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Neural functional and structural correlates of childhood maltreatment in women with intimate-partner violence-related posttraumatic stress disorder

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Abstract

Childhood maltreatment (CM) is a strong risk factor for development of posttraumatic stress disorder (PTSD) upon adult exposure to extreme adverse events. However, the neural underpinnings of this relationship are not well understood. Here, we test the hypothesis that severity of CM history is positively correlated with emotion-processing limbic and prefrontal brain activation/connectivity and negatively correlated with prefrontal gray matter volumes in women with PTSD due to intimate-partner violence (IPV-PTSD). Thirty-three women with IPV-PTSD underwent structural and functional magnetic resonance imaging while completing a facial emotion processing task. Multivariate regressions examined the relationship of CM to patterns of activation, connectivity, and gray matter volumes. CM severity was: a) positively correlated with ventral ACC activation while processing angry faces; b) negatively correlated with dorsal ACC and insula activation while processing fear and angry faces, arising from positive correlations with the shape-matching baseline; c) positively correlated with limbic-prefrontal connectivity while processing fear faces but negatively correlated with amygdalo-insular connectivity while processing fear and angry; and d) negatively correlated with prefrontal gray matter volumes. These results suggest CM exposure may account for variability in limbic/prefrontal brain function and prefrontal structure in adulthood PTSD and offer one potential mechanism through which CM confers risk to future development of PTSD.

Keywords

early life stress; anxiety; imaging; trauma; abuse; neglect

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1. Introduction

Intimate-partner violence (IPV) is a leading cause of posttraumatic stress disorder (PTSD) among adult women (Pico-Alfonso, 2005). PTSD is an anxiety disorder which may develop following a traumatic experience and is characterized by reexperiencing of the traumatic event, avoidance of trauma-related people/places/stimuli or avoidance of discussing or thinking about the trauma, emotional numbing or restricted range of affect, and symptoms of hyperarousal (American Psychiatric Association, 2000). Prior PTSD neuroimaging studies have identified structural and emotion-processing functional differences in affective, limbic/paralimbic, and prefrontal brain structures such as the amygdala, insula, anterior cingulate (ACC), and prefrontal cortex (PFC) (Liberzon and Sripada, 2008). The amygdala, a core affective brain structure consistently implicated in the pathophysiology of PTSD (Rauch et al., 2006), is comprised of gray matter nuclei located within the medial temporal lobe which processes the emotional/motivational salience of an exteroceptive stimulus (Costafreda et al., 2008). Its intact functioning seems to be particularly crucial for the generation of fear responses (Feinstein et al., 2011) and acquisition of conditioned fear (Duvarci et al., 2011). The insula is a cortical structure buried within the Sylvian fissure behind the superior temporal lobe which is crucial for the representation and processing of interoceptive (i.e. internal bodily) signals thought to form the basis for subjective emotional states (Craig, 2009). The ACC and associated medial prefrontal cortices (mPFC) are frontal structures involved in higher-order constructs such as self-referential processing (Blair et al., 2008), emotional/cognitive context (Rougemont-Bucking et al., 2010), and social cognition (Amodio and Frith, 2006) while the lateral prefrontal cortices are implicated in more deliberate or effortful mental states such as emotion regulation (Campbell-Sills et al., 2011), attentional manipulation (Sharp et al., 2010), or executive function (Ball et al., 2011). These higher-order frontal structures are often implicated in the inhibition of limbic activity to emotional stimuli (Schulz et al., 2009) and also have shown consistent abnormalities in PTSD neuroimaging studies (Francati et al., 2007).

Prior PTSD imaging studies have generally observed decreased grey matter volumes and increased reactivity of the amygdala and insula to threat-related emotional cues such as fearful or angry faces (Liberzon and Garfinkel, 2009; Woodward et al., 2009), although decreased amygdala activation and null findings for amygdalar structural differences have been observed as well (Etkin and Wager, 2007; Woon and Hedges, 2008). This increased reactivity is thought to underlie the hypersensitivity to threatening cues and dysregulated fear responses which are characteristic of the disorder (Lanius et al., 2006). Studies have also observed both decreased ACC/prefrontal structural volumes (Rogers et al., 2009) as well as no volumetric differences (Landre et al., 2010), while functional studies have observed both increased (Bryant et al., 2008) and decreased (Shin et al., 2005; Kim et al., 2008) ACC/medial PFC responses to emotional stimuli in PTSD. These functional differences have often been interpreted as either compensatory engagement to limbic hyperactivity (Bryant et al., 2008) or as deficient inhibition of limbic reactivity (Shin et al., 2005), respectively (due to the crucial role of these structures in downregulating amygdalar responses (Quirk et al., 2003)). Furthermore, the directionality of these ACC/mPFC group differences seems to depend upon several factors such as location in the dorsal “cognitive” subdivision or the more ventral “emotional” subdivision (Morey et al., 2008) as well as level of autonomic arousal (Felmingham et al., 2009) and presence of dissociative or depressive symptoms (Kemp et al., 2007; Felmingham et al., 2008). Furthermore, abnormalities of functional connectivity among and within limbic and prefrontal structures in PTSD have also shown variability. One study observed increased functional connectivity between the insula and ACC during emotional threat processing (Fonzo et al., 2010) while another observed decreased connectivity during symptom provocation (Lanius et al., 2004), while findings for decreased amygalar-insular connectivity have been more homogenous

(Simmons et al., 2008; Fonzo et al., 2010) . Findings for abnormalities of amygdala-ACC connectivity have also varied, sometimes as a function of task conditions (Gilboa et al., 2004; St Jacques et al., 2011). In aggregate, there is a great deal of variability in functional and structural abnormalities associated with PTSD which may arise from clinical and demographic characteristics.

Little is known concerning characteristics of brain structure and function present before the traumatic experience that may influence or predispose individuals to the development of PTSD and/or promote variability in brain structure/function following the traumatic experience. Research indicates childhood maltreatment (CM) experiences, broadly defined as the intentional or unintentional commission of acts or withholding of resources by caregivers that adversely influence the health, growth, or adaptation of the child, convey an increased risk for the onset of anxiety or traumatic stress disorders in adulthood (Lang et al., 2008; Zlotnick et al., 2008), but the neural mechanism(s) underlying this predisposition are not well understood. Given findings that history of CM is associated in adulthood with structure and function of PTSD-relevant brain regions (e.g., amygdala, ACC, and PFC; Cohen et al., 2006; Williams et al., 2009; Croy et al., 2010; Hanson et al., 2010) as well as the substantial heterogeneity of brain responses observed in adulthood PTSD (Lanius et al., 2006), the evidence suggests risk factors such as preexisting CM history may influence brain structure and function in a way that contributes to development or severity of PTSD and/or variability in subsequent neural structure/function following exposure to trauma in adulthood. Although neural substrates affected by CM have been studied in the context of CM-related PTSD (Bremner et al., 2005) and in non-clinical populations (Mueller et al., 2010), characterizing the neural correlates of a developmental risk factor for PTSD following trauma exposure in adulthood may provide useful information for hypothesizing potential neural mechanisms underlying this relationship.

The primary purpose of this investigation was to examine how CM history relates to patterns of brain structure and emotion-processing function in women with IPV-PTSD. Prior studies have shown that both CM and PTSD are associated with reduced prefrontal structural volumes (Cohen et al., 2006; Karl et al., 2006; Hanson et al., 2010), hyperactivation of the amygdala, insula, ACC, and prefrontal cortex (PFC) (Williams et al., 2009; Croy et al., 2010; Fonzo et al., 2010; Mueller et al., 2010), and increased frontal-amygdalar connectivity (Gilboa et al., 2004; Taylor et al., 2006; St. Jacques et al., 2010). Therefore, we chose a facial emotion processing task which robustly engages these neural substrates as our experimental paradigm of interest (Hariri et al., 2005). Prior evidence indicates that CM influences behavioral responses to angry and fearful faces, with trend-level effects for happy faces as well (Masten et al., 2008; Gibb et al., 2009). Thus, neural responses to these three emotional expressions were examined. Consistent with convergent findings for increased limbic/prefrontal activation and connectivity and reductions in prefrontal structural volumes in both PTSD (Karl et al., 2006; Bryant et al., 2008; St Jacques et al., 2011) and maltreated samples (Cohen et al., 2006; Williams et al., 2009; Hanson et al., 2010; Mueller et al., 2010), we expected severity of CM to be negatively correlated with prefrontal gray matter volumes and positively correlated with amygdala, insula, ACC, and PFC activation and frontal-amygdalar connectivity in all three emotional face processing conditions.

2. Methods

2.1 Subjects

Thirty-three women (n=33) with DSM-IV PTSD as a result of exposure to IPV were recruited through community advertisement to participate in functional magnetic resonance imaging (fMRI; Table S1 in supplement). IPV trauma was operationalized as physical and/or sexual abuse by a romantic partner occurring within 5 years of study recruitment and

ending at least 1 month prior to enrollment. All women in the IPV-PTSD group met full DSM-IV criteria for PTSD, verified through the Clinician-Administered PTSD Scale (CAPS) (Blake et al., 1995) and the Structured Clinical Interview for Diagnosis-DSM IV (SCID-IV) (First et al., 1998) administered by a doctoral-level clinical psychologist in an outpatient treatment center. Exclusion criteria included: 1) substance abuse in the past year; 2) history of greater than 2 years of alcohol abuse; 3) use of psychotropic medications in the past 4 weeks (or fluoxetine in the past 6 weeks); and 4) irremovable ferromagnetic bodily material, pregnancy, claustrophobia, bipolar disorder, or schizophrenia. IPV-PTSD subjects with comorbid depressive/anxiety disorders were included as long as PTSD was judged to be the clinically predominant disorder. After complete description of the study to subjects, written informed consent was obtained. The study protocol was approved by the UCSD Human Research Protections Program and the VA San Diego Healthcare System Research and Development Office and is in compliance with the guidelines laid down in the Declaration of Helsinki (Anonymous, 1968).

2.2 Self-report maltreatment/symptom measures

The total score from the 28-item Short Form version of the Childhood Trauma Questionnaire (CTQ-SF) (Bernstein et al., 2003) was used to assess extent of CM exposure. This measure encompasses 25 items rated on a 5 point Likert scale (1= “Never true”, 5 = “Very often true”) that assesses the subscale domains of emotional abuse, emotional neglect, physical abuse, physical neglect, and sexual abuse. A total score is calculated by summing the totals for each subscale. The CTQ has been demonstrated to have good test-retest reliability, high internal reliability, good convergent validity with clinician-rated measures of childhood maltreatment, and display measurement equivalence across gender and ethnic groups (Bernstein et al., 1994; Thombs et al., 2007). Clinical variables of no interest were assessed to control for potential confounding effects. The Beck Depression Inventory-II (BDI) (Beck et al., 1961) was used to assess current depressive symptoms. Chronicity of IPV trauma was quantified using the self-reported number of years of exposure to IPV within the most recent abusive relationship. PTSD symptom severity was quantified using the total score from the CAPS.

2.3 Task

Participants completed a modified version of the Emotion Face Assessment Task (Hariri et al., 2005; Paulus et al., 2005). For each 5-second trial, subjects were presented with a target face on the top of the screen and instructed to match its facial expression to one of two faces presented below on the same screen through key-press of a button box. A block consisted of six consecutive trials wherein the target face was angry, happy, or fearful. A sensorimotor control condition, in which a target shape was presented and subjects were told to pick the matching shape, was also presented in similar format. Each target condition was presented in three blocks of six trials each in pseudorandomized order, with an eight-second fixation crossed presented between each block and at the beginning and end of the task. The task lasted 512 seconds, and behavioral data was recorded for each trial.

2.4 Image acquisition

See supplemental methods.

2.5 Activation preprocessing/individual-level analysis

See supplemental methods.

2.6 Functional connectivity preprocessing/individual-level analyses

See supplemental methods.

2.7 Activation/connectivity task effect analyses

Brain regions significantly activated/deactivated by each of the task contrasts or displaying significant positive/negative task-evoked connectivity with seed regions were identified using a voxelwise one-sample t-test of percent signal changes (PSCs) and psychophysiological interaction (PPI) Fisher-Z transformed correlation coefficients (rFzs) against the null hypothesis, respectively. In addition to an exploratory whole-brain (WB) analysis, voxelwise analyses constrained within *a-priori* region of interests (ROIs) were conducted on limbic brain regions previously implicated in studies of PTSD and CM: bilateral insula, bilateral amygdala, and ACC. Boundaries of these ROIs were based upon both anatomical criteria (see supplementary methods) and standardized locations taken from the Talairach atlas (Talairach and Tournoux, 1998). A threshold adjustment based upon Monte-Carlo simulations (using AFNI's program AlphaSim) was used to guard against false positives in both the WB and ROI analyses. *A-priori* voxelwise probability threshold of $p < 0.05$ with a 4mm search radius and cluster size of 320 μl (5 contiguous voxels) for the amygdala, 960 μl (15 contiguous voxels) for the ACC and insula, and 3968 μl (62 contiguous voxels) for the WB analysis resulted in *a-posteriori* probability of $p < 0.05$ in each constrained region. Average PSCs or rFzs were extracted from areas of significant association and subjected to further analysis in SPSS 15.0 for confirmation of significance.

2.8 Optimized voxel-based morphometry

See supplemental methods.

2.9 Robust regression of individual activation/connectivity/GM values

To identify activation/connectivity/GM volumes (GMVs) associated with CM in each contrast, whole-brain PSC/rFz/GMV data were analyzed using a “robust” multivariate linear regression implemented within the statistical package R (Huber, 1964; Venables and Ripley, 2002; R Development Core Team, 2011). Regression models were fit to group-level voxelwise GMVs and PSCs/rFzs for each of the three face conditions and/or seed regions. The model explored the contribution of CM to the post-traumatic brain state by simultaneously regressing voxelwise PSCs/rFzs/GMVs on CM (total CTQ score) as well as the following covariates of no interest to control for potential confounding effects: depression (BDI-II total score), IPV trauma chronicity (number of years of IPV exposure), and PTSD symptom severity (CAPS total score). For the VBM analysis, age was also added as a nuisance variable due to the well-characterized relationships between age and GMV (Grieve et al., 2011). CM effects were thresholded at $p < 0.05$ and only clusters meeting the minimum spatial extent to maintain the α level at 0.05 in each search region were considered significant. To correct for multiple comparisons and further reduce likelihood of Type-I error, we required correlations of CTQ total scores and post-hoc extracted activation estimates in significant clusters to meet a Bonferonni corrected p-value of $p < 0.017$ (0.05 divided by 3 task contrasts), and we required correlations of CTQ total scores and post-hoc extracted connectivity estimates in significant clusters to meet a Bonferonni corrected p-value of 0.05 divided by the number of seed regions examined in each contrast.

3. Results

3.1 Sample demographics/comorbidity

All of the participants met full criteria for PTSD due to IPV according to DSM-IV criteria. Participants mean age was 39.27 years (*sd* = 8.46, range = 23-56), and the mean number of years of education was 13.58 (*sd* = 1.95, range = 10-18). The mean number of years of exposure to IPV was 5.98 (*sd* = 5.70, range = 0.5-27). Although we required IPV-PTSD to be the predominant clinical disorder, slightly over half of the participants (18 of 33) met diagnostic criteria for current major depressive disorder, while 9 of 33 met current criteria

for panic disorder and 13 of 33 met current criteria for generalized anxiety disorder[1]. These rates of comorbidity are consistent with those observed in other PTSD samples (Stein and Kennedy, 2001; Kessler et al., 2005).

3.2 Self-report and symptom severity measures

The mean CAPS total score was 80.45 (*sd* = 17.9, range = 50-117), and the mean CTQ total score was 59.12 (*sd* = 23.23, range = 25-111). Across all five subscales of the CTQ, the participants reported on average moderate levels of maltreatment which ranged from none (subscale score of 5-9, depending upon the particular subscale) to extreme severity (greater than 13-18, depending upon the particular subscale) (Bernstein and Fink, 1998). The mean BDI-II total score was a 21.69 (*sd* = 9.47, range = 2-41), indicating on average moderate severity of depressive symptoms which ranged from minimal to severe (Beck et al., 1996). None of the factors entered into the regression model were significantly correlated (all *p*'s greater than 0.05) (Table S1 in supplement).

3.3 Behavioral data

See supplemental results.

3.4 Functional activation

3.4.1 Angry vs. shapes contrast

3.4.1.1 Task effect: Analysis constrained to a limbic ROI mask revealed significant activation of the bilateral amygdala and the left posterior insula. A WB analysis demonstrated significant activation of the bilateral lingual gyri, fusiform gyri, declive, parahippocampal gyri, middle occipital gyri, superior/middle temporal gyri, and middle frontal gyri (dorsolateral PFC) (Table S3 in supplement).

3.4.1.2 Correlations with childhood maltreatment: A multivariate regression constrained within a limbic ROI mask revealed CTQ total score was positively correlated with a cluster of activation in the ventral ACC (Figure 1) and negatively correlated with activation in the left middle insula and the right dorsal ACC. Post-hoc extraction estimates within each task condition (angry and shape-matching) revealed the positive correlation in the ventral ACC was due to a positive correlation between CTQ total score and activation during the angry (Spearman's rho = 0.499, $p = 0.003$) but not shape-matching condition (correlation non-significant), while the negative correlations in the left middle insula and dorsal ACC were due to significant or trend-level positive correlations between CTQ total score and activation during the shape-matching condition (left middle insula: Spearman's rho = 0.319, $p = 0.07$; dorsal ACC: Spearman's rho = 0.431, $p = 0.012$) but no relationship during matching of angry faces (correlations nonsignificant). A WB analysis also identified activation in the dorsal ACC extending into the dorsal medial frontal gyri that was negatively correlated with CTQ total score. Post-hoc extractions revealed this effect was also due to a positive correlation between CTQ total score and activation during the shape-matching condition (Spearman's rho = 0.457, $p = 0.007$) but no relationship during the angry face matching condition (correlation nonsignificant) (Table 1).

3.4.2 Fear vs. shapes contrast

3.4.2.1 Task effect: Analysis constrained to a limbic ROI mask revealed significant activation of the bilateral amygdala, bilateral anterior insula, and left posterior insula. A WB analysis revealed significant activation of the bilateral amygdala, globus pallidus/putamen,

[1]See Table S1 in supplemental materials.

caudate, thalamus, declive, culmen, lingual gyri, fusiform gyri, parahippocampal gyri, middle occipital gyri, superior/middle temporal gyri, posterior insula, posterior cingulate, precuneus, middle frontal gyri (dorsolateral PFC), and dorsal medial frontal gyri (Table S4 in supplement).

3.4.2.2 Correlations with childhood maltreatment: A voxelwise multivariate regression constrained to a limbic ROI mask revealed CTQ total score was negatively correlated with activation in the right anterior insula and the right dorsal ACC. Post-hoc extraction estimates within each task condition (fear and shape-matching) revealed the negative correlations in the right anterior insula and dorsal ACC were both due to significant or trend-level positive correlation between CTQ total score and activation during the shape-matching condition (right anterior insula: Spearman's rho = 0.306, $p = 0.083$; dorsal ACC: Spearman's rho = 0.424, $p = 0.014$) but no relationship during the fearful face matching condition (correlations nonsignificant). A WB analysis identified a large cluster spanning the dorsal ACC and dorsal medial/middle frontal gyri in which activation was also negatively correlated with CTQ total score. Post-hoc extractions within each condition revealed this effect was also due to a positive correlation between CTQ total score and activation within the shape-matching condition (Spearman's rho = 0.590, $p < 0.001$) but no correlation with activation during the fearful face condition (correlation nonsignificant) (Table 2).

3.4.3 Happy vs. shapes contrast

3.4.3.1 Task effect: Analysis constrained to a limbic ROI mask revealed significant activation of the bilateral amygdala and bilateral posterior insula. A WB analysis revealed significant activation of the bilateral amygdala, globus pallidus/putamen, caudate, thalamus, declive, culmen, lingual gyri, fusiform gyri, parahippocampal gyri, middle occipital gyri, superior/middle temporal gyri, posterior cingulate, precuneus, and right middle frontal gyrus (dorsolateral PFC) and significant deactivation of the bilateral inferior parietal lobule (Table S5 in supplement).

3.4.3.2 Correlations with childhood maltreatment: Both limbic-ROI constrained and WB analyses revealed no significant clusters of activation that were correlated with CTQ total score for this contrast.

3.5 Psychophysiological Interactions

Since there were no significant relationships between activation for the happy vs. shapes contrast and CTQ total scores, psychophysiological interactions and their relationships with childhood maltreatment were examined only for the angry vs. shapes and fear vs. shapes contrasts. Clusters in limbic and prefrontal regions that were significantly activated by the task contrast were used as seed regions. We examined connectivity in 5 seed regions for the angry vs. shapes contrast; thus, the *a-priori* threshold for correlations of extracted connectivity estimates and CTQ total scores was set at $p < 0.01$. In the fear vs. shapes contrast, we examined connectivity in 7 seed regions; thus, the *a-priori* threshold for correlations between extracted connectivity estimates and CTQ total scores was set at $p < 0.007$.

3.5.1 Angry vs. shapes contrast

3.5.1.1 Task effects: See supplemental results and Table S6.

3.5.1.2 Correlations with childhood maltreatment: Multivariate regressions revealed no significant correlations of CTQ total score with right amygdala task-evoked connectivity. Connectivity between the left posterior insula task effect seed and a cluster in the right

amygdala was negatively correlated with CTQ total score. Connectivity between the left amygdala task effect seed and a cluster in the left middle insula was also negatively correlated with CTQ total scores. Connectivity between the left middle frontal gyrus task effect seed and two clusters spanning the bilateral culmen, declive, fusiform gyri, lingual gyri, and parahippocampal gyri were positively correlated with CTQ total scores. Connectivity between the right middle frontal gyrus task effect seed and a cluster in the right perigenual ACC was positively correlated with CTQ total score (Table 3).

3.5.2 Fear vs. shapes contrast

3.5.2.1 Task effects: See supplemental results and Table S7.

3.5.2.2 Correlations with childhood maltreatment: CTQ total scores were negatively correlated with connectivity between the left amygdala task effect seed and a cluster in the right posterior insula but positively correlated with connectivity between the left amygdala task effect seed and a cluster in the ventral ACC. Connectivity values for the right amygdala task effect seed displayed no significant correlations with CTQ total scores. Connectivity between the left anterior insula task effect seed and clusters in the right posterior insula, perigenual ACC, and the mid-cingulate/medial frontal gyri were positively correlated with CTQ total scores. Connectivity between the left posterior insula task effect seed and a cluster in the right posterior insula was positively correlated with CTQ total scores. Connectivity values from the left middle frontal gyrus task effect seed displayed no significant correlations with CTQ total scores. Connectivity values from the right middle frontal gyrus task effect seed displayed no significant correlations with CTQ total scores. Connectivity between the dorsal medial frontal gyri task effect seed and two clusters in the bilateral posterior insula were positively correlated with CTQ total scores (Table 4).

3.6 Voxel-based morphometry

Limbic ROI-constrained analyses revealed there were no clusters in the amygdala, insula, or ACC in which GM volume correlated with CTQ total score after cluster-size correction for multiple comparisons. The WB analysis revealed GM volumes in the right inferior occipital, middle occipital, lingual gyri, and cuneus were negatively correlated with CTQ total score, as were GM volumes in the bilateral precentral/postcentral gyri. Additionally, GM volumes in the right middle and superior frontal gyri (dorsolateral PFC) were inversely correlated with CTQ total scores, while GM volumes in the left middle and superior temporal gyri extending into the left ventral mid-insula were positively correlated with CTQ total score (Table 5).

3.7 Complementary group-difference analyses

As a complementary method to assess neural correlates of CM and bolster significance of correlational findings, we split the sample of IPV-PTSD participants into high (n=16) and low (n=17) CM-exposure groups based upon a median split of CTQ total score (median score = 55; see Table S8 for group characteristics) and compared between groups the extracted % signal changes, Fisher Z-transformed PPI correlation coefficients, and gray matter volumes from clusters displaying significant correlational relationships with CTQ total score. The groups were well matched on age, ethnicity, comorbidity, years of education, PTSD/depression symptom severity, years of IPV abuse, and task performance measures. We observed that all functional and structural clusters displaying significant correlational relationships with CM severity also significantly differed between the high and low CM-exposure groups (see Group Diff. column in Tables 1-5), indicating these CM correlational relationships index significant differences in neural structure and function in women with IPV-PTSD with high vs. low exposure to CM.

4. Discussion

This study examined the hypothesis that severity of CM exposure relates to patterns of both brain structure and emotion-processing function in women with IPV-PTSD. The results support this hypothesis and revealed that CM severity may contribute to variability in brain structure and emotion-processing brain function in PTSD in adulthood. Specifically, extent of CM exposure correlated with prefrontal gray matter volume and activation/connectivity in and among the insula, ACC, and prefrontal cortices, brain structures that are important for processing, expression, and regulation of emotional states (Craig, 2009; Campbell-Sills et al., 2011) and which have been previously implicated in the functional neuroanatomy of PTSD (Lanius et al., 2004, 2006, 2010; Liberzon and Garfinkel, 2009). The correlations between CM severity and brain function in these regions provide further evidence for the notion that early life experiences characterized by stressful and/or maladaptive rearing conditions may exert enduring neural effects which persist into the posttraumatic state in adulthood and contribute to variability in brain function. In line with this idea prior studies have demonstrated convergent relationships between CM or early life stress and brain function in these regions in non-clinical samples (Taylor et al., 2006; Williams et al., 2009; Mueller et al., 2010). Furthermore, such neural effects may represent one potential mechanism whereby CM confers risk for development of PTSD upon adult exposure to extreme adverse events. Given observed relationships between variable function in these regions and characteristics of PTSD symptom manifestations (Hopper et al., 2007; Felmingham et al., 2008, 2009), such CM-related neural effects may also contribute to variability in relative predominance of specific PTSD symptom clusters. With this study we aimed to illuminate the neural correlates of a developmental risk factor for PTSD and a potential source of heterogeneity in PTSD functional/structural abnormalities, and we hope the present findings will encourage further research into the potential enduring neural effects of early life stressors such as CM and their relationship to the future development/ manifestation of PTSD.

Contrary to our hypotheses, we observed negative correlations between CM severity and insula and dorsal ACC/PFC activation to fearful and angry faces. Post-hoc extraction estimates revealed these relationships were due to positive correlations between CM severity and activation during the sensorimotor baseline, suggesting CM severity was most strongly associated with variability in these regions during sensorimotor rather than emotional processing *per se*. The dorsal ACC/PFC and anterior insula have both been implicated in cognitive/attentional function in prior studies (Wager and Barrett, 2004; Torta and Cauda, 2011) and are considered part of a neural network implicated in evaluating and assigning motivational value to stimuli (Medford and Critchley, 2010), suggesting these relationships may have arisen from a CM-related compensatory attentional engagement or motivational appraisal of task demands. Although unexpected, these results are not inconsistent with prior studies of CM which have demonstrated impairments in cognitive control with concomitant functional abnormalities of prefrontal and insular regions (Carrion et al., 2008; Mueller et al., 2010). Furthermore, the negative correlation between CM severity and right dorsolateral prefrontal GM volumes is also indicative of a relationship between CM and potentially impaired or abnormal cognitive function in adulthood PTSD, given the role of this region in cognitive control and executive function (Savine and Braver, 2010; Ball et al., 2011). A recent study also observed a negative relationship between dorsolateral prefrontal cortical thickness and post-trauma PTSD symptom reductions (Lyoo et al., 2011), highlighting a potential neural structural characteristic which may relate CM to poor health outcomes in women with PTSD (Lang et al., 2008).

We did observe a positive correlation between ventral ACC activation and CM severity during the processing of angry faces which arose from the emotional face condition,

suggesting CM relationships with IPV-PTSD prefrontal function also extend to the processing of emotional stimuli—consistent with prior findings in non-clinical samples (Williams et al., 2009). The ventral ACC/mPFC has been implicated in downregulation of amygdala activity (Quirk et al., 2003) and parasympathetic processes such as heart rate deceleration to emotional faces (Critchley et al., 2005) and fear extinction (Milad et al., 2009) which suggests those IPV-PTSD women with more severe history of CM may have deployed greater ventral ACC neural resources towards limbic inhibition in response to threat cues, consistent with the positive correlation between CM and ventral ACC-amygdalar functional connectivity observed during fear processing. Recent studies have illuminated variability in ACC function in PTSD as relating to several factors such as level of arousal (Felmingham et al., 2009) as well as predominantly dissociative or reexperiencing responses to trauma-related stimuli (Felmingham et al., 2008; Lanius et al., 2010), suggesting variability in this brain region may be particularly important in contributing to heterogeneity in symptom manifestations. These results highlight another potential source of ACC functional variability in PTSD, and further characterization of this relationship may help to reconcile seemingly contradictory findings in the literature.

No significant correlations between CM severity and amygdala activation to emotional faces were observed, which was contrary to expectations given other findings for CM relationships with amygdala function in non-psychiatric samples (Taylor et al., 2006; Williams et al., 2009). However, to our knowledge no prior studies have observed a dimensional relationship between CM or early life stress and amygdala activation but have instead demonstrated group differences, raising the possibility these differences may relate to other between-group factors rather than CM or early life stress *per se*. Additionally, amygdala activation in PTSD has been previously demonstrated to be associated with other factors such as depression (Kemp et al., 2007) and PTSD symptom severity (Rauch et al., 2000), suggesting the absence of significant CM-amygdala relationships may reflect Type-II error due to the incorporation of other model factors known to relate to amygdalar function as well as the relatively small sample size employed here. Future studies will need to employ larger samples to resolve this apparent contradiction.

The correlations of CM severity with connectivity contribute to an emerging literature demonstrating varying abnormalities of limbic-prefrontal and amygalo-insular functional relationships in PTSD (Gilboa et al., 2004; Lanius et al., 2004, 2005; Simmons et al., 2008), suggesting extent of CM exposure may account for some of this variability. Specifically, the pattern of results indicates CM severity was primarily correlated with greater connectivity between limbic (insula/amygdala) and prefrontal regions (ACC and dorsal PFC) during fear processing as well as lesser amygdalo-insular connectivity during both fear and anger processing. Findings for abnormalities of insula-ACC connectivity in PTSD have varied in directionality (Lanius et al., 2004; Fonzo et al., 2010), and given the complimentary roles of these brain structures in interoceptive awareness and emotional experience (Craig, 2003, 2004) these findings may reflect variation in the subjective emotional responses of individuals with PTSD to threatening stimuli. Findings for reductions in amygdalo-insular connectivity have been more homogenous (Simmons et al., 2008; Fonzo et al., 2010), including a study that observed this pattern of abnormalities in a similar sample utilizing the same emotional face processing paradigm. This convergence of findings highlights the possibility that functional differences observed in the posttraumatic state may reflect the influence of risk factors or other endogenous vulnerabilities rather than the manifestation of the disorder *per se*, and future studies may wish to incorporate measures of such risk/vulnerability factors in analyses to further disentangle these contributions.

This study has several limitations. First, it is important to point out that these results are correlational, retrospective with regard to CM assessment, and not longitudinal. Thus, one

cannot draw any firm conclusions as to the causal effects of CM on brain function/structure or how any such effects may influence susceptibility to development or manifestation of PTSD. Specifically, it is possible a third, unmeasured variable may account for the relationships between CM and brain structure/function observed here. Therefore, these results should be interpreted cautiously until future, well-controlled prospective studies can address these questions. Second, the IPV-PTSD group consisted exclusively of women with exposure to IPV, so these findings may not be generalizable to males or persons with other forms of PTSD. Similarly, the relationships between CM and brain characteristics may be specific to this type of PTSD population and may not generalize to other maltreated and/or clinical populations. Third, we chose to include IPV-PTSD participants with comorbid depression or other anxiety disorders, which may limit the specificity of the findings. Fourth, self-report measures of childhood maltreatment are susceptible to reporting biases or inaccuracies. Fifth, we did not control the experiment-wise alpha level; given the exploratory nature of the analyses, we felt it best to balance power and risk of Type-I error by controlling for multiple comparisons on a family-wise level (i.e., activation, connectivity, and structure). Sixth, our dimensional regression-based approach to characterizing neural correlates of CM is only one of several valid approaches (e.g., group comparisons between matched IPV-PTSD participants with low and high exposure to CM).

In summary, severity of CM history in women with IPV-PTSD accounts for variation in limbic and prefrontal function and prefrontal structure in adulthood, potentially implicating maladaptive early life experiences as a prime source of variability in posttraumatic neural characteristics. Further attention to the neural effects of risk factors such as CM which promote individual variation in neural function/structure, increase susceptibility to the development of psychopathology, and moderate clinical characteristics such as symptom severity and quality of life may allow for further refinement of systems-neuroscience etiological theory and the identification of neural risk markers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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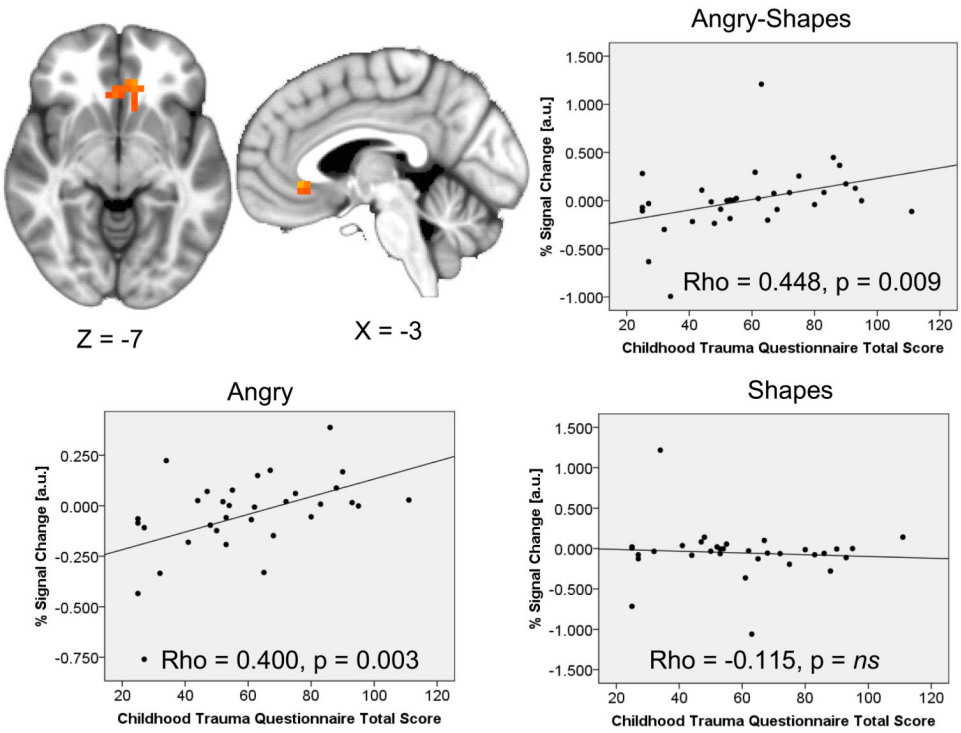

Figure 1. Severity of childhood maltreatment correlates with ventral anterior cingulate activation while processing angry faces

Scatterplots represent extracted cluster % signal changes against Childhood Trauma Questionnaire Total Score; Scatterplots for the within-subject contrast and for both angry and shape-matching are presented; Results displayed on an average anatomical; au=arbitrary units; ns=nonsignificant.

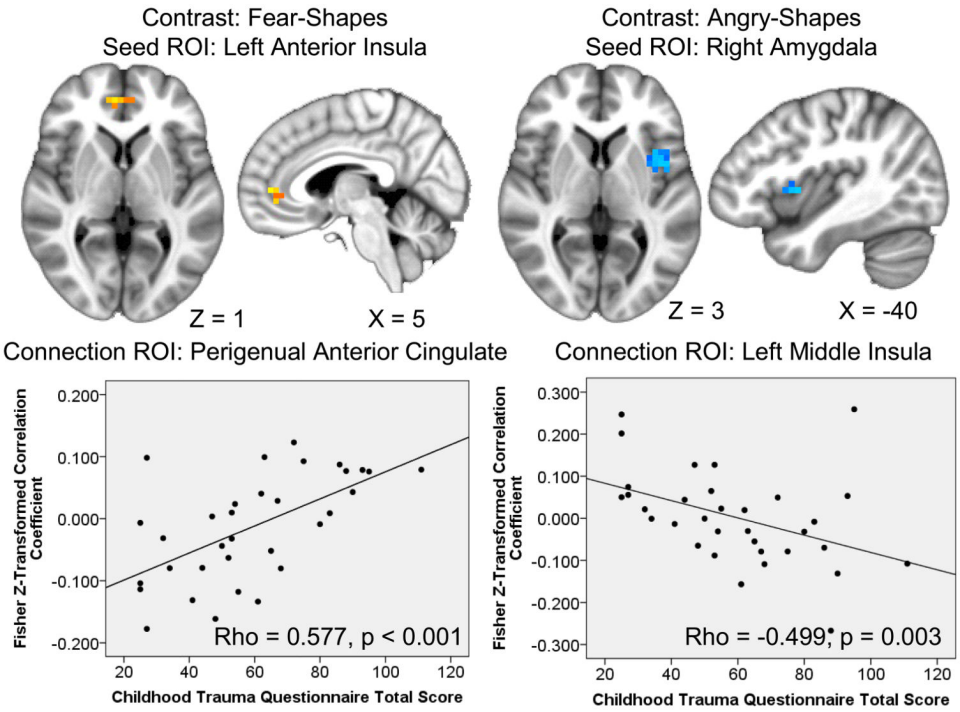

Figure 2. Severity of childhood maltreatment correlates with limbic-prefrontal and amygalo-insular functional connectivity during threat processing

Scatterplots represent extracted cluster Fisher Z-transformed correlation coefficient against Childhood Trauma Questionnaire Total Score; Results displayed on an average anatomical; ROI=region of interest.

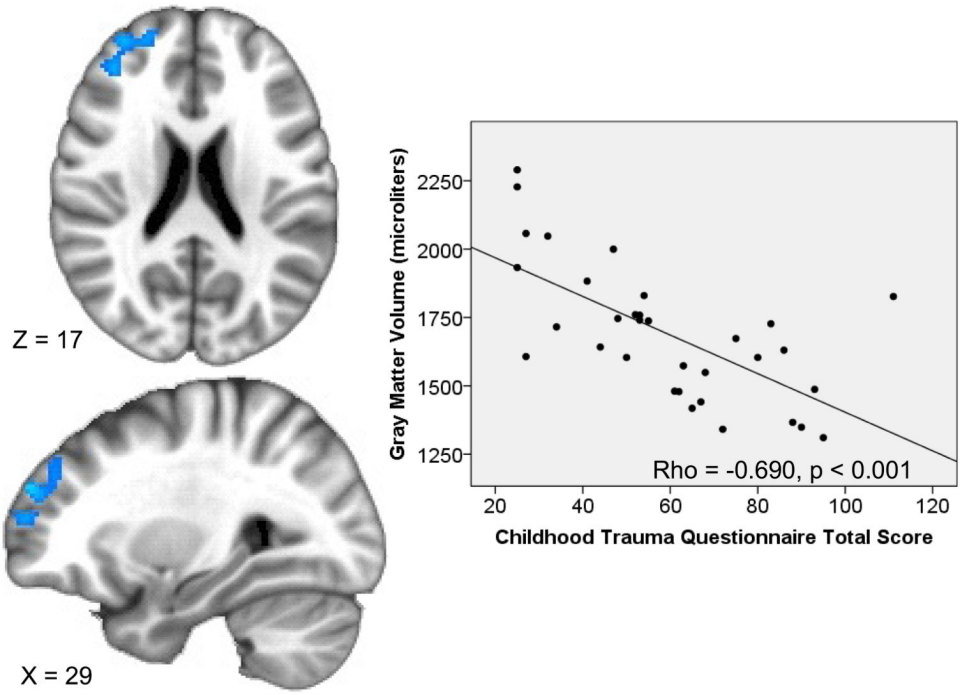

Figure 3. Severity of childhood maltreatment correlates with right middle/superior frontal gyrus gray matter volume

Table 1

Functional activation correlates of childhood maltreatment during angry face vs. shape processing

Mask	Hemisphere	Anatomical Area	Volume(μl)	X	Y	Z	Voxelwise Stats: Mean (SD)		Extracted rho (sig)†	ΔR²(sig.) †	Group Diff.†
							T	*p*			*T, p*
ROI	L/R	Anterior Cingulate (v)	1344	−5	30	−7	2.59(0.51)	0.021(0.017)	0.448(0.009)	0.142(0.036)	2.882, 0.007
ROI	L	Insula (m)(−)	1216	−41	−5	4	−2.67(0.42)	0.019(0.016)	−0.423(0.014)	0.141(0.037)	−2.940, 0.006
ROI	R	Anterior Cingulate (d)(−)	960	6	31	17	−2.54(0.33)	0.021(0.015)	−0.542(0.001)	0.269(0.003)	−3.586, 0.001
WB	L/R	Anterior Cingulate/Medial Frontal Gyrus (d)(−)	11392	−12	12	28	−2.54(0.39)	0.022(0.014)	−0.697(<0.001)	0.387(<0.001)	−4.196, <0.001

Cluster coordinates are for cluster center of mass as defined by Talairach stereotactic space; Negative (-) signs following anatomical area indicate a negative relationship; Extracted rho is the spearman's correlation of extracted % signal change and Childhood Trauma Questionnaire total score; ΔR^2 represents the change in full model R^2 from inclusion of CTQ total score in a post-hoc regression of extracted cluster % signal changes against other model factors; Group Diff. column represents the post-hoc t-test (High CM vs. Low CM) of extracted % signal changes based upon a median split of IPV-PTSD sample into low and high CM-exposure groups; Descriptors for anatomical areas do not reflect stereotactic distinctions, but are estimates based upon the relative location of activation on the group map; Statistics with a † indicate a circular estimate and therefore may be inflated estimates of the true population parameter; d=dorsal; L=left; m=middle; R=right; ROI=region of interest; v=ventral; WB=whole-brain.

Table 2

Functional activation correlates of childhood maltreatment during fearful face vs. shape processing

Mask	Hemisphere	Anatomical Area	Volume(μl)	X	Y	Z	Voxelwise Stats: Mean (SD)		Extracted rho (sig) †	ΔR^2(sig.) †	Group Diff.†
							T	*p*			*T, p*
ROI	R	Insula (a)(−)	1728	35	18	6	−2.76(0.58)	0.018(0.016)	−0.521(0.002)	0.175(0.008)	−3.239, 0.003
ROI	R	Anterior Cingulate (d)(−)	960	12	34	15	−2.84(0.69)	0.016(0.014)	.0.444(0.010)	0.183(0.015)	−3.688,0.001
WB	L/R	Anterior Cingulate/Medial Fronal Gyrus/Middle Frontal Gyrus (d)(−)	38784	3	41	14	−2.57(0.46)	0.022(0.014)	−0.629(<0.001)	0.329(<0.001)	−3.568, 0.001

Cluster coordinates are for cluster center of mass as defined by Talairach stereotactic space; Negative (−) signs following anatomical area indicate a negative relationship; Extracted rho is the spearman's correlation of extracted % signal change and Childhood Trauma Questionnaire total score; ΔR^2 represents the change in full model R^2 and significance from inclusion of CTQ total score in a post-hoc regression of extracted cluster % signal changes against other model factors; Group Diffi column represents the post-hoc t-test (High CM vs. Low CM) of extracted % signal changes based upon a median split of IPV-PTSD sample into low and high CM-exposure groups; Descriptors for anatomical areas do not reflect stereotactic distinctions, but are estimates based upon the relative location of activation on the group map; Statistics with a † indicate a circular estimate and therefore may be inflated estimates of the true population parameter; a=anterior; d=dorsal; L=left; R=right; ROI=region of interest; WB=whole-brain.

Table 3

Functional connectivity correlates of childhood maltreatment during angry face vs. shape processing

Seed	Mask	Hemisphere	Anatomical Area	Volume(μl)	X	Y	Z	Voxelwise Stats: Mean (SD)		Extracted rho (sig) †	ΔR^2(sig.) †	Group Diff.†
								T	*p*			*T, p*
RAmyg	--	--	No significant associations	--	--	--	--	--	--	--	--	--
LPIns	ROI	R	Amygdala (−)	320	23	−3	−12	−2.58(0.41)	0.020(0.017)	−0.503(0.003)	0.178(0.016)	−2.274, 0.030
LAmyg	ROI	L	Insula (m)(−)	960	−41	5	3	−2.75(0.47)	0.016(0.015)	−0.499(0.003)	0.193(0.009)	−2.045, 0.049
LMFG	WB	L	Culmen/Declive/Fusiform Gyrus/Parahippocampal Gyrus	7552	−11-	−47	−10	2.60(0.51)	0.022(0.015)	0.599(<0.001)	0.335(<0.001)	3.943, <0.001
LMFG	WB	R	Culmen/Declive/Lingual Gyrus/Parahippocampal Gyrus	4352	18	−62	−9	2.65(0.44)	0.019(.013)	0.558(0.001)	0.258(0.001)	3.870, 0.001
RMFG	ROI	R	Anterior Cingulate (pg)	960	5	39	−4	2.89(0.83)	0.021(0.017)	0.500(0.003)	0.225(0.007)	2.239, 0.032

Cluster coordinates are for cluster center of mass as defined by Talairach stereotactic space; Negative (−) signs following anatomical area indicate a negative relationship; Extracted rho is the spearman's correlation of extracted Fisher Z-transformed correlation coefficient and Childhood Trauma Questionnaire total score; ΔR^2 represents the change in full model R^2 and significance from inclusion of CTQ total score in a post-hoc regression of extracted Fisher Z-transformed correlation coefficients against other model factors; Group Diff. column represents the post-hoc t-test (High CM vs. Low CM) of extracted Fisher Z-transformed correlation coefficients based upon a median split of IPV-PTSD sample into low and high CM-exposure groups; Descriptors for anatomical areas do not reflect stereotactic distinctions, but are estimates based upon the relative location of activation on the group map; Seed regions and descriptors were derived from task-dependent activation for the contrast of interest; Statistics with a † indicate a circular estimate and therefore may be inflated estimates of the true population parameter; L=left; LAmyg=left amygdala; LMFG=left middle frontal gyrus; LPIns=left posterior insula; m=middle; pg=perigenual; R=right; ROI=region of interest; RAmyg=right amygdala; RMFG=right middle frontal gyrus; WB=whole-brain.

Table 4

Functional connectivity correlates of childhood maltreatment during fearful face vs. shape processing

Seed	Mask He	tnisphere	Anatomical Area	Volume(μl)	X	Y	Z	Voxelwise Stats: Mean (SD)		Extracted rho (sig) †	ΔR²(sig.) †	Group Diff. †
								T	*P*			*T, p*
LAmyg	ROI	R	Insula (p)(−)	1664	41	−18	15	−2.52(0.43)	0.022(0.018)	−0.487(0.004)	0.214(0.005)	−3.258, 0.003
LAmyg	ROI	L/R	Anterior Cingulate (v)	1024	−1	40	−6	2.57(0.41)	0.019(0.016)	0.583(<0.001)	0.411(<0.001)	3.927, <0.001
RAmyg	--	--	No significant associations	--	--	--	--	--	--	--	--	--
LAIns	ROI	L/R	Anterior Cingulate (pg)	960	3	44	1	2.75(0.36)	0.013(0.010)	0.577(<0.001)	0.336(<0.001)	4.357, <0.001
LAIns	ROI	R	Insula (p)	960	44	−20	15	2.93(0.70)	0.014(0.014)	0.695(<0.001)	0.419(<0.001)	3.752, 0.001
LAIns	WB	L/R	Cingulate Gyrus/Medial Frontal Gyrus (SMA)	3968	−1	−15	50	2.72(0.60)	0.016(0.013)	0.746(<0.001)	0.422(<0.001)	4.698, <0.001
LPIns	ROI	R	Insula (p)	1024	40	−17	16	2.67(0.34)	0.015(0.012)	0.515(0.002)	0.256(0.003)	4.125, <0.001
LMFG	--	--	No significant associations	--	--	--	--	--	--	--	--	--
RMFG	--	--	No significant associations	--	--	--	--	--	--	--	--	--
DMedFG	ROI	L	Insula (p)	960	−41	−22	16	2.78(0.96)	0.024(0.025)	0.573(<0.001)	0.370(<0.001)	3.876, 0.001
DMedFG	ROI	R	Insula (p)	960	44	−21	17	2.57(0.39)	0.016(0.014)	0.516(0.002)	0.288(0.001)	2.996, 0.005

Cluster coordinates are for cluster center of mass as defined by Talairach stereotactic space; Negative (-) signs following anatomical area indicate a negative relationship; Extracted rho is the spearman's correlation of extracted Fisher Z-transformed correlation coefficient and Childhood Trauma Questionnaire total score; ΔR^2 represents the change in full model R^2 and significance from inclusion of CTQ total score in a post-hoc regression of extracted Fisher Z-transformed correlation coefficients against other model factors; Group Diff. column represents the post-hoc t-test (High CM vs. Low CM) of extracted Fisher Z-transformed correlation coefficients based upon a median split of IPV-PTSD sample into low and high CM-exposure groups; Descriptors for anatomical areas do not reflect stereotactic distinctions, but are estimates based upon the relative location of activation on the group map; Seed regions and descriptors were derived from task-dependent activation for the contrast of interest; DMedFG=dorsal medial frontal gyri; L=left; LAmyg=left amygdala; LAIns=left anterior insula; LMFG=left middle frontal gyrus; Statistics with a † indicate a circular estimate and therefore may be inflated estimates of the true population parameter; LPIns=left posterior insula; m=middle; pg=perigenual; R=right; RAmyg=right amygdala; RMFG=right middle frontal gyrus; ROI=region of interest; SMA= supplementary motor area; WB=whole-brain.

Table 5

Gray matter volumetric correlates of childhood maltreatment

Mask	Hemisphere	Anatomical Area	Volume (μl)	X	Y	Z	Voxelwise Stats: Mean (SD)		Extracted rho (sig) †	ΔR²(sig.) †	Group Diff. †
							T	*p*			*T, p*
ROI	--	No significant associations	--	--	--	--	--	--	--	--	--
WB	L	Middle Temporal Gyrus/Superior Temporal Gyrus/Insula (m)	7200	−52	1	−13	2.57(0.36)	0.020(0.013)	0.523(0.002)	0.212(0.006)	2.057, 0.048
WB	R	Inferior Occipital Gyrus/Middle Occipital Gyrus/Lingual Gyrus/Cuneus (−)	7064	14	−90	0	−2.58(0.38)	0.021(0.014)	−0.664(<0.001)	0.419(<0.001)	−2.930, 0.006
WB	R	Precentral Gyrus/Postcentral Gyrus (−)	4504	37	−13	39	−2.78(0.61)	0.018(0.014)	−0.691(<0.001)	0.371(<0.001)	−5.663, <0.001
WB	L	Precentral Gyrus/Postcentral Gyrus (−)	3992	−46	−12	37	−2.57(0.39)	0.021(0.013)	−0.540(0.001)	0.371(<0.001)	−3.401, <0.001
WB	R	Middle Frontal Gyrus/Superior Frontal Gyrus (−)	3968	31	49	19	−2.54(0.36)	0.022(0.013)	−0.690(<0.001)	0.423(<0.001)	−5.423, <0.001

Cluster coordinates are for cluster center of mass as defined by Talairach stereotactic space; Negative (−) signs following anatomical area indicate a negative relationship; Extracted rho is the spearman's correlation of extracted gray matter volume and Childhood Trauma Questionnaire total score; AR^2 represents the change in full model R^2 and significance from inclusion ofCTQ total score in a post-hoc regression of extracted cluster GM volumes against other model factors; Group Diff column represents the post-hoc t-test (High CM vs. Low CM) of extracted gray matter volumes based upon a median split oflPV-PTSD sample into low and high CM-exposure groups; Descriptors for anatomical areas do not reflect stereotactic distinctions, but are estimates based upon the relative location of activation on the group map; Statistics with a † indicate a circular estimate and therefore may be inflated estimates of the true population parameter; L=left; m=middle; R=right; ROI=region of interest; WB=whole-brain.