priori* to be associated with inhibitory Stroop task performance (Cieslik et al., 2015; Laird et al., 2005; Neumann et al., 2005). Given the functional heterogeneity of the ACC, the study focused on ROIs localized in the anterior rostral cingulate zone (rCZa) and posterior rostral cingulate zone (rCZp) of the ACC. These ROIs were shown in a meta-analysis to support the verbal Stroop Word-Color task (Laird et al., 2005), which was similarly employed in the current study. This approach enabled independent ROI analyses, and focused on validated inhibitory control regions that showed convergence across multiple studies (Cieslik et al., 2015; Laird et al., 2005; Neumann et al., 2005). We hypothesized that childhood trauma would moderate the effect of inhibitory Stroop performance on ACC functional responses to personalized stressful stimuli. Follow-up analyses were conducted to examine associations between Stroop performance and stress-cue-induced activation in the *a priori* ROIs, and subjective reports of anxiety and food craving during the guided imagery stress fMRI task.

2 METHODS

2.1 Participants

Sixty-four adolescents (62.5% boys) between 14 and 17 years of age (mean=14.83, sd=.94) were recruited for fMRI scanning as part of a larger, ongoing longitudinal study of youths

who were recruited at birth and followed every 6 months thereafter (Elsey et al., 2015). The sample was of low socioeconomic status with 31.3% of mothers having not received a high-school diploma and was predominantly African American (79.7%), with a minority of Caucasian (9.4%) or other (10.9%) participants. IQ (mean=94.11, sd=13.21) was determined using the Kaufman Assessment Battery for Children composite score. Forty-four (68.8%) of the adolescents were prenatally exposed to cocaine, as determined at prenatal visits during pregnancy or delivery by mother's self-report and urine toxicology. A subset of cocaine-using mothers indicated marijuana (58%), alcohol (76%), and cigarette (70%) use, while non-cocaine-using mothers indicated only alcohol (23%) and cigarette (5%) use, but no illicit drug use over the 30-days prior to perinatal interview. Prenatal drug exposure and maternal education level were considered in all analyses as previously (Elsey et al., 2015; Hommer et al., 2013).

Childhood trauma was assessed at 7–9.5 years of age (mean=7.6 years, sd=.8) using the Childhood Trauma Questionnaire Short-Form (CTQ; mean=35.67, sd=9.94), a validated and reliable self-reported measure of past abuse and neglect (Scher et al., 2001). The CTQ has been shown to have a good-fitting higher-order factor model, which supports the presence of a broad childhood-trauma dimension assessed by the full scale (Spinhoven et al., 2014). A summary score for maltreatment was calculated by summing the scores for all 25 clinical items. Higher-trauma (>33, n=31, mean=43.45, sd=8.82) and lower-trauma (≤33, n=33, mean=28.36, sd=2.8) groups were defined by median split as previously (Elsey et al., 2015). According to normative data (Scher et al., 2001), the mean CTQ values of the higher-trauma-group is in the 90^{th} percentile and the lower-trauma group is between the 25^{th} and 50^{th} percentile for traumatic experiences. This median-split approach generated higher- and lower-trauma-exposed groups, consistent with a prior study of this sample which demonstrated stress-related ACC activation differences between trauma groups (Elsey et al., 2015). This approach may also circumvent diminished power from moderation analysis with continuous predictors and moderators (McClelland and Judd, 1993).

Inhibitory control was assessed contemporaneously with childhood trauma (mean=7.6 years, sd=.8) during visits prior to MRI scanning using a verbal Stroop Word-Color task containing two sets of stimuli (Bridgett and Mayes, 2011). The first set of stimuli consisted of three color-names printed in congruent color (e.g., the word 'red' printed in red type) and the second set consisted of three color-names printed in incongruent color type (e.g., the word 'red' printed in blue) presented on a white background. Subjects were tasked to verbally name the color of the type instead of reading the word. The current study focused on completion errors for the incongruent stimuli, which reflect prepotent response inhibition (i.e., inhibitory control). To reduce the possible effects of outliers, Stroop error scores were logarithmically transformed for subsequent analyses.

Procedures were approved by the Yale Human Investigation Committee, and written informed consent was received from the parent (with participant assent) or participant. While low socioeconomic status and prenatal drug exposure have been related to higher prevalence rates of psychopathology in epidemiological samples, use of psychotropic medication may confound responses in fMRI procedures. Hence, exclusion criteria assessed at the time of scanning for this subset of MRI participants included having significant

medical illness, use of psychotropic medication(s) that might influence autonomic responses, non-removable metal in the body, and significant discomfort with MRI due to body size or claustrophobia. No participants met criteria for any Axis-I disorder assessed with the well validated National Institute of Mental Health Diagnostic Interview Schedule for Children (NIMH DISC-IV).

2.2 Imagery Script Development

Imagery script development and fMRI scanning were conducted between ages 14–17 years (mean=14.76, sd=.90). This prospective approach better tests the moderation hypothesis and enables stronger inferences to be made regarding the relationship between inhibitory control and brain function. The individualized guided-imagery procedure has been used extensively in conjunction with fMRI to study neural responses to stress, craving (e.g., favorite-food), and neutral-relaxing cues (Elsey et al., 2015; Hommer et al., 2013; Yip et al., 2014). Prior to fMRI scanning, individually tailored scripts were generated via a standardized, structured interview using the Scene Development Questionnaires (Sinha et al., 2005) from participants' experience of stressful, appetitive, and neural-relaxing situations. For stress scripts, participants recounted stressful events and rated their distress levels on a 10-point Likert scale (1=not at all distressing; 10=most distressing), and only situations rated ≥8 were used for script development (Hommer et al., 2013). The appetitive and neutral scripts, as well as script style format, content and length are described in Supplement 1

2.3 fMRI Trials

To decrease variability in imagery ability, all participants performed a single relaxation and guided-imagery session prior to scanning. During fMRI, participants were presented with 6 individualized audiotaped scripts (two neutral-relaxing, two stressful, and two favorite-food) through headphones in a randomized, counterbalanced order. In each trial, a 1.5 min baseline period preceded a 2.5 min script presentation, and followed by a 1 min recovery period, in which participants lay quietly in the scanner. Immediately before and after each trial, participants verbally rated their subjective anxiety and food craving on a 10-point scale. To prevent any carry-over effects, each trial was followed by a 2 min progressive relaxation session, and the next trial commenced only after anxiety and craving ratings returned to baseline. The resulting fMRI data were analyzed in a block design. Pursuant to the hypothesis, the study focused on fMRI data, and anxiety and craving ratings from the stress condition.

2.4 Image Acquisition

Imaging data were acquired using a 3T Siemens Trio MRI system with a standard quadrature head coil and a T2*-sensitive gradient-recalled single shot echo-planar pulse sequence. The same functional and structural acquisition parameters were reported in previous studies using this task and sample (Elsey et al., 2015; Yip et al., 2014) and described in Supplement 1.

2.5 fMRI analysis

Functional image preprocessing, first-level analyses, and second-level analyses with random mixed-effects modeling, which derived whole-brain BOLD-signal response during the stress condition, were conducted in BioImage Suite (www.bioimagesuite.org) using the same approach as previously reported. Images were motion-corrected in SPM5 using motion-correction algorithms in BioImage Suite for three translational and three rotational directions (Friston et al., 1996). Trials with linear motion >1.5mm or rotation >2mm were excluded. All subsequent analytic steps were conducted using algorithms developed in-house for the BioImage Suite. Individual participant data were analyzed using general linear models (GLMs) on each voxel in the entire brain volume. The regressor was the time-block during imagery (2.5min) as compared with the baseline period (1.5min) for each trial. Images were temporally filtered by including drift correction in the GLM to remove the mean time course, linear trend, quadratic trend, and cubic trend for each run. The recovery period (1min) was excluded from the analysis to prevent any carryover effects from preceding imagery periods. Each trial was normalized against the baseline immediately preceding the script. The two trials of the same condition (e.g. stress scripts) were averaged and spatially smoothed with a 6mm Gaussian kernel to produce normalized beta maps in the acquired space (3.44mm×3.44mm×4mm).

Three registrations were applied to normalized beta-maps to bring data into a common reference space. First, linear regression was computed to register each participant's functional images with their corresponding 2D anatomical images. Second, linear regression was computed to register these 2D anatomical images to each participant's 3D structural image. Finally, a nonlinear registration was computed between the individual 3D image and a standard reference 3D image, the Colin27 Brain (Holmes et al., 1998). The three registrations were concatenated and applied as registration to the normalized beta-maps.

While meta-analytic research has shown high concordance in the association between ACC activation and inhibitory control across multiple fMRI studies (Cieslik et al., 2015; Laird et al., 2005; Neumann et al., 2005), significant sub-regions of the anterior rostral cingulate zone (rCZa) and posterior rostral cingulate zone (rCZp) were also specifically identified to support performance on the verbal Stroop Word-Color task similarly employed in the current study (Laird et al., 2005). While error processing continues to develop, ACC functioning in inhibitory motor control typically undergoes relatively earlier maturation and remains stable over adolescent development (Ordaz et al., 2013). Pursuant of the hypothesis, an additional ROI-specific step was applied and statistical modeling focused on these *a priori*-defined rCZa and rCZp regions during the stress condition (Figure 1). Briefly, center-of-mass Talairach coordinates within significant clusters found by previous meta-analysis (Laird et al., 2005) were entered into BioImage Suite and automatically converted to corresponding MNI coordinates (rCZa: x=4, y=44, z=19; rCZp: x=1, y=17, z=38) as previously described (Lacadie et al., 2008). Cubic ROIs (9mm×9mm×9mm) centered on these coordinates were generated (see Figure 1). ROIs were applied to individuals' beta-maps for the stress condition to extract mean parameter estimates. Extracted activation values during each condition were entered into SPSS for subsequent statistical analyses. As Type-I errors typically do not survive replication, ROIs that show convergence across multiple studies by

meta-analysis may better indicate brain regions supporting inhibitory control during the Stroop task (Lieberman and Cunningham, 2009).

2.6 Statistical Analyses

Statistical analyses were conducted using SPSS 24. Pearson and bi-serial correlations were used to determine the relationships between Trauma Group, Stroop Errors, and activation in *a-priori*-defined ROIs during stress cues. Analyses on the moderating effect of childhood trauma on the relationship between inhibitory control and brain activation during stress cues were conducted in PROCESS (Hayes, 2013) for SPSS, which has the added benefit of better handling limited sample sizes and non-normal distributions through bootstrapping. Stroop Error score, ROI activation, and Trauma Group status (higher-CTQ, lower-CTQ) were included respectively as the independent, dependent, and moderator variables. In addition to the interaction effects of Stroop Errors and Trauma Group, the statistical procedure also used simple slopes analysis to calculate the conditional effects of Stroop Errors on ROI activation in the higher- and lower-CTQ groups of the moderator. A significant moderating effect was indicated when the Trauma Group and Stroop Errors interaction reached $p \leq .05$ and the model accounted for significant variance in ROI activation ($p \leq .05$). Moderation analyses, with 5000 bootstrap resamples, were conducted and 95% confidence intervals (95%CIs) were calculated. Follow-up regression analyses were used to examine associations between *a-priori*-defined ROIs and feelings of anxiety and craving during stress-cue trials. All analyses controlled for the potential confounding effects of demographic variables of prenatal drug exposure, maternal education, IQ, age and sex.

3 RESULTS

3.1 Demographics

Demographic information on the trauma groups is displayed in Table 1. The distribution of gender, race/ethnicity, and maternal education were comparable between higher- and lower-trauma groups (all $p > .1$). Age and IQ were also equivalent between groups (all $p > .1$). Prenatal-drug exposure was not related to CTQ group ($\chi^2(3)=4.41$, $p=.22$) and all subsequent analyses controlled for this variable. Additionally, Stroop Error scores were significantly different between higher- and lower-CTQ groups ($t(47.15)=-2.5$, $p=.02$).

3.2 Correlations between Trauma Group, Stroop Errors, and Regional Activation

The results of correlation analyses are shown in Table 2. Regional activation during the stress condition was correlated between each ROI tested ($p \leq .001$). Stroop Errors were significantly correlated with Trauma Group (Pearson $r=.32$, $p=.01$) and activation during the stress condition in the rCZa within the ACC (Pearson $r=-.23$, $p=.040$). As no significant correlations were found between Stroop Error scores and rCZp activation ($p=.36$), which precludes the independent-dependent variable relationship for moderation (Baron and Kenny, 1986), subsequent analyses focused on the rCZa.

3.3 Moderation of Trauma Group and Regions of Activation by Stroop Errors

In the overall moderation model, Trauma Group, Stroop Errors, and their interaction accounted for significant variance in activation for the rCZa ($R^2=.28$, $p=.01$). A significant

Stroop-Errors-by-Trauma-Group interaction effect on rCZa activation during stress-cue exposure was found (b=−1.26, p=.02, 95%CI=−2.33, −.20). The interaction accounted for a significant proportion of variance in the rCZa activation beyond the individual variables (ΔR^2=.07, f(1,54)=5.64, p=.02). After accounting for the interaction necessary for determining significant moderation, the main effects for Trauma-Group (b=.14, p=.16, 95%CI=−.06,.34) and Stroop-Errors (b=−.18, p=.45, 95%CI=−.67,.30) were not significant. Simple slopes analysis of the conditional effects in the moderation relationship showed that Stroop Errors were significantly and inversely associated with rCZa activation in the higher-CTQ-group (b=−.83, p=.007, 95%CI=−1.40, −.25), but not in the lower-CTQ-group (b=.44, p=.31, 95%CI=−.43,1.30), as shown in Figure 2.

3.4 ACC Associations with Subjective Anxiety and Craving

Given the association differences between higher- and lower-CTQ groups, follow-up regression analyses controlled for Trauma Group. Regression results (Figure 3) demonstrated that stress-cue reactivity in the rCZa of the ACC was inversely associated with subjective anxiety at baseline (R^2=.19, b=−.44, p=.001, 95%CI=−4.20, −1.09) and after stress-cue presentation (R^2=.14, b=−.34, p=.01, 95%CI=−3.82,−.44). No associations were found between rCZa activation and food craving at baseline or after stress-cue presentation (all p>.05). Additionally, Stroop-Errors were directly associated with anxiety at baseline (R^2=.09, b=.27, p=.048, 95%CI=.02, 5.8) and trended towards significant association with anxiety after stress-cue presentation (R^2=.09, b=.25, p=.067, 95%CI=−.21, 5.9). Skewness tests showed that data for rCZa activity (.59, se=.28), and subjective anxiety before (.12, se=.29) and after (.07, se=.07) stress condition trials were within accepted limits (−1 to 1). Hence, greater inhibitory control and activation in the rostral cingulate zone to stress cues are related to lower anxiety, regardless of levels of childhood trauma.

4. DISCUSSION

This is the first study to investigate the moderating effect of childhood trauma on the relationship between childhood inhibitory control and brain reactivity to stress during adolescence. Given the clinical importance of inhibitory control circuits on anxiety, this study focused on *a-priori*-defined ROIs in the ACC that were previously associated with inhibitory Stroop Color-Word task performance (Laird et al., 2005). Study findings suggest that poorer inhibitory control is related to higher levels of childhood trauma and reduced stress-cue reactivity in the rCZa of the cingulate. Within this ROI, a significant moderation effect of childhood trauma was found such that poorer inhibitory control was related to lower rCZa activation only among the higher-trauma group. Furthermore, regardless of the level of childhood trauma, stress-cue-induced activation of the rCZa was inversely associated with trait-like anxiety, as indicated by anxiety ratings before and after stress-cue presentation. While controlling for childhood trauma, inhibitory control was also associated with anxiety at baseline, and trended towards significant association with anxiety after stress-cue-presentation.

The current findings indicate that higher-trauma is correlated with poorer inhibitory control on the Stroop in childhood, which is consistent with recent findings regarding performance

on other inhibitory-control tasks in early trauma-exposed groups (Cowell et al., 2015; Marshall et al., 2016). Owing to the rapid creation and modification of neuronal connections in childhood, early maltreatment and other traumatic experiences may be particularly detrimental and may produce cascading effects on later development of neural circuits supporting higher-order self-regulatory processes (Cowell et al., 2015). Specifically, during distress which engages self-regulatory mechanisms (Li and Sinha, 2008), the current findings indicate that inhibitory control deficiencies during childhood are related to hypo-activation in the rCZa. This is in parallel with evidence that greater activation in the ACC relates to better inhibitory control in previous studies (Li et al., 2006). Taken in light of the heightened stress responsivity commonly observed in trauma-exposed adolescents (Marusak et al., 2015), these data support a link (discussed below) between variability in inhibitory control among youth with varying levels of trauma exposure and adolescent ACC recruitment during stress exposure and processing.

Adverse situations may be more challenging for adolescents with early higher-trauma exposure, particularly in instances requiring effortful control and stress regulation (Ansell et al., 2012). The primary finding of the current study demonstrated that childhood trauma moderated the relationship between inhibitory control and stress-induced ACC activation. Poor inhibitory control at age 7–9.5 years was more strongly associated with lower stress-induced activation at age 14–17 years in the *a-priori*-defined rCZa among adolescents with greater childhood trauma. These results suggest that among those with childhood-trauma exposure, individuals with poor inhibitory control that emerged earlier in development may have difficulty recruiting ACC-dependent self-regulatory mechanisms in response to stressful situations. This possibility is congruent with emerging evidence that trauma appears related to failure to sufficiently engage anterior/rostral-ACC and associated inhibitory control regions for autonomic regulation, which may explain in part the elevated stress sensitivity among trauma-exposed adolescents (Marusak et al., 2015). Exposure to childhood physical abuse has been related to smaller prefrontal cortical and ACC gray-matter volumes, while subsequent elevated stress hormones in childhood may have long-lasting effects on development of frontal cortical regions that facilitate self-control and affect regulation and heighten stress responsiveness (Blair, 2010; Heim and Nemeroff, 2001; Tomoda et al., 2009). Additionally, impairments to cognitive development may appear as early as 5–12 years of age in trauma-exposed children (Bucker et al., 2012). Together, data suggest inhibitory control deficiencies in childhood may portend protracted development in ACC-mediated stress-regulation among trauma-exposed youth.

The moderation analysis focused on the associative strength of inhibitory control and rCZa activation during stress between higher- and lower-trauma groups, which allowed us to explicate the conditional effect of inhibitory control on rCZa activation within each group. As moderation does not assume a correlation between independent (inhibitory control) and moderator (childhood trauma) variables, the direction and magnitude of their individual associations with rCZa activation may differ (Baron and Kenny, 1986). Additionally, the lack of correlation between childhood trauma and rCZa activation may be attributed to differences in the rCZa brain region hypothesized to be associated with inhibitory control and affect regulation, and ACC regions shown by Elsey and colleagues (2015) to be associated with childhood trauma. The lack of correlation also precluded childhood trauma

from consideration as the independent variable in the model, which supported the use of childhood trauma as a moderator and partly addressed the limitations of contemporaneous assessments of childhood trauma and inhibitory control. While the direct relationship between childhood trauma and adolescent rCZa activation was not supported in the moderation analysis, the model suggested that childhood inhibitory control contributes to adolescent rCZa activation that differed between the higher- and lower-childhood-trauma groups. Together, the current evidence suggests that childhood inhibitory control may be an early indicator identifying trauma-exposed adolescents who may subsequently develop difficulties in ACC-dependent self-regulatory mechanisms during distress. However, this hypothesis needs additional testing. In light of the importance of inhibitory control regulating stress reactivity, future prevention research among high-risk trauma-exposed individuals may explore the effects of inhibitory-control training on stress management and functional brain reactivity to distressing signals.

Individuals with PTSD, compared to trauma-exposed and non-trauma-exposed control participants, have demonstrated lower rostral ACC activation to stressful emotional stimuli, which may be required to regulate responses to affective stimuli, and rostral-ACC activation was negatively correlated with PTSD symptom severity (Offringa et al., 2013; Patel et al., 2012; Shin et al., 2001). Comparisons between PTSD and control groups demonstrated that reductions in activation of several frontal cortical regions were greater between PTSD and non-trauma-exposed subjects,than between PTSD and trauma-exposed subjects, which suggests trauma-symptom-severity may diminish top-down regulation (Patel et al., 2012). Though PTSD was not directly examined herein, these studies suggest that trauma-related symptom severity may differentially influence inhibition-associated ACC development and the ACC's ability to regulate stress. In parallel, PTSD and trauma-exposed individuals have demonstrated reduced gray-matter volume in rostral-ACC compared to non-trauma-exposed control subjects (Eckart et al., 2011). However, further research is necessary to elucidate the relationship between PTSD and trauma symptoms, inhibition, and ACC-related stress regulation.

Within the ACC, the anterior/rostral region is involved in processing affective information, including emotional salience, motivation, and regulation of affective responses, and has been linked to psychiatric symptoms of anxiety and phobias (Bush et al., 2000; Devinsky et al., 1995; Drevets and Raichle, 1998; Vogt et al., 1992; Whalen et al., 1998). Consistent with this, study findings indicate a significant association between greater rCZa activation to stressful stimuli and lower feelings of anxiety in adolescents. Previous reports by Drevets and Raichle (1998) have indicated increased activation of the anterior/rostral-ACC subdivision to emotional counting Stroop tasks, though the relationship between ACC reactivity and subsequent subjective responses to affective stimuli was not directly addressed. Extending previous research, the significant relationship between greater rCZa stress reactivity and reduced subjective anxiety supports the hypothesis that regulation of stress-induced anxiety may rely in part on adequate engagement of ACC functioning. In light of evidence that greater inhibitory control is also associated with reduced subjective anxiety, this pattern may represent a mechanism for potential dampening of anxiety in those individuals with varying degrees of inhibitory control, who may be identifiable by childhood for early, targeted prevention. Future studies may directly examine whether ACC activation

may mediate the indirect relationship between inhibitory control and anxiety, particularly with regards to differences between trauma-exposed and non-trauma-exposed youth.

Considering evidence that individuals with substance dependence demonstrated blunted recruitment of anterior/rostral ACC regions associated with stress and impulse control (Beauregard et al., 2001; Sinha et al., 2005), Li and Sinha (2008) proposed that self-regulation under stressful situations that induce motivational states may require an ACC-mediated braking mechanism to prevent these experiences from leading to anxiety and craving. Though speculative, failure to sufficiently engage ACC control regions may also in part explain data linking childhood abuse to maladaptive behaviors involving obesity and stress-eating among those with poor control (Brown et al., 2017). This speculation is supported by associations between PTSD and both addictive disorders and reduced stress-related ACC reactivity (Shin et al., 2001; Sinha et al., 2005). However, follow-up studies on the relationship between inhibitory control, childhood trauma, and ACC reactivity to stress should be conducted in patients with behavioral and substance addictions to confirm a potential moderating role of inhibitory control in addiction psychopathology. Results may potentially further elucidate the mechanism underlying poor addiction treatment outcomes and high rates of relapse in those with childhood trauma (Hyman et al., 2008).

Several study limitations should be considered. The childhood-trauma groups were defined by a median split of summary self-reported CTQ scores and may not reflect the variety of traumatizing experiences and their severities. While they were not included in the current study due to concerns of multiple comparisons, further examinations of childhood-trauma impact may be supplemented by testing different types of adverse childhood experiences and reports from other observers in future studies. The single time-point assessments of childhood trauma and inhibitory control, respectively, make it difficult to identify the independent and moderating variables and limit causal inferences. However, the CTQ queried past experiences of trauma, while the Stroop task tapped inhibitory control contemporaneous to the assessment visit. Measures of maternal psychopathology were not collected, but maternal education was controlled for in all analyses. Furthermore, the non-significant associations between trauma group and ACC stress reactivity precluded childhood trauma as the independent variable in the moderation model. While multiple participants were prenatally exposed to drugs, it and several other demographic covariates were included in analyses to control for their potential effects. While potential psychopathology was assessed as exclusion criteria with the well validated NIMH DISC-IV, additional assessments of psychopathology and personality were not obtained. Future studies using other instruments may be important. Furthermore, previous research on neural responses to personalized stress cues did not reveal differences between adolescents with and without prenatal cocaine exposure (Yip et al., 2014). It is still important for future studies to examine these covariates within larger samples. Additionally, analyses were specific to Stroop-Word-Color-task-associated ROIs defined *a priori* in the ACC. Additional regions not in our hypotheses may relate to the interaction between childhood trauma and inhibitory control during stress. Finally, our sample was disadvantaged and largely of racial/ethnic minority status. The extent to which the findings may generalize to other groups warrants investigation.

5. CONCLUSIONS

Despite these limitations, this is the first study to demonstrate the moderating role of childhood trauma on the effect of inhibitory control on ACC activation to stressful stimuli. Furthermore, it examined these effects in ACC regions defined *a priori* by meta-analytic findings across multiple studies to be associated with inhibitory control. This study utilized a prospective design that modeled Stroop and CTQ scores at younger ages preceding fMRI assessment, which may allow for stronger inferences regarding childhood-trauma effects on the relationship between inhibitory control and ACC-dependent stress regulation. Higher-childhood-trauma exposure may facilitate neurodevelopmental changes that impede recruitment of ACC, particularly rostral/anterior regions linked to affect processing and regulation, during distressing situations among adolescents with poor inhibitory control. Childhood trauma may further burden the functioning of self-regulatory neurocircuitry during distress, leading to subsequent feelings of anxiety. These findings have implications for understanding the developmental pathophysiology of addiction and the mechanisms contributing to addictive behaviors among trauma-exposed individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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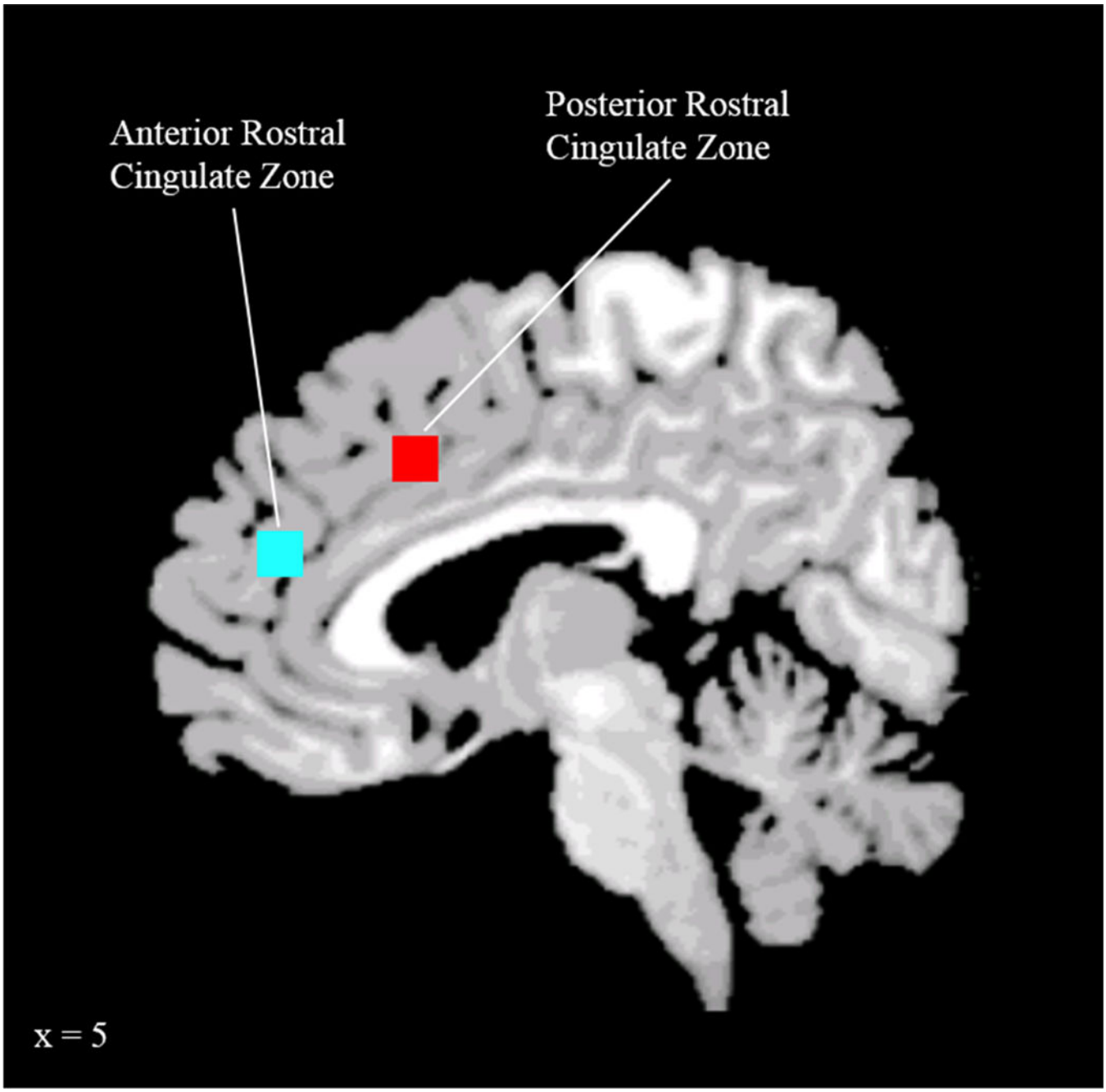

Figure 1.

A-priori-defined regions of interest of the anterior (x=4, y=44, z=19) and posterior cingulate (x=1, y=17, z=38) zones within the anterior cingulate cortex centered on MNI coordinates. Identified in meta-analysis to be associated with verbal Stroop Color-Word performance (Laird et al., 2005). Sagittal x=5.

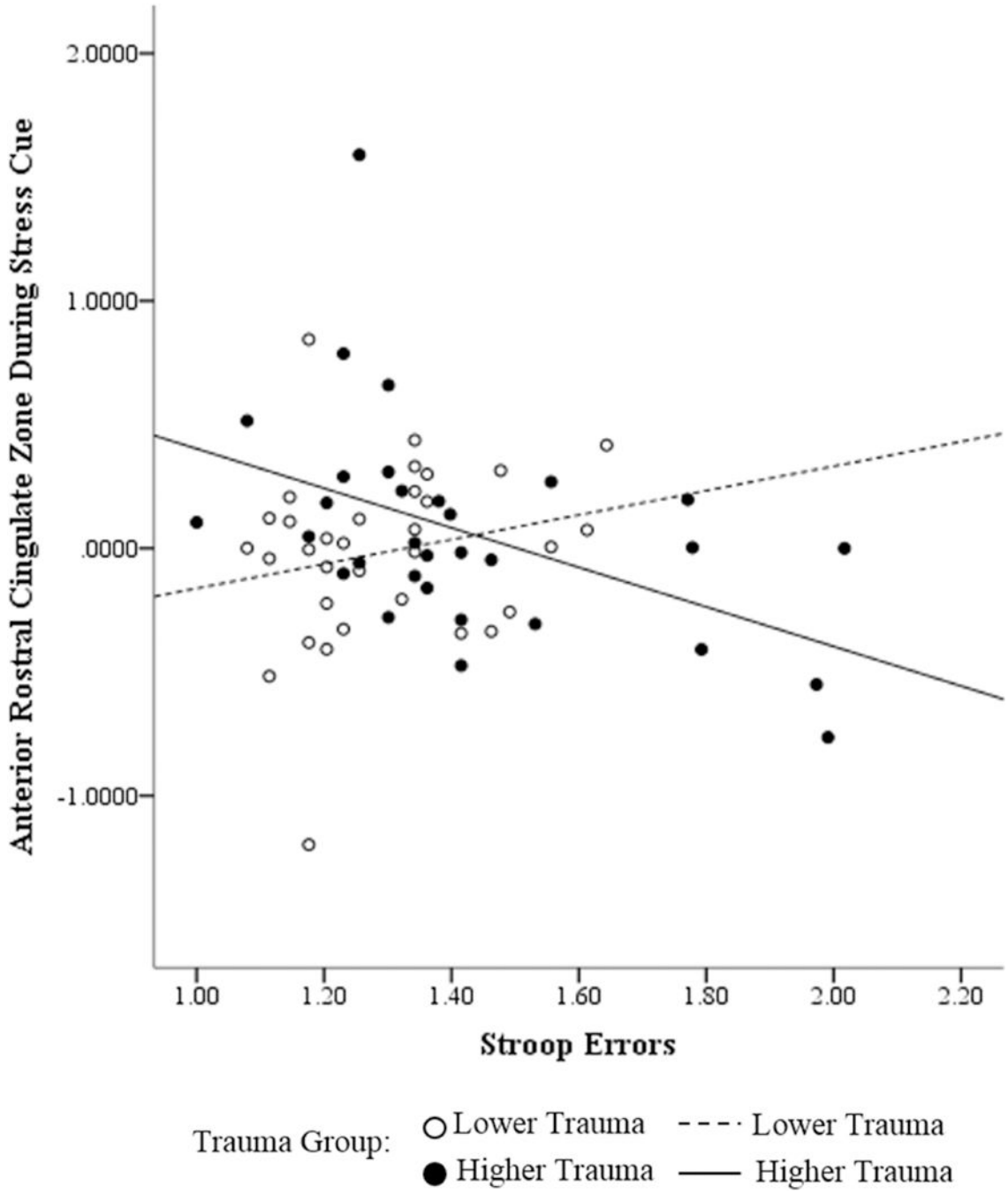

Figure 2.

Stroop error responses are associated with anterior rostral cingulate zone (rCZa) activation as a function of childhood trauma. Significant overall model and interaction term indicate that childhood trauma is a significant moderator.

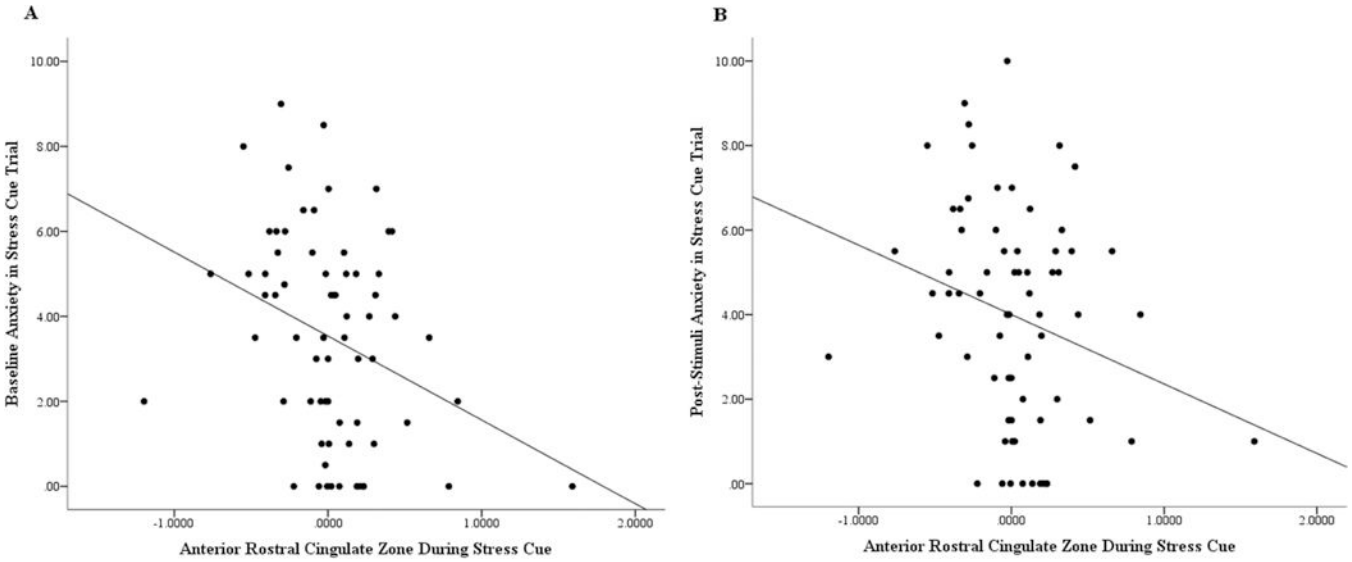

Figure 3.

(A) Baseline anxiety and (B) Post-Stimuli anxiety in stress cue trial as a function of anterior rostral cingulate zone (rCZa) activation to stress. Greater rCZa activation to stress cues was associated with lower trait-like anxiety.

Table 1.

Trauma Group Demographic Information and Group Comparison

	Low CTQ (SD)	High CTQ (SD)	t/x2
Age at MRI scanning (Years)	14.7 (.81)	14.97 (1.05)	−1.16
Gender (Male/Female)	19/14	21/10	.71
Race (AA:C:O)	25:03:05	25:04:02	1.24
Stroop Error Score	1.29 (.15)	1.43 (.26)	−2.5*
Prenatal Drug Exposure (Cn:CnS:S:NS)	4:15:4:10	4:21:1:5	4.41
Maternal Education (High-School Diploma)	22/11	22/9	.14
KABC mental processing	92.84 (15.13)	95.46 (10.91)	−.79

Abbreviations: Childhood Trauma Questionnaire (CTQ), African-American (AA), Caucasian (C), Other (O), Kaufman assessment battery for children (KABC); Cocaine only (Cn), Cocaine and other substances (CnS), Other substances only (S), No substance use (NC).

*p≤.05

Table 2.

Correlations Between Stroop Error, Trauma Group and ROI Activation During Stress Condition

Variables	1	2	3
1. Stroop Error			
2. Trauma Group	.32**		
3. Anterior Rostral Cingulate Zone	−.23*	.14	
4. Posterior Rostral Cingulate Zone	−.05	.21	.76***

* p≤.05

** p≤.01

*** p≤.001