**Appendix**

**Supplementary Methods**

Emotion-Processing 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.

Activation Preprocessing and Individual Analysis

Data were processed using the AFNI software package (Cox 1996). Voxel time-series data were co-registered to an intra-run volume using a three-dimensional co-registration algorithm, and they were then mapped to the anatomical space of each participant. Voxel time-series data were corrected for artifact intensity spikes through fit to a smooth-curve function. Those time points with greater than 2 *s.d.* more voxel outliers than the subject’s mean were excluded from analysis. Rotational parameters (roll, pitch, and yaw) were used as nuisance regressors for motion artifact. Each subject’s time-series data was normalized to Talairach coordinates using AFNI’s built-in anatomical atlas (as specified by the Talairach Daemon (Lancaster *et al* 2000)), and a Gaussian smoothing filter with a full-width half max (FWHM) of 4 mm was applied to each participant’s time-series to account for individual variability in anatomical landmarks. A deconvolution analysis was conducted in which orthogonal regressors of interest were target trials of: 1) happy faces; 2) angry faces; 3) fearful faces; and 4) shapes. The outcome measures of interest were activation magnitudes for the within-subject contrasts of trials in which the subject engaged in emotion matching for each of the emotional face types (anger, fear, happy) vs. the shape processing baseline. Regressors of interest were convolved with a modified gamma-variate function to account for delay and dispersion of the hemodynamic response. Baseline and linear drift variables were also entered into the regression model. The average voxelwise response magnitude was fit and estimated using AFNI’s 3dDeconvolve program. Beta coefficients for each regressor were normalized to voxelwise % signal changes (%SCs) before being carried to second-level analysis.

Optimized Voxel-Based Morphometry

Gray matter (GM) volumes were assessed using FSL-VBM, a voxel-based morphometry style analysis (Ashburner and Friston 2000, Good *et al* 2001) implemented using FSL tools (Smith *et al* 2004). First, structural images were skull-stripped using AFNI’s 3dSkullStrip (Cox 1996). Tissue segmentation was implemented using FAST4 (Zhang *et al* 2001). Resulting gray-matter (GM) partial volume images in a 2 x 2 x 2mm resolution were realigned to MNI152 standard space first using affine registration with FLIRT (Jenkinson and Smith 2001, Jenkinson *et al* 2002) followed by nonlinear registration with FNIRT (Andersson *et al* 2007a, Andersson *et al* 2007b). Resulting realigned images were then averaged to create a study-specific template to which native GM images were then non-linearly reregistered. The reregistered partial volume images were then modulated to correct for local expansion/contraction by dividing by the Jacobian of the warp field. The modulated GM images were then smoothed with a 4.0 mm FWHM Gaussian kernel.

Type-I Error Control in Imaging Analyses

For the mediation and ROI task effect analyses of functional data, an a-priori voxelwise probability threshold of *p* < 0.025 (or the 95% confidence interval for mediation analyses) with a 4mm search radius and cluster size of 192 μl (3 contiguous voxels) for the amygdala, 320 μl (5 contiguous voxels) for the ACC and insula, and 704 μl (11 contiguous voxels) for the whole brain resulted in a-posteriori probability of *p* < 0.05 in each constrained region. The corrected voxelwise probabilities for each region are as follows: amygdala (*p* = 0.0025), insula (*p* = 0.0007), ACC/mPFC (*p* = 0.0007), and whole brain (*p* = 0.00004). For the WB analysis of task effect activations, a more conservative voxelwise threshold of *p* < 1e-10 was utilized in order to provide more anatomical specificity. For this voxelwise threshold, clustering with a 4 mm search radius and cluster size of 256 μl (4 contiguous voxels) maintained the *a-posteriori* probability at *p* < 0.05. For the mediation analyses of GM volumes, an *a-priori* voxelwise probability threshold of *p* < 0.025 (or the 95% confidence interval) with a 2mm search radius and cluster size of 120 μl (15 contiguous voxels) for the amygdala, 304 μl (38 contiguous voxels) for the insula, 312 μl (39 contiguous voxels) for the ACC, and 688 μl (86 contiguous voxels) for the whole brain resulted in *a-posteriori* probability of *p* < 0.05 in each constrained region. The corrected voxelwise probabilities for each region are as follows: amygdala (*p* = 0.004), insula (*p* = 0.0008), ACC/mPFC (*p* = 0.0008), and whole brain (*p* = 0.00003).

**Supplementary Results**

Effects in Non-Hypothesized Regions that Partially Mediated Functional Maltreatment-Anxiety Relationships

For the contrast of fear vs. shapes, greater activation in the left fusiform gyrus partially mediated the relationship between EM and anxiety (Indirect effect = 0.021, 95% bootstrapped CI = 0.002 – 0.040; χ2(1)= 14.41, *p* = 0.0007; RMSEA = 0.185, 90% CI: 0.103-0.279; CFI = 0.594; SRMR = 0.104). The indirect effect was significant but model fit was poor, consistent with a partial mediation effect. The alternative model indirect effect was non-significant (Indirect effect = 0.002, 95% bootstrapped CI = -0.006 – 0.010; χ2(1)= 27.68, *p* < 0.0001; RMSEA = 0.266, 90% CI: 0.183-0.358; CFI = 0.159; SRMR = 0.136) and model fit was also poor. The indirect effect remained significant when controlling for structural characteristics.

Effects in Non-Hypothesized Regions that Partially Mediated Structural Maltreatment-Anxiety Relationships

In addition to the right dorsolateral prefrontal cortex, we observed that decreasing GM volumes in the left precentral gyrus partially mediated the relationship between EM and anxiety (Indirect effect = 0.018, 95% bootstrapped CI = 0.002 – 0.034; χ2(1)= 13.529, *p* = 0.0002; RMSEA = 0.262, 90% CI: 0.151-0.395; CFI = 0.573; SRMR = 0.085). The indirect effect for the alternative model was non-significant (Indirect effect = -0.161, 95% bootstrapped CI = -0.390 – 0.069; χ2(1)= 18.004, *p* < 0.0001; RMSEA = 0.294, 90% CI: 0.181-0.407; CFI = 0.421; SRMR = 0.101) and the model fit statistics were likewise poor.

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Supplementary Table S1. Task-Evoked Activation for Processing Fear vs. Shapes

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Mask** | **H** | **Region** | **Vol.**  **(μl)** | **X** | **Y** | **Z** | **Voxelwise Stats**  **Mean (sd)** | |
| ***t*** | ***p*** |
| Activation | | | | | | | | |
| ROI | L | Insula (a/p) | 10880 | -37 | 1 | 8 | 4.22 (1.40) | 0.003 (0.005) |
| ROI | R | Insula (a) | 4672 | 37 | 16 | 4 | 4.80 (1.80) | 0.002 (0.004) |
| ROI | R | Insula (p) | 2496 | 37 | -20 | 12 | 3.49 (0.90) | 0.005 (0.008) |
| ROI | R | Amygdala | 1728 | 23 | -5 | -14 | 6.04 (2.08) | 0.0001 (0.0004) |
| ROI | L | Amygdala | 1536 | -22 | -5 | -14 | 5.85 (2.18) | 0.0007 (0.0003) |
| ROI | L/R | Anterior Cingulate (sg) | 448 | -1 | 9 | -6 | 3.26 (0.74) | 0.005 (0.006) |
| ROI | L | Insula (p) | 384 | -41 | -6 | -4 | 3.03 (0.51) | 0.005 (0.005) |
| ROI | R | Anterior Cingulate (sg) | 320 | 7 | 12 | -8 | 2.98 (0.43) | 0.005 (0.004) |
| WB | R | Visual Cortex (Fusiform Gyrus, Lingual Gyrus, Inferior/Middle Occipital Gyri) | 30976 | 31 | -73 | -7 | 9.43 (2.21) | 1e-11 (1.6e-11) |
| WB | L | Visual Cortex (Fusiform Gyrus, Lingual Gyrus, Inferior/Middle Occipital Gyri) | 18944 | -30 | -75 | -9 | 9.18 (1.91) | 1e-11 (1.8e-11) |
| WB | L/R | Thalamus/Caudate Body | 18112 | 5 | -24 | 6 | 8.13 (1.14) | 1e-11 (2.2e-11) |
| WB | R | Dorsolateral Prefrontal Cortex (Inferior/Middle/Superior Frontal Gyri, Precentral Gyrus) | 13248 | 42 | 10 | 33 | 9.11 (1.77) | 1e-11 (1.9e-11) |
| WB | L | Dorsolateral Prefrontal Cortex (Inferior/Middle/Superior Frontal Gyri, Precentral Gyrus) | 9280 | -41 | 8 | 32 | 8.70 (1.42) | 1e-11 (1.7e-11) |
| WB | R | Lingual Gyrus/Cuneus/Posterior Cingulate | 2944 | 14 | -62 | 7 | 7.91 (0.78) | 1e-11 (2.1e-11) |
| WB | R | Precuneus/Angular Gyrus | 2752 | 30 | -59 | 38 | 8.20 (0.97) | 1e-11 (2.2e-11) |
| WB | L | Superior Temporal Gyrus | 1792 | -49 | -45 | 10 | 7.57 (0.52) | 2e-11 (2.3e-11) |
| WB | L | Cuneus/Posterior Cingulate | 1536 | -15 | -66 | 7 | 7.74 (0.63) | 1e-11 (1.6e-11) |
| WB | L/R | Culmen/Declive | 1408 | -1 | -56 | -12 | 7.62 (0.63) | 2e-11 (3.0e-11) |
| WB | L | Precuneus/Angular Gyrus | 1344 | -29 | -58 | 39 | 7.99 (0.88) | 1e-11 (1.5e-11) |
| WB | R | Insula (a) | 1216 | 31 | 18 | 8 | 7.93 (0.74) | 1e-11 (2.3e-11) |
| WB | R | Precuneus | 1152 | 3 | -64 | 35 | 7.80 (0.53) | 1e-11 (1.4e-11) |
| WB | L | Parahippocampal Gyrus/Amygdala | 832 | -22 | -7 | -12 | 8.59 (1.32) | 1e-11 (8e-12) |
| WB | L | Insula (a) | 768 | -31 | 18 | 7 | 7.51 (0.61) | 2e-11 (2.4e-11) |
| WB | L/R | Superior Frontal Gyrus (dm) | 640 | -2 | 13 | 51 | 7.97 (0.53) | 1e-11 (2.4e-11) |
| WB | R | Parahippocampal Gyrus/Amygdala | 512 | 18 | -10 | -10 | 8.16 (1.24) | 1e-11 (1e-11) |
|  |  |  |  |  |  |  |  |  |
| Deactivation | | | | | | | | |
| ROI | L/R | Anterior Cingulate (pg) | 6656 | 0 | 40 | 10 | -3.39 (0.82) | 0.005 (0.006) |

X, Y, and Z are the Talairach coordinates for the cluster center of mass; Voxelwise stats report mean t and p value with standard deviations in parentheses; Locational descriptors in parentheses do not denote actual anatomical distinctions but are based upon the relative location of the cluster in standardized space; a=anterior; dm=dorsomedial; H=hemisphere; L=left; p=posterior; pg=perigenual; R=right; ROI=region of interest masks; sd=standard deviation; sg=subgenual; Vol. = volume; WB=whole-brain masks.

Supplementary Table S2. Task-Evoked Activation for Processing Anger vs. Shapes

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Mask** | | **H** | | **Region** | **Vol.**  **(μl)** | **X** | | **Y** | **Z** | | **Voxelwise Stats**  **Mean (sd)** | | | |
| ***t*** | ***p*** | | |
| Activation | | | | | | | | | | | | | |
| ROI | | L | | Insula (p) | 5888 | | -39 | -18 | 13 | 3.58 (0.91) | | | 0.004 (0.006) |
| ROI | | R | | Insula (p) | 3840 | | 38 | -21 | 13 | 3.70 (0.96) | | | 0.003 (0.005) |
| ROI | | L | | Insula (a) | 2560 | | -33 | 18 | 4 | 3.46 (0.80) | | | 0.005 (0.007) |
| ROI | | R | | Insula (a) | 2112 | | 37 | 17 | 4 | 3.45 (0.91) | | | 0.005 (0.007) |
| ROI | | R | | Amygdala | 1728 | | 23 | -5 | -14 | 5.40 (1.34) | | | 0.0001 (0.0002) |
| ROI | | L | | Amygdala | 1344 | | -22 | -5 | -14 | 5.28 (2.34) | | | 0.001 (0.002) |
| ROI | | L/R | | Anterior Cingulate (sg) | 512 | | -2 | 13 | -5 | 2.83 (0.43) | | | 0.008 (0.007) |
| WB | | R | | Visual Cortex (Fusiform Gyrus, Lingual Gyrus, Inferior/Middle Occipital Gyri) | 28736 | | 31 | -73 | -6 | 8.98 (1.96) | | | 1e-11 (1.8e-11) |
| WB | | L | | Visual Cortex (Fusiform Gyrus, Lingual Gyrus, Inferior/Middle Occipital Gyri) | 16704 | | -30 | -75 | -9 | 9.08 (1.82) | | | 1e-11 (1.9e-11) |
| WB | | R | | Dorsolateral Prefrontal Cortex (Inferior/Middle/Superior Frontal Gyri, Precentral Gyrus) | 7424 | | 42 | 9 | 32 | 8.49 (1.29) | | | 1e-11 (2.1e-11) |
| WB | | L | | Dorsolateral Prefrontal Cortex (Inferior/Middle/Superior Frontal Gyri, Precentral Gyrus) | 3648 | | -41 | 6 | 34 | 8.00 (1.02) | | | 2e-11 (2.6e-11) |
| WB | | R | | Thalamus | 1152 | | 21 | -32 | 2 | 7.88 (0.68) | | | 1e-11 (1.4e-11) |
| WB | | L/R | | Precuneus | 896 | | 2 | -62 | 33 | 7.52 (0.54) | | | 2e-11 (2.6e-11) |
| WB | | L | | Parahippocampal Gyrus/Amygdala | 640 | | -21 | -7 | -12 | 7.95 (0.95) | | | 2e-11 (2.8e-11) |
| WB | | R | | Posterior Cingulate | 640 | | 20 | -60 | 7 | 7.23 (0.28) | | | 3e-11 (2.6e-11) |
| WB | | L | | Cuneus | 640 | | -15 | -68 | 7 | 7.69 (0.48) | | | 1e-11 (1.3e-11) |
| WB | | L | | Middle Frontal Gyrus (dl) | 384 | | -43 | 22 | 23 | 7.40 (0.39) | | | 1e-11 (1.4e-11) |
| WB | | R | | Thalamus | 320 | | 6 | -15 | 8 | 7.51 (0.40) | | | 1e-11 (1.3e-11) |
| WB | | R | | Posterior Cingulate | 320 | | 9 | -67 | 12 | 7.22 (0.18) | | | 2e-11 (1.4e-11) |
| WB | | R | | Parahippocampal Gyrus/Amygdala | 256 | | 31 | -8 | 13 | 7.44 (0.41) | | | 1e-11 (7e-12) |
| Deactivation | | | | | | | | | | | | | |
| ROI | L/R | | Anterior Cingulate (pg) | | 1856 | 1 | | 42 | 5 | | -2.74 (0.35) | 0.009 (0.008) | | |

X, Y, and Z are the Talairach coordinates for the cluster center of mass; Voxelwise stats report mean t and p value with standard deviations in parentheses; Locational descriptors in parentheses do not denote actual anatomical distinctions but are based upon the relative location of the cluster in standardized space; a=anterior; dl=dorsolateral; H=hemisphere; L=left; m=middle; p=posterior; pg=perigenual; R=right; ROI=region of interest masks; sd=standard deviation; sg=subgenual; Vol. = volume; WB=whole-brain masks.

Supplementary Table S3. Task-Evoked Activation for Processing Happy vs. Shapes

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Mask** | | **H** | | **Region** | **Vol.**  **(μl)** | **X** | | **Y** | **Z** | | **Voxelwise Stats**  **Mean (sd)** | | | |
| ***t*** | ***p*** | | |
| Activation | | | | | | | | | | | | | |
| ROI | | L | | Insula (p) | 5760 | | -38 | -18 | 13 | 3.89 (1.11) | | | 0.003 (0.006) |
| ROI | | R | | Insula (p) | 3520 | | 38 | -20 | 14 | 3.43 (0.87) | | | 0.005 (0.007) |
| ROI | | R | | Amygdala | 1728 | | 23 | -5 | -15 | 5.99 (1.68) | | | 0.00005 (0.0002) |
| ROI | | L/R | | Anterior Cingulate (sg) | 1664 | | 0 | 14 | -6 | 3.32 (0.70) | | | 0.004 (0.005) |
| ROI | | L | | Amygdala | 1600 | | -23 | -5 | -15 | 4.91 (1.66) | | | 0.002 (0.006) |
| WB | | R | | Visual Cortex (Fusiform Gyrus, Lingual Gyrus, Inferior/Middle Occipital Gyri) | 17088 | | 29 | -76 | -9 | 9.24 (1.99) | | | 1e-11 (1.7e-11) |
| WB | | L | | Visual Cortex (Fusiform Gyrus, Lingual Gyrus, Inferior/Middle Occipital Gyri) | 11968 | | -28 | -77 | -9 | 8.99 (1.73) | | | 1e-11 (1.9e-11) |
| WB | | R | | Parahippocampal Gyrus/Thalamus | 1664 | | 23 | -32 | 1 | 7.79 (0.96) | | | 1e-11 (2.1e-11) |
| WB | | R | | Parahippocampal Gyrus/Amygdala | 960 | | 25 | -6 | -11 | 7.78 (0.70) | | | 2e-11 (2.8e-11) |
| WB | | R | | Middle Temporal Gyrus | 704 | | 42 | -61 | 18 | 7.34 (0.37) | | | 2e-11 (2.7e-11) |
| WB | | L | | Parahippocampal Gyrus/Amygdala | 384 | | -22 | -6 | -11 | 7.18 (0.24) | | | 3e-11 (3.8e-11) |
| WB | | L/R | | Precuneus | 384 | | 1 | -60 | 34 | 7.28 (0.53) | | | 4e-11 (3.5e-11) |
| WB | | R | | Posterior Cingulate | 256 | | 19 | -66 | 11 | 7.23 (0.52) | | | 5e-11 (4.3e-11) |
| Deactivation | | | | | | | | | | | | | |
| ROI | L/R | | Anterior Cingulate (pg) | | 2240 | 1 | | 34 | 22 | | -2.98 (0.48) | 0.006 (0.007) | | |

Notes: X, Y, and Z are the Talairach coordinates for the cluster center of mass; Voxelwise stats report mean t and p value with standard deviations in parentheses; Locational descriptors in parentheses do not denote actual anatomical distinctions but are based upon the relative location of the cluster in standardized space; dl=dorsolateral; H=hemisphere; L=left; m=middle; p=posterior; pg=perigenual; R=right; ROI=region of interest masks; sd=standard deviation; sg=subgenual; Vol. = volume; WB=whole-brain masks.

C:\Users\Greg Fonzo\Desktop\Supplemental Figure 1.tifSupplementary Figure S1. Ventral Striatal and Visual Cortical Activation to Happy Faces vs. Shapes Mediates the CEM-Anxiety Relationship

Graphs depict the relationship between regional brain activation and anxiety symptoms at different levels of CEM (the additive combination of the CTQ emotional abuse and emotional neglect subscales), with the center fitted line indicating the activation-anxiety relationship at the CEM sample mean and each line above or below representing one standard deviation above or below the CEM mean, respectively. A.U. = arbitrary units; BSI = Brief Symptom Inventory; CEM = childhood emotional maltreatment; CTQ = Childhood Trauma Questionnaire Short Form.