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Early Life Stress and the Anxious Brain:

Neural Structure and Function Underlying the Relationship Between Childhood Emotional

Maltreatment and Anxiety in Adulthood

A dissertation submitted in partial satisfaction of the requirements for the degree

Doctor of Philosophy

in

Clinical Psychology

by

Gregory Anthony Fonzo

Committee in charge:

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2013

The Dissertation of Gregory Anthony Fonzo is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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University of California, San Diego

San Diego State University

2013

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DEDICATION

This work is dedicated to my loving parents, Robert and Joan Fonzo, and to my brother, Jason Fonzo, for their unwavering support, love, humor, and understanding provided along the arduous and trying path from dirty diapers to doctoral degrees.   Thank you for all you have done and will continue to do.

This work is also dedicated to the one and infinite source of creation, existence, and consciousness which makes everything possible.

EPIGRAPH

Enslavement by illusion is comfortable; it is the liberation by Truth that people fear.

Straight and narrow is the path…

Waste no time.

Gloria in Excelsis Deo!

David R. Hawkins, M.D., Ph.D.

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ACKNOWLEDGEMENTS

VITA

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PUBLICATIONS

Fonzo, G. A., Flagan, T. M., Sullivan, S., Allard, C. B., Grimes, E. M., Simmons, A. N., et al (2013). Neural functional and structural correlates of childhood maltreatment in women with intimate-partner violence-related posttraumatic stress disorder. *Psychiatry Research: Neuroimaging*, *211*(2), 93-103. doi:10.1016/j.pscychresns.2012.08.006

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ABSTRACT OF THE DISSERTATION

Early Life Stress and the Anxious Brain: Neural Structure and Function Underlying
the Relationship Between Childhood Emotional Maltreatment and Anxiety in Adulthood

by

Gregory Anthony Fonzo

Doctor of Philosophy in Clinical Psychology

University of California, San Diego, 2013
San Diego State University, 2013

Professor Murray Stein, Chair
Professor Martin Paulus, Co-Chair

Childhood maltreatment (CM), particularly emotional abuse (EA) and emotional

neglect (EN), is a significant risk factor for the development of excessive anxiety in

adulthood. However, the neurobiological mechanisms which underlie the relationship

between CM and later development of anxiety are poorly understood. The purpose of this

investigation is to delineate brain structure/function in adulthood which underlies the

relationship between childhood EA/EN and adult anxiety.

One-hundred eighty-two (n=182) adults with normal to clinical levels of anxiety underwent functional magnetic resonance imaging (fMRI) while completing a facial emotion processing task. CM history was assessed using the EA and EN subscale scores from the Childhood Trauma Questionnaire (CTQ). Anxiety symptoms were assessed using the anxiety subscale of the Brief Symptom Inventory. Gray matter volumes and functional activation and connectivity during emotion-processing trials targeted towards angry vs. happy and fearful vs. happy faces were examined. Mediation analyses were used to identify brain function/structure accounting for the relationship between self-reported childhood emotional abuse/neglect and anxiety symptoms in adulthood.

Increasing activation in the insula and amygdala mediated the relationship between childhood EA/EN and anxiety, respectively. Decreasing activation and smaller gray matter volumes in the right dorsolateral prefrontal cortex mediated the relationship between childhood EN and anxiety. Decreasing connectivity between anterior insula and dorsal prefrontal seed regions with posterior medial (posterior cingulate/precuneus) and sensory/motor (precentral/postcentral gyri) cortices mediated the relationship between childhood EA/EN and anxiety symptoms. All functional effects were significant after controlling for symptoms of depression and gray matter volumes. A structural/functional interaction effect was found in the left amygdala such that the mediation effect of left amygdala activation on the relationship between EN and anxiety symptoms was strongest for those with the smallest gray matter volumes.

This study provides initial evidence for a neuroetiological mechanism linking childhood emotional maltreatment to anxiety in adulthood through a potentiation of limbic and an attenuation of prefrontal responses to socioemotional threat cues. Findings from this investigation could be used in the initial construction of hypothesized neurodevelopmental

models which relate early distal risk factors to endogenous brain changes that serve to

predispose individuals to developing anxiety disorders as adults.

Executive Summary

Background

Anxiety disorders are a major public health problem with a high prevalence and a substantial burden of suffering (Kessler, Chiu, Demler, Merikangas, & Walters, 2005; Mendlowicz & Stein, 2000). Great effort has been directed towards elucidating the underlying neurobiological dysfunction which may be responsible for the development of excessive anxiety, yet the majority of studies have focused only on descriptive characterization of dysfunctional brain substrates in participants that have already developed anxiety disorders (M. P. Paulus, 2008). Although such studies are useful in directing the focus of research towards relevant brain regions, they are unable to offer information concerning etiological neural mechanisms which may potentially underlie the development of clinical anxiety. In order to leverage our knowledge towards useful efforts at early identification and prevention, it is necessary to move beyond a descriptive focus on end-state neural abnormalities towards the characterization of such etiological neural mechanisms which may lead to the manifestation of anxiety disorders.

One such developmental risk factor for adult anxiety is childhood maltreatment, a prevalent and particularly damaging from of early life stress which can be 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 (Goodman, Quas, & Ogle, 2010). Childhood maltreatment is not only reliably associated with more severe anxiety in adulthood (Kuo, Goldin, Werner, Heimberg, & Gross, 2011; Simon et al., 2009; Zlotnick et al., 2008), there is also a substantial overlap of affected neural substrates (Dannlowski et al., 2012; Etkin & Wager, 2007; Williams et al., 2009), suggesting investigation of the overlapping neural correlates of this risk factor and adulthood anxiety may offer a prime opportunity for the development of a neurodevelopmental etiological model.

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Prior neuroimaging studies have revealed anxiety disorders are associated with abnormal structure and function of limbic brain regions such as the amygdala and insula as well as higher-order prefrontal cortical regions. The amygdala is a subcortical region that plays a role in detection of salient environmental stimuli (particularly emotional or social stimuli) and initiation of secondary cognitive, emotional, and behavioral responses (Costafreda, Brammer, David, & Fu, 2008). The amygdala frequently displays hyperactivation in anxious samples to threatening or negative emotional stimuli, such as fearful faces or fear-invoking pictures (Etkin & Wager, 2007), as well as abnormal structural characteristics (M. D. De Bellis et al., 2000; Karl et al., 2006; Hayano et al., 2009; Asami et al., 2009). The insula is a mass of cortex located beneath the Sylvian fissure which plays a crucial role in the construct of interoception, or the sense of the overall physiological condition of the body (Craig, 2003). Insular hyperactivation in the context of emotion-processing paradigms has been demonstrated in adult anxiety manifestations (G. A. Fonzo et al., 2010; Gentili et al., 2008; Shah, Klumpp, Angstadt, Nathan, & Phan, 2009; Straube, Mentzel, & Miltner, 2005) where it has been interpreted as part of a hyperactive bottom-up emotional salience processing system (Phan et al., 2004). Structural insular abnormalities have also been demonstrated, specifically reduced gray matter density in adult posttraumatic stress disorder (PTSD) relative to combat-exposed controls (Chen et al., 2006; Kasai et al., 2008) and both increased gray matter density and decreased gray matter volumes in adult panic disorder (PD) (Asami et al., 2009; Uchida et al., 2008).

The prefrontal cortex (PFC) is important for higher-order cognitive, emotional, and social processes, particularly for the modulation/regulation of stress and fear responses (Monk et al., 2006; A. Simmons et al., 2008). The midline PFC, known as the anterior cingulate/medial prefrontal cortex (ACC/mPFC), is involved in higher-order anxiety-related integrative constructs such as implicit regulation of emotional/physiological state (Critchley et

al., 2003; Etkin et al., 2010), processing of emotional context (Rougemont-Bucking et al., 2011), self-relevance (Blair et al., 2008), and social cognition (Amodio & Frith, 2006). In the context of anxiety, ACC/mPFC abnormalities are often interpreted in the context of compensatory engagement to downregulate limbic hyperactivity or as excessive appraisal of emotional stimuli or expression of emotional responses (Etkin, Egner, & Kalisch, 2011). There are many findings for both hyperactive and hypoactive ACC/mPFC function in anxious samples (Blair et al., 2008; Etkin et al., 2010; Pillay et al., 2007; Shin et al., 2005). Furthermore, this region has been found to display reduced volume or gray matter density in multiple anxious samples (Karl et al., 2006; Asami et al., 2009; Uchida et al., 2008). The lateral portions of the PFC are involved in more deliberate forms of emotion regulation (Campbell-Sills et al., 2011) and attentional manipulation (Sharp et al., 2010) and have displayed varying functional and structural abnormalities in anxious samples, such as both increased and decreased activation in adult GAD to emotional faces (Blair, Shaywitz et al., 2008; Palm, Elliott, McKie, Deakin, & Anderson, 2011) and both increased and decreased activation during symptom provocation paradigms in PTSD (Bremner et al., 1999; Hou et al., 2007; Lanius et al., 2007). The lateral PFC has also demonstrated reductions in gray matter volumes in adult anxious samples (Woodward, Schaer, Kaloupek, Cediel, & Eliez, 2009; Yoo et al., 2005).

Consistent with these findings, childhood maltreatment has also been found to be associated qualitatively similar abnormal function and structure of these limbic and prefrontal brain structures, such as greater amygdala volumes in adolescents exposed to early neglect due to rearing in an institutional setting (Mehta et al., 2009) and greater activation of the amygdala during nonconscious fear processing in a group of adults with high levels of early life stress (Williams et al., 2009). A study in healthy participants observed a strong positive association between amygdala activation to threat-related (i.e., angry and fearful) emotional faces and

childhood maltreatment, with the strongest contributors being emotional abuse and emotional neglect (Dannlowski et al., 2012). A study examining cognitive control in maltreated adolescents observed increased insula activation during an inhibition paradigm (Mueller et al., 2010). Increased insula activation was also observed during fear acquisition and extinction in women exposed to childhood sexual abuse with PTSD (Bremner et al., 2005). Greater levels of childhood maltreatment were also related to smaller insula gray matter volumes in psychiatrically-healthy adults (Dannlowski et al., 2012). In a sample of adolescents exposed to early life stress, greater medial and lateral prefrontal activation was observed during a cognitive control paradigm (Mueller et al., 2010). In healthy adults, greater levels of early life stress were related to greater dorsal and ventral ACC activation during conscious processing of fearful faces (Williams et al., 2009). During acquisition of fear responses, women with PTSD due to childhood sexual abuse displayed increased activation of the lateral PFC (Bremner et al., 2005). In psychiatrically-healthy adults, greater than two adverse childhood experiences was related to significantly smaller volumes of the ACC relative to those which experienced no adverse childhood events (Cohen et al., 2006). A study examining childhood emotional maltreatment in individuals with and without depressive and anxiety disorders demonstrated that emotional maltreatment was associated with reduced left dorsal medial PFC volumes irrespective of diagnosis (van Harmelen et al., 2010).

Thus, the neural abnormalities implicated in childhood maltreatment and clinical anxiety overlap to a great extent and are characterized by a qualitatively similar pathology. More specifically, both populations demonstrate an enhanced reactivity of limbic (e.g., amygdala and insula) and prefrontal substrates to threat cues and negative emotional stimuli, perturbed corticolimbic interactions, and reductions in prefrontal cortical volumes. This substantial convergence of evidence suggests that childhood maltreatment experiences may instantiate long-lasting brain changes which predispose individuals to the development of

anxiety as adults. In order to test this hypothesis, one would ideally prospectively follow individuals whom have experienced childhood maltreatment and examine them longitudinally. However, this approach is impractical and time as well as cost-prohibitive. Instead, one can begin to examine this relationship by retrospectively investigating brain processes in a cross-sectional sample of participants dimensionally encompassing various levels of anxiety and maltreatment experiences.

The purpose of this investigation is to attempt to retrospectively identify a neural etiological mechanism which links childhood maltreatment experiences to the later development of anxiety. Given that emotional forms of childhood maltreatment (i.e., emotional abuse/neglect) are most reliably associated with the development or severity of anxiety in adulthood (Kuo et al., 2011; Mathews et al., 2008; Simon et al., 2009; Spinhoven et al., 2010; Teicher et al., 2010; Wright et al., 2009) and anxiety-relevant brain structure and function (Dannlowski et al., 2012; Edmiston et al., 2011; van Harmelen et al., 2010), this investigation will be limited to the neural correlates of emotional maltreatment. Functional maltreatment effects will be probed using a threat-related contrast from a facial emotion processing paradigm which robustly activates anxiety-relevant brain structures also demonstrated to be sensitive to early life stressors (Dannlowski et al., 2012; Williams et al., 2009). It is hypothesized increasing activation in and connectivity between limbic (i.e., amygdala and insula) and prefrontal cortical regions will underlie (i.e., mediate) the relationship between childhood emotional maltreatment and anxiety in adulthood. Additionally, it is predicted that decreasing gray matter volumes in prefrontal regions will also mediate this relationship. Lastly, given the role of the prefrontal cortex in emotion regulation and regulation of activity in limbic brain structures (Campbell-Sills et al., 2011; Etkin et al., 2009; Etkin et al., 2010; Quirk et al., 2003; Shin et al., 2005), it is predicted that prefrontal activity which mediates the maltreatment-anxiety relationship will also moderate the strength

of the mediating effect in limbic structures, such that greater prefrontal activity will be associated with a weaker limbic mediating effect.

Methods

Participants

One-hundred eighty-two participants ($n = 182$) were recruited through local online and print advertisement and referral from university-affiliated primary care clinics. These participants were composed of psychiatrically-healthy controls as well as individuals with various clinical and subclinical anxiety manifestations. Clinical participants were recruited for a primary diagnosis of PTSD, social anxiety disorder (SAD), generalized anxiety disorder (GAD), or panic disorder (PD). All diagnoses were confirmed through structured clinical interview by experienced clinicians using the Clinician-Administered PTSD Scale (CAPS) (Blake, Weathers, Nagy, & Kaloupek, 1995), Structured Clinical Interview for Diagnosis-DSM IV (SCID-IV) (First, Spitzer, Gibbon, & Williams, 1998), or Mini International Neuropsychiatric Interview (Sheehan et al., 1998). All participants were medication-free, not undergoing current psychotherapy for anxiety or related symptoms, and did not meet criteria for substance abuse or dependence. After complete description of the study to subjects, they provided informed written consent according to University of California-San Diego Institutional Review Board guidelines. See Table 1 for more information.

Self-Report Measures

The emotional abuse (EA) and emotional neglect (EN) subscales from the 28-item Short Form version of the Childhood Trauma Questionnaire (CTQ-SF) (D. P. Bernstein et al., 2003) were used to assess extent of exposure to childhood emotional maltreatment. Anxiety symptoms were quantified using the score from the anxiety subscale (BSIAnx) of the Brief Symptom Inventory-18 (Derogatis & Fitzpatrick, 2004), a six-item subscale in which

participants rate on a five-point Likert scale how often they were distressed by a list of symptoms within the past week.

<u>Emotion-Processing Task</u>

Participants completed a modified version of the Emotion Face Assessment Task (A. R. Hariri et al., 2005; M. P. Paulus, Feinstein, Castillo, Simmons, & Stein, 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.

<u>Image Acquisition</u>

Data were collected during task completion using fMRI image parameters sensitive to BOLD contrast on a 3.0T GE Signa EXCITE (GE Healthcare, Milwaukee, Wisconsin) scanner (T2*-weighted echo planar imaging, TR = 2000 msec, TE= 32 msec, field of view (FOV) = 250 x 250 mm, 64 x 64 matrix, 30 2.6mm axial slices with 1.4mm gap, 256 repetitions). A high-resolution T1-weighted image (172 sagitally acquired spoiled gradient recalled 1mm thick slices, inversion time (TI) = 450 msec, TR = 8 msec, TE = 4 msec, flip angle = 12 degrees, FOV = 250 x 250 mm) was also collected from each participant for anatomical reference. Images were preprocessed by interpolating voxel time-series data to correct for non-simultaneous slice acquisition in each volume.

<u>Activation Preprocessing and Individual Analysis</u>

Data were processed using the AFNI software package (Cox, 1996). Voxel time-series data were coregistered to an intra-run volume using a three-dimensional coregistration algorithm and then 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 timeseries 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 timeseries 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 directed towards angry vs. happy and fearful vs. happy faces. 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.

Functional Connectivity Preprocessing and Individual Analysis

For each contrast, task-related activation clusters in the amygdala, anterior insula, and prefrontal cortex were chosen as seed regions for connectivity analyses in order to test *a-priori* hypotheses concerning connectivity among these regions. Functional connectivity analyses were conducted according to previously established methods (G. A. Fonzo et al., 2010) but

slightly modified using a recently-published preprocessing pathway which maps and removes sources of artifact in scanner signal (Jo, Saad, Simmons, Milbury, & Cox, 2010). In brief, each participant's high-resolution anatomical was used to construct subject-specific gray matter (GM), white-matter (WM), and ventricular masks using FSL's FAST (fMRIB's Automated Segmentation Tool)(Smith, 2002; Smith et al., 2004; Woolrich et al., 2009). WM masks were then eroded by one voxel in each direction to prevent leakage of GM signal into the mask. Voxelwise local WM regressors for each subject were constructed by using a 30 mm sphere to average across voxels containing WM in the adjacent vicinity of each voxel, thus resulting in a region-specific WM time series at each voxel in the brain. Time series were also extracted from the lateral ventricles. Signal artifact arising from WM, ventricular cerebrospinal fluid, and six motion parameters was estimated using the AFNI program 3dTfitter, and the residual time series was calculated by removing these artifact effects from each subject's timeseries. The residual time series was then time-shifted, bandwidth filtered ($.009 < f < .08$), and smoothed using a 4 mm FWHM Gaussian kernel within each tissue-type (i.e., GM and WM) separately. The timeseries from clusters displaying task-dependent activation in seed regions was extracted from this blurred and filtered residual timeseries, and the psychophysiological interaction (PPI) of the seed timeseries and the effects-coded contrast of interest (i.e., angry vs. happy or fearful vs. happy) was then entered into a deconvolution analysis along with regressors for the seed timeseries, task contrast, and two baseline polynomials. The outcome measure of interest was the voxelwise Fisher-Z transformed correlation-coefficient (rFz) for the PPI regressor.

Optimized Voxel-Based Morphometry

Gray matter (GM) volumes were assessed using FSL-VBM, a voxel-based morphometry style analysis (Ashburner & 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, Brady, & Smith, 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 & Smith, 2001; Jenkinson, Bannister, Brady, & Smith, 2002) followed by nonlinear registration with FNIRT (J. L. R. Andersson, Jenkinson, & Smith, 2007a; J. L. R. Andersson, Jenkinson, & Smith, 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.

Task Effect Activation and Connectivity

In order to identify significant activations and connectivity within each contrast, t-tests against the null hypothesis were carried out on individual activation/connectivity maps across all participants.

Basic Mediation Analyses

Voxelwise basic mediation analyses were conducted using the MBESS package (Kelley & Lai, 2010) implemented in R (R Development Core Team, 2011). Emotional abuse (EA) and emotional neglect (EN) served as independent variables (in separate models) and anxiety symptoms served as the dependent variable in the mediation model. For each activation contrast, connectivity seed region, and GM volumetric map, voxelwise %SCs, rFzs, and GM volumes served as the respective mediating variable in the mediation model. The main outcome measure was the 95% confidence interval for the indirect effect (mediation effect). Bootstrapping of the indirect effect was utilized to determine the standard error and confidence intervals of the indirect effect (MacKinnon, Fairchild, & Fritz, 2007). At each voxel, a minimum of 200 bootstrap samples were utilized to derive standard error estimates.

Region of Interest and Whole Brain Analyses

Two types of analyses were conducted on the group level. In addition to a whole-brain (WB) exploratory analysis, *a-priori* region of interest (ROI) analyses were conducted on emotion-processing brain regions previously implicated in studies of anxiety and childhood maltreatment: bilateral insula, bilateral amygdala, and anterior cingulate/medial prefrontal cortex (ACC/mPFC). Boundaries of these ROIs were based upon both anatomical criteria and standardized locations taken from the Talairach atlas (Talairach & Tournoux, 1998). A threshold adjustment based upon Monte-Carlo simulations (using AFNI's program AlphaSim) was used to guard against false positives in the WB and ROI analyses.

Extended Mediation Analyses

In order to perform moderated mediation analyses and mediation with covariates, the average %SC, rFzs, and GM volumes were extracted from each participant from clusters displaying significant basic mediation effects in the voxelwise analyses. The PROCESS package (Hayes, In submission) implemented in IBM SPSS version 19.0 (SPSS Inc., an IBM company, 2010) was utilized for extended mediation analyses. Bootstrapping of the confidence interval of the indirect effect was utilized to determine significance. Several extended mediation analyses were conducted. To determine the robustness of mediation effects and their specificity to the relationship between childhood emotional maltreatment and anxiety, the depression subscale of the BSI was entered as a covariate in extended mediation analyses. To determine if mediating effects of brain function are significant irrespective of brain structure, GM volume was entered as a covariate. To test the potential moderating effect of corticolimbic interactions on mediation effects, moderated mediation analyses were conducted for basic mediation analyses which yielded significant mediation effects in both prefrontal and limbic regions. For these analyses, prefrontal activation was tested as a proposed moderator of the mediating effect of limbic activation on the relationship between

childhood emotional maltreatment and anxiety. To test the potential moderating role of brain structure on the mediation effect of brain function, in those activation clusters displaying functional mediation the average cluster GM volume was extracted from each participant and was tested as a proposed moderator of the mediating effect.

Results

Demographics and Symptoms

In brief, the sample was almost entirely female and displayed on average low-to-moderate levels of emotional maltreatment and anxiety symptoms. Maltreatment experiences and anxiety symptoms ranged from low to severe. See Table 1.

Relationships Among Childhood Emotional Maltreatment and Anxiety Symptoms

EA and EN were both significantly positive correlated with anxiety scores from the BSI (EA: Pearson's $r = 0.334$, $p < 0.001$; EN: Pearson's $r = 0.265$, $p < 0.001$). EA and EN were also significantly and highly positively correlated (Pearson's $r = 0.758$, $p < 0.001$). EA and EN were also significantly positively correlated with depression scores from the BSI (EA: Pearson's $r = 0.351$, $p < 0.001$; EN: Pearson's $r = 0.322$, $p < 0.001$). The anxiety and depression subscales of the BSI were also significant positively correlated (Pearson's $r = 0.694$, $p < 0.001$). The associations between EA/EN and anxiety and depression symptoms continued to remain significant after controlling for age, gender, years of education, and presence of a current anxiety or depressive disorder using multiple regression.

Behavioral Data

All participants completed the emotional face matching task with high levels of accuracy. There were no significant correlations between measures of accuracy and reaction time and measures of EA/EN, anxiety symptoms, or depressive symptoms (all p's > 0.05). See Table 1.

Task-Dependent Activation and Connectivity

In brief, the contrasts of matching to fearful vs. happy and angry vs. happy activated the bilateral anterior insula and dorsal prefrontal cortices. Positive connectivity was observed between the anterior insula seed regions and the amygdala as well as the dorsal prefrontal cortices. Positive connectivity was also observed between the dorsal prefrontal seed regions and the amygdala. Negative connectivity was observed between dorsal prefrontal seed regions and the posterior cingulate/precuneus. See Tables 2-5 for complete results.

Basic Mediation Analyses-Activation

Limbic ROIs

For the contrast of fearful vs. happy, greater activation in the left posterior insula partially mediated the relationship between EA and anxiety (Table 6 and Figure 1). There were no significant clusters found in limbic ROIs that mediated the relationship between EN and anxiety.

For the contrast of angry vs. happy, there were no clusters found in limbic ROIs that mediated the relationship between EA and anxiety. However, greater activation in the left amygdala partially mediated the relationship between EN and anxiety (Table 6 and Figure 3).

Whole Brain

For the contrast of fearful vs. happy, greater activation in the left temporal pole (middle/superior temporal gyri) partially mediated the relationship between EA and anxiety (Table 6). This effect remained significant when controlling for GM volumes, but it did not remain significant when controlling for depressive symptoms. Additionally, greater activation in the right fusiform gyrus partially mediated the relationship between EN and anxiety (Table 6).

For the contrast of angry vs. happy, decreasing activation in the right dorsolateral prefrontal cortex (inferior/middle frontal gyri; BA 10 and 46) partially mediated the relationship between EA and anxiety (Table 6 and Figure 2). Likewise, decreasing activation

in the right dorsolateral prefrontal cortex (inferior/middle frontal gyri; BA 10 and 46) also partially mediated the relationship between EN and anxiety (Table 6).

Basic Mediation Analyses-Connectivity

Limbic Seeds

For the contrast of fearful vs. happy, there were no regions of connectivity with task-dependent activity in the left anterior insula seed region or task-dependent activity in the right amygdala seed region which mediated the relationship between EA or EN and anxiety.

For the contrast of angry vs. happy, there were no regions of connectivity with task-dependent activity in the right anterior insula seed region which mediated the relationship between EA and anxiety. However, decreasing connectivity between task-dependent activity in the right anterior insula seed region and the posterior cingulate partially mediated the relationship between EN and anxiety (Table 8 and Figure 4). Furthermore, decreasing connectivity between task-dependent activity in the right anterior insula seed region and the left medial prefrontal cortex (medial/superior frontal gyri; BA 9 and 10) partially mediated the relationship between EN and anxiety (Table 8).

Prefrontal Seeds

For the contrast of fearful vs. happy, decreasing connectivity between task-dependent activity in the left dorsolateral prefrontal cortex (left inferior/middle frontal gyrus) seed region and the left precentral/postcentral gyri partially mediated the relationship between EA and anxiety (Table 7 and Figure 5). Furthermore, decreasing connectivity between these same two regions also partially mediated the relationship between EN and anxiety (Table 7).

For the contrast of angry vs. happy, decreasing connectivity between task-dependent activity in the right dorsolateral prefrontal cortex (right inferior/middle frontal gyrus) seed and activity in the left precentral/postcentral gyri partially mediated the relationship between EA and anxiety (Table 8). Similarly, decreasing connectivity between task-dependent activity in

the right dorsolateral prefrontal cortex seed and activity in the right precentral/postcentral gyri partially mediated the relationship between EN and anxiety (Table 8). Additionally, decreasing connectivity between task-dependent activity in the right dorsolateral prefrontal cortex seed and activity in the posterior cingulate partially mediated the relationship between EN and anxiety (Table 8 and Figure 6). There were no regions of connectivity with the dorsomedial prefrontal cortex (medial/superior frontal gyri) seed region which mediated the relationship between EA and anxiety. However, decreasing connectivity between task-dependent activity in the dorsomedial prefrontal cortex and activity in the posterior cingulate/precuneus partially mediated the relationship between EN and anxiety (Table 8).

Basic Mediation Analyses-Gray Matter Volumes

Limbic ROIs

There were no clusters in limbic ROIs in which GM volumes mediated the relationship between EA or EN and anxiety.

Whole Brain

There were no clusters in the whole brain analysis which mediated the relationship between EA and anxiety. However, decreasing GM volumes in the left precentral gyrus partially mediated the relationship between EN and anxiety (Table 9). However, this effect was no longer significant when controlling for depression. Furthermore, decreasing GM volumes in the right dorsolateral prefrontal cortex (inferior/middle frontal gyri; BA 10 and 46) partially mediated the relationship between EN and anxiety (Table 9 and Figure 7). As this structural cluster partially overlapped a functional cluster which mediated the relationship between EN and anxiety during processing of angry vs. happy faces, this structural mediation effect was also tested for significance when controlling for brain activation in this cluster. This effect continued to remain significant when controlling for functional activation to angry vs. happy faces.

Checking Anxiety Specificity of Mediation Effects

Except where noted, all of the aforementioned effects remained significant when covarying on depression and cluster GM volume. As an additional check to establish the specificity of these mediation effects to anxiety and not depression symptoms, all functional and structural clusters remaining significant after covarying on depression were also tested to see if they mediated the relationship between childhood EA/EN and symptoms of depression. None of the aforementioned effects significantly mediated the relationship between EA/EN and symptoms of depression, suggesting they are relatively specific mediating effects for symptoms of anxiety.

Extended Mediation Analyses

Testing Moderation of Limbic Functional Activation by Prefrontal Cortical Activity

As the basic voxelwise mediation analysis for activation to angry vs. happy faces on the relationship between EN and anxiety yielded a cluster in the left amygdala and right dorsolateral prefrontal cortex, the potential moderating effect of prefrontal activation on the mediation effect of amygdala activation was tested. The moderation effect of prefrontal activation on the amygdalar mediation of the EN-anxiety relationship was not significant on either path of the mediation model. Additionally, the converse model was also tested (i.e., amygdala activation as a potential moderator of the meditation effect of right dorsolateral prefrontal cortical activation). Again, the moderation effect was not significant on either mediation path. However, there was a marginally significant finding for an inverse correlation between activation magnitudes in these two mediating regions (Pearson's $r = -0.130$, $p = 0.079$), suggesting that individuals whom had greater activation in either the amygdala or prefrontal cortex tended to have less activation in the other region.

Testing Moderation of Functional Activation by Brain Structure

In order to test the potential interacting role of brain function and structure on the mediating effects of brain function, GM volumes were explored as potential moderators of mediation effects for all functional activation clusters (left amygdala, right dorsolateral prefrontal cortex, left posterior insula, and right fusiform gyrus). The only cluster which displayed a significant moderated mediation effect was the left amygdala mediation of the relationship between EN and anxiety for angry vs. happy. Specifically, on the path from EN to left amygdala activation there was a significant moderation by left amygdala GM volume (t = -2.7252, p = 0.0071; Figure 3) such that for increasing left amygdala GM volumes the mediation relationship grew increasingly weak and was nonsignificant at 1 SD above the mean GM volume. When the sample was split on median amygdala GM volume, those individuals with GM volumes below the median displayed a stonger positive relationship between EN and amygdala activation (standardized β = 0.290 vs. 0.043). There was no significant moderating effect of left amygdala GM volumes on the path from left amygdala activation to anxiety symptoms.

Discussion

This study produced three primary findings. First, increasing activation in limbic structures and decreasing activation in prefrontal regions during processing directed towards negative (angry and fear) vs. positive (happy) facial emotions mediated the relationship between EA/EN and adulthood anxiety. Second, greater disconnect of function between prefrontal seed regions and posterior medial and sensorimotor brain structures mediated the relationship between EA/EN and anxiety. Third, decreasing GM volumes in the right dorsolateral prefrontal cortex mediated the relationship between EN and aduldhood anxiety. All of these functional effects were significant irrespective of GM volumes and current depressive symptoms. Taken together, these findings suggest childhood maltreatment may predispose individuals to the eventual development of anxiety through long-lasting

dysregulatory influences on limbic and prefrontal brain responses to threat cues which are characterized by exaggerated reactivity of structures implicated in affective responses and attenuated function of higher-order frontal structures implicated in top-down control and affective regulation.

These results implicate increasing reactivity of limbic structures and decreasing engagement of frontal regions to negative or threatening socioemotional cues as a potential neural risk or vulnerability marker instantiated by early stressful life experiences which may promote the later manifestation of anxiety symptoms. This activation pattern is consistent with an *emotional dysregulation* mechanism of early life stress effects such that stressful experiences like childhood maltreatment disrupt normal socioemotional functioning by fostering enhanced states of fear and arousal in response to threatening interpersonal stimuli which cumulatively mount and ultimately result in a dysregulation of stress and fear responses and the emergence of anxiety disorder symptoms (Nolte, Guiney, Fonagy, Mayes, & Luyten, 2011). Both the amygdala and insula tend to be functionally important earlier in development (Decety & Michalska, 2010; Hoehl et al., 2010), and both regions also tend to show a protracted trajectory of gray matter development throughout the course of the lifespan (Grieve et al., 2011; Shaw et al., 2008), potentially indicating a prolonged period of neural plasticity and susceptibility to environmental influences. The current findings are therefore consistent with developmental studies and suggest that brain regions which are functionally important in childhood may be particularly sensitive to maladaptive environmental effects and these effects can persist into adulthood. It may be useful for future studies to attempt to disentangle the relative contributions of different types of emotional maltreatment (e.g., EA vs EN) towards increased amygdala and insula activation as well as the practical significance of the potential segregation of distinct effects in response to particular emotional stimuli.

Concomitant diminishment of dorsolateral prefrontal recruitment in response to angry facial cues due to the experience of both EA and EN also appears to promote the emergence of anxiety. This likely occurs through diminishing prefrontal cortical flexibility and subsequent capability for effective regulation of affective states, consistent with the observed decrements in emotion regulation skills observed in survivors of childhood maltreatment (Tottenham et al., 2010) as well as the importance of the dorsolateral prefrontal cortex in deliberate mechanisms of emotion regulation (Campbell-Sills et al., 2011). Although greater prefrontal activation was expected to mediate the relationship between EA/EN and anxiety, the opposite relationship was actually observed. This suggests that frequent findings for increased medial and lateral prefrontal activation in those exposed to childhood maltreatment or early life stress (Croy et al., 2010; Mueller et al., 2010; Williams et al., 2009) most likely reflect a compensatory adaptation rather than an underlying aspect of the psychopathological mechanism responsible for the emergence of poor mental health outcomes, consistent with the results observed here. This particular region of the dorsolateral PFC (inferior/middle frontal gyri; BA 10 and 46) is highly implicated in studies of executive function, working memory, and cognitive control (Yarkoni, Poldrack, Nichols, Van Essen, & Wager, In press), consistent with its proposed regulatory role over affective responses and limbic brain function. Convergent evidence was also found for a structural mediating effect of GM volumes in this same region on the relationship between EN and anxiety, consistent with our hypotheses. Both anxiety and childhood maltreatment have been found to be associated with reduced GM volumes in the lateral prefrontal cortices (Eckart et al., 2010; Gatt et al., 2010; Woodward et al., 2009; Yoo et al., 2005). This convergence of functional and structural effects across studies in the same brain region highly implicates the right dorsolateral prefrontal cortex (inferior/middle frontal gyri; BA 10 and 46) as a structure impacted by early maltreatment experiences which promotes an eventual susceptibility to the development of anxiety

symptoms. The lateral portions of the PFC, in particular, are some of the latest regions to fully mature over the course of brain development (Shaw et al., 2008), which suggests the relative immaturity of this region in childhood may render this structure particularly prone to a reduced functional capacity from chronic fear and stress states. Given the cross-sectional design of this study, it is impossible to determine if dorsolateral prefrontal structural changes preceded functional changes or vice-versa. However, the observation that both structural and functional mediating effects remained significant when controlling for the other suggests that there may be dual effects on both brain structure and function which result in a synergistic detrimental influence.

We did not observe evidence for significant interactions of prefrontal and limbic structures through moderation of the mediation effects of activity in either region on the relationship between EA/EN and anxiety symptoms. The lack of such a moderated mediation effect is plausible given the relative immaturity of the prefrontal cortex in childhood in comparison to limbic structures (Tamnes et al., 2010; Van Leijenhorst et al., 2010), suggesting prefrontal regions involved in top-down control and affective regulation may be relatively ineffective at "buffering" the detrimental impact of childhood maltreatment on limbic structures. Alternatively, the current study may not have been adequately powered to detect such a moderated mediation effect, which requires greater sample sizes that those necessary for detecting basic mediation effects (MacKinnon et al., 2007). Future studies are needed to determine if the functioning of prefrontal and/or limbic regions has the potential to buffer or potentiate the mediating effects of the other region on the relationship between childhood emotional maltreatment and anxiety symptoms in adulthood.

There were also no significant mediation effects of limbic-prefrontal connectivity on the relationship between childhood emotional maltreatment and anxiety in adulthood, contrary to expectations. Alterations in limbic-prefrontal connectivity are quite prevalent in anxious

populations (Etkin et al., 2009; G. A. Fonzo et al., 2010; A. E. Guyer et al., 2008b; Klumpp, Angstadt, & Phan, 2012), although less evidence for alterations in limbic-prefrontal connectivity is present in samples exposed to childhood maltreatment (G. A. Fonzo et al., in submissionb; Taylor et al., 2006). Instead, we observed several findings for decreased connectivity between limbic seed regions such as the anterior insula and dorsal prefrontal seed regions such as the medial and middle frontal gyri with activity in posterior medial (i.e., posterior cingulate/precuneus) and sensory/motor cortices (i.e., precentral/postcentral gyri) as mediators of the relationship between childhood emotional maltreatment and anxiety symptoms. Although not expected *a-priori*, there are other findings in the literature which relate a similar disconnect between posterior medial and prefrontal regions as a functional impact of childhood maltreatment and anxiety (Bluhm et al., 2009; Lanius et al., 2009). The posterior medial cortices are heavily implicated in the brain's default-mode network, so-named due to frequent observations for increased function in these regions while at rest compared to completion of some active task (Dosenbach et al., 2010). The precentral and postcentral gyri are the brain's primary motor and sensory cortices, respectively, and as such are implicated in a sensory-motor neural network (Dosenbach et al., 2010). Dorsal prefrontal regions are implicated in a frontoparietal executive control network involved in adaptive online control of behavior, while the anterior insula is implicated in a cinguloopercular salience network involved in the detection and response to salient environmental stimuli (Dosenbach et al., 2010). Posterior and sensory/motor cortical regions are some of the first to reach peak levels of GM volumes in the course of development (Gogtay et al., 2004; Shaw et al., 2008), while dorsal prefrontal regions tend to have a longer period of protracted development and reach peak GM volumes in late childhood/early adolescence (Gogtay et al., 2004; Shaw et al., 2008). Taken together, these findings suggest that childhood emotional maltreatment may disrupt long-distance coherent functioning between frontal-posterior and

frontal-sensory/motor functional networks, and this disrupted coherence may increase susceptibility to the later development of anxiety. This disruption of network coherence may occur as a consequence of maltreatment-related maladaptive influences on brain development which differentially impact the functioning of frontal and posterior cortical networks due to their disparate developmental trajectories. Given the functional implications of these networks, these findings may practically implicate an etiological psychological process in which top-down executive control and salience processing of socioemotional cues is unable to be brought into coherent functioning with resting-state self-relevant thought processes and basic sensory/motor functions. Longitudinal studies in maltreated populations will be useful in delineating the developmental characteristics of this process as well as the associated psychological effects.

There are several limitations to the current study. First, the design of this study was cross-sectional and retrospective and the results were correlational in nature. Thus, one cannot draw any firm conclusions as to the causal effects of childhood emotional maltreatment on brain function/structure or how any such effects may influence susceptibility to development or manifestation of anxiety. Although informed by theory and prior evidence, longitudinal studies are necessary to establish that childhood emotional maltreatment exerts effects on brain structure and function which promote susceptibility to the emergence of later anxiety symptoms. Second, the sample utilized was relatively heterogenous and composed of healthy participants as well as several clinical and non-clinical manifestations of anxiety. Given power constraints, we are unable to determine whether mediation effects are specific to a particular syndromal manifestation or whether diagnostic status moderated the strength of mediation effects. Third, many of the clinical anxiety participants met criteria for additional depressive disorders and this may reduce specificity of the results to the relationship between childhood emotional maltreatment and anxiety. However, statistical methods were employed

to attempt to control for any confounding effects of depressive symptoms. Inclusion of these subjects is also most consistent with the high comorbidity among anxiety/depressive disorders in the population (Kessler et al., 2005). Fourth, the majority of the sample was composed of adult Caucasian females. Thus, these results may not generalize well to male populations, populations of predominantly non-Caucasian ethnicity, or child/adolescent populations. Fifth, self-report measures of childhood maltreatment are susceptible to reporting biases or inaccuracies. Furthermore, maltreatment experiences may have occurred outside the time range queried by the self-report measure (e.g.., at a later stage of development). Sixth, the emotion-processing task used here does not directly isolate effects related to the target emotional expression due to the presence of a non-congruent face (i.e., the distractor) on each trial. Accordingly, participants must engage in several mental computations for matching, and group differences may arise due to the assessment of the target/matching face, inhibition of the distractor, or both. Thus, the results of this study are not directly comparable to those presenting single faces.

In summary, this study produced initial evidence for a neuroetiological mechanism linking childhood emotional maltreatment to anxiety in adulthood through a potentiation of limbic and an attenuation of prefrontal responses to socioemotional threat cues, consistent with existing evidence for emotional dysregulation as a psychological characteristic in survivors of childhood maltreatment (Pechtel & Pizzagalli, 2010; Tottenham et al., 2010; Wright et al., 2009) as well as those with anxiety (Cornwell, Johnson, Berardi, & Grillon, 2006; Larson, Nitschke, & Davidson, 2007; Tsunoda et al., 2008). Currently, functional neuroanatomical models of clinical anxiety focus almost exclusively on neural abnormalities manifested in the psychopathological state with little attention towards etiological pathways which may underlie these manifestations. Ultimately, the retrospective elucidation of neural effects which underlie the relationship between childhood emotional maltreatment and

adulthood anxiety demonstrated here may provide an initial impetus for the consideration of developmental characteristics such as early life experiences in systems neuroscience etiological models of anxiety. Such efforts may ultimately lead to the identification of several distinct developmental pathways and circumscribed neural effects which predispose persons to develop clinical anxiety as adults. The identification of these pathways could then be used to refine existing theory, inform the development of specialized/targeted treatments, identify at-risk individuals, and modify existing treatments for distinct sub-groups of anxious individuals.

Introduction

Anxiety disorders are a major public health problem with a high prevalence and a substantial burden of suffering (Kessler, Chiu, Demler, Merikangas, & Walters, 2005; Mendlowicz & Stein, 2000). Great effort in recent years has been directed towards elucidating the underlying neurobiological dysfunction which may be responsible for the development of excessive anxiety, yet the majority of studies have focused only on descriptive characterization of dysfunctional brain substrates in participants that have already developed anxiety disorders (M. P. Paulus, 2008). Although such studies are useful in directing the focus of research towards relevant brain regions, they are unable to offer information concerning etiological neural mechanisms which may potentially underlie the development of clinical anxiety. In order to leverage our understanding of the neurobiology of anxiety disorders towards useful efforts at early identification and prevention, it is necessary to move beyond a descriptive focus on end-state neural abnormalities towards the characterization of such etiological neural mechanisms which may lead to the manifestation of anxiety disorders. Developmental psychopathology emphasizes the interplay of individual risk & resilience factors in governing the emergence of mental disorders (Ialongo et al., 2006), and useful information for the postulation of etiological neural mechanisms may be gleaned from studies which examine neural structure and function that relate to developmental risk factors known to predispose individuals to the later development of anxiety disorders as adults. One such developmental risk factor for adult anxiety is childhood maltreatment, a prevalent and particularly damaging from of early life stress which can be 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 (Goodman, Quas, & Ogle, 2010). Childhood maltreatment is not only reliably associated with more severe anxiety in adulthood (Kuo, Goldin, Werner, Heimberg, & Gross, 2011; Simon et al., 2009; Zlotnick et al., 2008),

there is also a substantial overlap of affected neural substrates (Dannlowski et al., 2012; Etkin & Wager, 2007; Williams et al., 2009), suggesting investigation of the overlapping neural correlates of this risk factor and adulthood anxiety may offer a prime opportunity for the development of a neurodevelopmental etiological model.

Therefore, the main purpose of this study is to determine if functional and structural magnetic resonance imaging can be used to retrospectively identify brain structure and function which underlies the relationship between history of childhood maltreatment and anxiety symptoms in adulthood. Ultimately, such information may be useful in the postulation, development, and refinement of working models which link specific patterns of brain structure and function from early development to the onset of clinical anxiety in adulthood. First, the existing literature will be reviewed concerning the relationship between childhood maltreatment and anxiety in adulthood as well as the structural and functional changes associated with both populations. Second, a hypothesized working model informed by relevant theoretical constructs will be proposed in order to relate the neural effects of childhood maltreatment to the development of adulthood anxiety. Third, the methods and results of the current investigation will be presented and the implications of the findings will be discussed.

Review of Literature

Childhood Maltreatment and Anxiety

There is abundant evidence in the literature for a relationship between childhood maltreatment and adverse health outcomes (Walker et al., 1999), including the development of clinical and sub-clinical anxiety manifestations. For example, childhood emotional maltreatment predicts greater adulthood levels of anxiety, depression, and dissociation in college students, and these effects were mediated by influences on early maladaptive cognitive schemas (Wright, Crawford, & Del Castillo, 2009). Prolonged institutional rearing, or late adoption from a minimally-adequate orphanage setting, was associated with greater symptoms of anxiety in childhood and adolescence and greater likelihood of meeting criteria for an anxiety disorder (Tottenham et al., 2010). Peer and parental verbal abuse was related to greater levels of anxiety and depression in a large sample of young adults (ages 18-25) (Teicher, Samson, Sheu, Polcari, & McGreenery, 2010). Greater levels of early life stress were related to a larger negativity bias, or an attributional bias towards expecting and perceiving negative events and outcomes, as well as greater autonomic reactivity to fear cues in a large sample of healthy adults (Williams et al., 2009); moreover, these same effects are frequently observed in anxious subjects, highlighting a potential attributional construct which fosters manifestation of sub-clinical anxiety symptoms.

Similar relationships have been observed between childhood maltreatment and clinical manifestations of anxiety. Childhood sexual and physical abuse was associated with greater state and trait anxiety in outpatients of an anxiety disorders clinic (Mancini, Van Ameringen, & MacMillan, 1995). Childhood abuse was found to predict greater levels of posttraumatic stress disorder (PTSD) symptoms in a sample of low-income African-Americans seeking general medical care in an urban public hospital (Binder et al., 2008) as well as South African adolescents (Fincham, Altes, Stein, & Seedat, 2009), and these effects were even more

pronounced in combination with a specific genetic polymorphism of the stress-related gene *FKBP5* (Binder et al., 2008). Childhood nonsexual maltreatment was also associated with development of PTSD in a sample of female Veteran's Affairs primary care patients (Lang et al., 2008). Childhood abuse and neglect was associated with greater severity of social anxiety disorder (SAD) symptoms, trait anxiety, and depression and poorer quality of life, function, and resilience in treatment-seeking individuals (Kuo et al., 2011; Simon et al., 2009), and greater number of types of maltreatment present had an additive effect on these outcomes (Simon et al., 2009). Childhood trauma was associated with greater severity of sub-threshold obsessive-compulsive disorder (OCD) symptoms in college students, even after controlling for general anxiety symptoms (Mathews, Kaur, & Stein, 2008). Childhood maltreatment was found to be a risk factor for development of generalized anxiety disorder (GAD) in a large longitudinal sampling of New Zealanders, and this effect was relatively distinct for GAD as compared to major depressive disorder (MDD) and comorbid GAD/MDD (Moffitt et al., 2007). The experience of a potentially-traumatic event in childhood was associated with greater lifetime probability of development of panic disorder (PD) in adulthood in a household-stratified sample of Chilean adults, and interpersonal trauma in childhood compared to interpersonal trauma in adulthood was associated with greater likelihood of developing PD, agoraphobia, and PTSD (Zlotnick et al., 2008). Additionally, controlling for comorbidity the association between childhood adversity and development of mood/anxiety disorders was greater than the relationship between negative events across the lifespan and development of mood and anxiety disorders (Spinhoven et al., 2010). These latter findings, in particular, illustrate the deleterious consequences of traumatic/stressful events in childhood in relation to ongoing psychological and biological development potentially due to adverse influences on the normative developmental trajectory. Taken together, these findings demonstrate that maladaptive early-life environmental influences such as childhood

maltreatment have the potential to shift developmental trajectories towards the eventual emergence of adverse mental health outcomes such as clinical and sub-clinical anxiety. In the next section, evidence for potential psychological mechanisms which may mediate this process is reviewed.

Childhood Maltreatment and Psychological Function

In addition to risk for specific anxious diagnoses and sub-clinical anxiety symptoms, childhood maltreatment and other forms of early life stress (ELS) have also been shown to exert detrimental effects on a broad range of cognitive and emotional processes which persist for years and may increase susceptibility to development of anxiety (Pechtel & Pizzagalli, 2010). In the cognitive domain, adolescents exposed to ELS display impairments in inhibitory control (Mueller et al., 2010) as do college students exposed to sexual abuse (Navalta, Polcari, Webster, Boghossian, & Teicher, 2006), and neglected children score lower on intelligence quotient tests relative to non-neglected children in various domains such as language, memory/learning, and attention/executive function (M. D. De Bellis, Hooper, Spratt, & Woolley, 2009). Furthermore, greater deficits are related to greater PTSD symptoms, suggesting preserved cognitive function may provide some mitigating influence on severity of anxiety symptoms. Memory function has also been found to be impaired in survivors of maltreatment, particularly visual memory (Bos, Fox, Zeanah, & Nelson, 2009; Navalta et al., 2006), and this was observed even without development of PTSD, a condition often associated with memory impairments (Bremner, 2006a).

In the emotional domain, childhood adversity was associated with elevated symptoms of anhedonia and less positive responses to reward cues in a monetary incentive reward paradigm (Dillon et al., 2009), which is notable given that robust reward brain function may serve as a resiliency factor protecting individuals from development of PTSD following severe trauma (Vythilingam et al., 2009). Maltreated children were found to display quicker reaction

times in identifying fearful faces (Masten et al., 2008) as well as greater preferential attention to angry faces and increased sensitivity to detection of an angry facial expression at a lower emotional intensity (Gibb, Schofield, & Coles, 2009), which is consistent with the "negativity bias" and its relation to early life stress observed in a sample of healthy adults (Williams et al., 2009). Moreover, an attention bias towards threatening stimuli is a prominent feature of many anxiety disorders (N. Amir, Taylor, Bomyea, & Badour, 2009; N. Amir & Bomyea, 2010), highlighting another potential psychological construct which may be shaped by early maltreatment experiences and predispose individuals to the later development of anxiety. Anxiety was found to be positively associated with greater severity of early maladaptive cognitive schemas in the domains of vulnerability to harm, self-sacrifice, and defectiveness/shame in college students (Wright et al., 2009), consistent with the prominent early maladaptive schemas observed in several manifestations of anxiety (Hawke & Provencher, 2011). Prolonged institutional rearing was found to be associated with deficits in emotion regulation in childhood and adolescence, another skill found to be deficient in individuals with anxiety (Campbell-Sills et al., 2011; Cloitre, Miranda, Stovall-McClough, & Han, 2005; Etkin & Schatzberg, 2011).

In summary, there are numerous cognitive and affective functions influenced by early life stressors such as childhood maltreatment which may serve to increase vulnerability to the development of anxiety in adulthood. Furthermore, these effects appear to be pervasive and long-lasting, characteristics which are best explained by the developmental concept of *hierarchic motility*—the concept that various cognitive, affective, and social competencies (or incompetencies) at earlier stages in development will carryover and influence successful negotiation of developmental requirements at the next phase (Cicchetti & Cohen, 1995). In normal development, successful incorporation of basic psychological processes influences the later successful integration of intermediate and eventually advanced psychological processes.

In cases of abnormal development, an early life stressor such as childhood maltreatment detrimentally impacts the integration of basic psychological processes, and this deficient integration then detrimentally affects the successful integration of intermediate and later advanced psychological processes. Such an iterative process can explain how discrete early experiences can exert such long-lasting, maladaptive psychological effects, which occurs concomitant with biological and neural changes (Pechtel & Pizzagalli, 2010). In the following sections, the neurobiological abnormalities associated with childhood maltreatment and anxiety disorders will be reviewed.

Anxiety-Related Brain Abnormalities

In recent years, a burgeoning research base demonstrating abnormal brain structure and function in anxiety has been developed utilizing neuroimaging tools such as structural (sMRI) and functional magnetic resonance imaging (fMRI). Such studies have generally yielded evidence for abnormalities of limbic and prefrontal brain structures across different anxious populations and paradigms.

<u>Amygdala</u>

One brain structure which has been consistently demonstrated to display anxiety-related abnormalities is the amygdala, an almond-shaped collection of cell nuclei located within the medial temporal lobe of each hemisphere. This subcortical region is interconnected with sensory, motor, efferent autonomic, and higher-order associative brain structures--consistent with its role in detection of salient environmental stimuli (particularly emotional or social stimuli) and initiation of secondary cognitive, emotional, and behavioral responses (Costafreda, Brammer, David, & Fu, 2008). The amygdala is critically implicated in bottom-up processes such as nonconscious reactivity to masked fearful faces (Rauch et al., 2000), fear conditioning (Duvarci, Popa, & Pare, 2011), and induction or generation of an exteroceptive fear response, or fear in response to an external cue (Feinstein, Adolphs, Damasio, & Tranel,

2011). Given its primacy in fear-related processes, amygdala abnormalities in anxious

samples are frequently observed. In particular, the amygdala frequently displays

hyperactivation in anxious samples to threatening or negative emotional stimuli such as fearful

faces or fear-invoking pictures (Etkin & Wager, 2007). For example, the amygdala has

displayed hyperactivity in response to both conscious (G. A. Fonzo et al., 2010; Shin et al.,

2005) and nonconscious fearful face-processing paradigms (Bryant et al., 2008; Rauch et al.,

2000) in samples with PTSD. Similar hyperactivity has been observed in SAD in response to

fearful, angry, and contemptuous faces (Phan, Fitzgerald, Nathan, & Tancer, 2006; M. B.

Stein, Goldin, Sareen, Zorrilla, & Brown, 2002). Amygdalar abnormalities have also been

observed in subclinical anxious manifestations such as high trait-anxious college students (M.

B. Stein, Simmons, Feinstein, & Paulus, 2007), suggesting this enhanced amygdalar reactivity

may be a diagnosis-nonspecific phenotype which renders individuals prone to the

development of anxiety disorders—also consistent with evidence descending from studies of

serotonin transporter polymorphism influences on amygdalar function (A. R. Hariri et al.,

2005). In addition to more general threat-related stimuli (such as emotional faces), the

amygdala has also demonstrated hyperactive function in the context of behavioral paradigms

which target constructs particularly relevant to a specific disorder, such as anticipated peer

evaluation in pediatric SAD (A. E. Guyer et al., 2008b), symptom provocation in adult PTSD

(I. Liberzon, Britton, & Luan Phan, 2003), and processing of self-referential critical statements

in adult SAD (Blair et al., 2008). Although the amygdala consistently displays abnormal

function in anxious relative to non-anxious samples, the directionality of these differences

varies. A recent meta-analysis identified the amygdala as a brain region displaying abnormal

function across several manifestations of anxiety (Etkin & Wager, 2007), although it also

highlighted findings for both increased and decreased amygdalar activation in adult PTSD,

albeit in slightly different anatomical regions. Similarly, the amygdala has demonstrated both

increased and decreased activation during emotion processing paradigms in GAD (Blair, Shaywitz et al., 2008; Nitschke et al., 2009) and both decreased activation and no significant differences during emotional face processing in PD (Pillay, Gruber, Rogowska, Simpson, & Yurgelun-Todd, 2006; Pillay, Rogowska, Gruber, Simpson, & Yurgelun-Todd, 2007). Some of this variability may relate to differences in task-evoked functional connectivity between studies, or the degree of coordinated function among different brain regions during completion of a given task. Accordingly, findings for abnormal amygdalar connectivity in anxious samples are also prominent, including less distinct amygdalo-frontal connectivity among different amygdalar nuclei in adult GAD (Etkin, Prater, Schatzberg, Menon, & Greicius, 2009), disrupted amygdalo-insular and amygdalo-cingulate connectivity in adult PTSD (G. A. Fonzo et al., 2010), and altered amygdalo-prefrontal connectivity in adult and pediatric SAD (A. E. Guyer et al., 2008b; Liao et al., 2010).

The amygdala has also been demonstrated to display abnormal structure in anxious samples, such as greater bilateral total volumes (M. D. De Bellis et al., 2000) in children with GAD relative to non-anxious comparison subjects as well as increased gray matter density in the bilateral amygdala in adult patients with GAD (Etkin et al., 2009). In contrast, reductions in amygdalar volumes have also been observed, such as reduced left amygdala gray matter volume in children with anxiety disorders (mainly GAD and SAD) (Milham et al., 2005), reduced left amygdala volume in a meta-analysis of adult PTSD (Karl et al., 2006), reduced bilateral amygdala volumes in adult PD (Hayano et al., 2009), and reduced gray matter volume in the right amygdala in adult PD (Asami et al., 2009). Although some of these findings differ in directionality of structural differences, differences in study methodology (i.e. measurement of total volume vs. measurement of gray matter density) or diagnostic composition may account for these conflicting results. Overall, the implicated role of the amygdala in functional processes relevant for the etiology of anxiety (e.g., fear conditioning,

fear induction, salient stimulus processing) as well as the strong convergent evidence for structural and functional amygdala abnormalities in individuals with anxiety disorders across the lifespan strongly implicates this brain region as a crucial component of the pathophysiology of these disorders. In particular, the amygdala is an important component of the neural architecture underlying the acquisition and initiation of fear responses, thus demonstrating its circumscribed role in bottom-up aspects of the anxiety response requiring evaluation of an external stimulus and initiation of appropriate physiological/behavioral responses.

Insula

Recent attention has been drawn to a previously-understudied mass of cortex located beneath the Sylvian fissure known as the insula due to evidence indicating its crucial role in the construct of interoception, or the sense of the overall physiological condition of the body (Craig, 2003). Interoceptive sensations are posited to form the basis for all subjective feeling states (Craig, 2004), and as such are therefore critically important to the manifestation of anxious feelings and sensations (O. Pollatos, Traut-Mattausch, Schroeder, & Schandry, 2007). Core interoceptive signals converge in the posterior portions of the insula and are sequentially re-represented along the body of the insula in a posterior-to-anterior fashion wherein interoceptive representations become progressively more complex as they are integrated with signals converging from other brain regions such as the amygdala, entorhinal cortex, anterior cingulate, and prefrontal cortex (Craig, 2009). Convergent evidence for the potential role of abnormal interoception in predisposing individuals to experience clinical anxiety (M. P. Paulus & Stein, 2010) descends both from physiological challenge (Domschke, Stevens, Pfleiderer, & Gerlach, 2010) and neuroimaging studies which demonstrate insular hyperactivation across a wide range of anxious manifestations (Etkin & Wager, 2007). In particular, insular hyperactivation in the context of emotion-processing paradigms has been

demonstrated in adult PTSD (G. A. Fonzo et al., 2010) and adult SAD (Gentili et al., 2008; Shah, Klumpp, Angstadt, Nathan, & Phan, 2009; Straube, Mentzel, & Miltner, 2005) where it has been interpreted as part of a hyperactive bottom-up emotional salience processing system (Phan et al., 2004). Insula hyperactivity during processing of angry vs. happy faces was also observed in PD (G. A. Fonzo et al., in submissiona), consistent with the potential role of the insula in spontaneous panic attacks (Dresler et al., 2011). Structural insular abnormalities have also been demonstrated, specifically reduced gray matter density in adult PTSD relative to combat-exposed controls (Chen et al., 2006; Kasai et al., 2008) and both increased gray matter density and decreased gray matter volumes in adult PD (Asami et al., 2009; Uchida et al., 2008). Insula abnormalities have also been observed in subclinical anxiety manifestations such as high-trait anxious young adults, such as increased insula activation during anticipation of negative images (A. N. Simmons et al., 2010; A. Simmons, Strigo, Matthews, Paulus, & Stein, 2006) and processing of emotional faces (M. B. Stein et al., 2007), suggesting increased insular reactivity may also be an underlying neural phenotype which precedes the manifestation of clinical anxiety. Consistent with this evidence, abnormal interoception and insula function has been proposed to play a crucial role in the development and maintenance of anxiety symptoms (M. P. Paulus & Stein, 2006; M. P. Paulus & Stein, 2010), and the insula was observed in a recent meta-analysis to be one of only two regions (along with the amygdala) which displays hyperactive function across PTSD, SAD, and specific phobia (Etkin & Wager, 2007).

<u>Prefrontal Cortex</u>

The prefrontal cortex (PFC) is a cytoarchitecturally-complex and recently-evolved portion of the frontal lobes important for higher-order cognitive, emotional, and social processes, particularly for the modulation/regulation of stress and fear responses (Monk et al., 2006; A. Simmons et al., 2008), which is consonant with its functional implication in top-

down anxiety processes such as worry (Paulesu et al., 2010), intolerance of uncertainty (Krain et al., 2008), and emotion regulation (Campbell-Sills et al., 2011; Etkin, Prater, Hoeft, Menon, & Schatzberg, 2010). The midline PFC, known as the anterior cingulate/medial prefrontal cortex (ACC/mPFC), is involved in higher-order anxiety-related integrative constructs such as implicit regulation of emotional/physiological state (Critchley et al., 2003; Etkin et al., 2010), processing of emotional context (Rougemont-Bucking et al., 2011), self-relevance (Blair et al., 2008), and social cognition (Amodio & Frith, 2006). The ACC/mPFC can be considered a spatially heterogenous processing area, with the more ventral portions (vACC/mPFC) being implicated in more automatic and parasympathetic processes such as inhibition of amygdalar activity (Quirk, Likhtik, Pelletier, & Pare, 2003), heart-rate deceleration to emotional faces (Critchley et al., 2005), and reward processing (Beckmann, Johansen-Berg, & Rushworth, 2009) whereas the more dorsal portions (dACC/mPFC) are implicated in more effortful and sympathetic processes such as conflict monitoring (Amodio & Frith, 2006), sympathetic arousal (Critchley et al., 2003), and implicit emotion regulation (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006).

In the context of anxiety, anterior cingulate & medial prefrontal abnormalities are often interpreted in the context of compensatory engagement to downregulate limbic hyperactivity, particularly in PTSD (Bryant et al., 2008), or as excessive appraisal of emotional stimuli or expression of emotional responses (Etkin, Egner, & Kalisch, 2011). Given the disparate functional nature of subregions of the ACC/mPFC, there are many findings for both hyperactive and hypoactive ACC/mPFC function in clinical samples. Such results include vACC/mPFC hyperactivation to fearful faces in pediatric GAD (McClure et al., 2007) and dACC/mPFC hyperactivation during a resting state following worry induction in adult GAD (Paulesu et al., 2010), but decreased dACC/mPFC activation during an implicit emotion regulation paradigm in adult GAD (Etkin et al., 2010). In SAD, the ACC/mPFC was

shown to hyperactivate in response to pictures of disgust faces (N. Amir et al., 2005) and angry faces (Goldin, Manber, Hakimi, Canli, & Gross, 2009) as well as contemplation of negative self-referential statements (Blair et al., 2008) in adults, while greater ACC/mPFC activation was associated with intolerance of uncertainty in adolescents with GAD and SAD (Krain et al., 2008). However, dACC/mPFC hypoactivation in adult SAD has also been observed during emotion regulation (Goldin et al., 2009) and completion of a mentalizing task (Sripada et al., 2009). In PD, this region has demonstrated both increased and decreased activation to happy faces (Pillay et al., 2007) as well as decreased activation to fearful faces, but increased activation to neutral faces (Pillay et al., 2006). The heterogenous nature of functional ACC/mPFC abnormalities is most apparent in studies of PTSD where both ventral hypoactivity and hyperactivity has been observed in response to fearful face processing (Bryant et al., 2008; Shin et al., 2005), while other studies have reported dACC/mPFC hyperactivation in the context of cognitive/attentional paradigms (Carrion, Garrett, Menon, Weems, & Reiss, 2008; Felmingham et al., 2009; Morey, Petty, Cooper, Labar, & McCarthy, 2008). Furthermore, this region has been found to display reduced volume or gray matter density in multiple samples of adults with PTSD (Karl et al., 2006; Kitayama, Quinn, & Bremner, 2006; Woodward et al., 2006) as well as in a twin study which suggests this volume reduction is due specifically to development of PTSD following trauma (Kasai et al., 2008). This reduction is not specific to PTSD, however, as recent studies in adult PD have demonstrated reduced gray matter density/volume (Asami et al., 2009; Uchida et al., 2008) relative to non-anxious comparison subjects.

Given the immense variability of ACC/mPFC abnormalities across anxious paradigms and samples, this region has recently been proposed to play an important role in a construct known as contextualization of experience, or the perception, representation, processing, and integration of contextual cues from the environment for establishing the relationship of the

organism to its environment and guiding appropriate emotional/behavioral responses (I. Liberzon & Sripada, 2008). This construct is appropriately broad to capture the implicated role of this brain region across a diverse variety of behavioral tasks and is supported by recent evidence indicating the ACC/mPFC is involved in integrating emotional stimuli with an appropriate context (G. A. Fonzo et al., 2010; Rougemont-Bucking et al., 2011). Furthermore, the ACC/mPFC is also implicated in the construct of interoception (in addition to the insula) as demonstrated by its role in cardiovascular awareness (O. Pollatos, Schandry, Auer, & Kaufmann, 2007), suggesting that structural/functional abnormalities observed in anxious populations may also relate to a more general propensity for altered processing of visceral sensations.

The lateral portions of the PFC are involved in more deliberate forms of emotion regulation (Campbell-Sills et al., 2011) and attentional manipulation (Sharp et al., 2010) and therefore might be expected to display hyperactive function in anxious samples in the context of behavioral tasks which require goal-oriented inhibition/manipulation of attention/emotional state in response to salient emotional cues. However, similar to the ACC/mPFC, directionality of lateral PFC group differences in anxious manifestations varies. For example, studies have reported increased ventrolateral PFC (vlPFC) activation in adolescents with GAD relative to non-anxious controls during an attentional probe task with angry faces (Monk et al., 2006) and increased activation in adult GAD to angry faces relative to controls (Blair, Shaywitz et al., 2008), but decreased activation in the lateral PFC during worry suppression in elderly GAD subjects (Andreescu et al., 2011) and during emotional face processing in adult women with GAD (Palm, Elliott, McKie, Deakin, & Anderson, 2011). In adult PTSD the lateral PFC has demonstrated decreased activation during emotion regulation (New et al., 2009), both increased and decreased activation during symptom provocation paradigms (Bremner et al., 1999; Hou et al., 2007; Lanius et al., 2007), and increased activation during an attentional

control paradigm with emotional distracters (Morey et al., 2008). Similarly, in adult SAD studies have demonstrated increased lateral PFC activation during the processing of harsh emotional faces (N. Amir et al., 2005; M. B. Stein et al., 2002) but decreased activation during anticipation of public speaking (Lorberbaum et al., 2004) and during cognitive reappraisal of angry faces (Goldin et al., 2009); however, temporal dynamics of emotion regulation may also play a role as another study observed greater late vs. early lateral PFC responses for adult SAD subjects relative to controls during reappraisal of negative self beliefs (Goldin, Manber-Ball, Werner, Heimberg, & Gross, 2009). Results for lateral PFC abnormalities in adult PD have been more homogenous, demonstrating increased activation during auditory processing (Pfleiderer et al., 2010) and in response to threat-related words (Maddock, Buonocore, Kile, & Garrett, 2003). Similar abnormalities have been observed in subclinical anxiety manifestations, such as greater activation of the left vlPFC during an emotional Stroop task with threatening stimuli in high trait-anxious young adults (Engels et al., 2007).

The literature is also replete with findings for prefrontal structural differences in PTSD samples, such as significantly larger gray matter volumes in the middle-inferior and ventral PFC in youth with maltreatment-related PTSD relative to non-maltreated controls (Carrion et al., 2009; Richert, Carrion, Karchemskiy, & Reiss, 2006), attenuated frontal lobe asymmetry in a similar cross-sectional comparison (Carrion et al., 2001), reduced lateral orbitofrontal and inferior/middle frontal gyrus cortical volume in adult PTSD relative to trauma-exposed controls (Woodward, Schaer, Kaloupek, Cediel, & Eliez, 2009) and non-traumatized controls (Eckart et al., 2010) and reduced cortical PFC thickness in adults with PTSD relative to combat-deployed controls (Geuze et al., 2008). Additionally, one study has demonstrated reduced lateral PFC gray matter volumes in adults with PD relative to non-anxious controls (Yoo et al., 2005). Thus, findings for lateral PFC volumetric abnormalities in anxiety disorders are relatively segregated to adult and pediatric PTSD, although the

commonality of gray matter or cortical volume/density reductions across multiple studies is suggestive of a homogenous detrimental effect on PFC gray matter integrity.

<u>Summary</u>

In aggregate, these findings implicate functional and structural abnormalities of a widely-dispersed emotion-processing network in anxiety disorders, primarily characterized by: a) hyperactivity of core limbic structures such as the amygdala and insula to emotional stimuli with concomitant hyperactivity of prefrontal structures such as the ACC/mPFC and lateral PFC; and b) reductions in limbic and prefrontal structural volumes, particularly in adult samples. Although findings for directionality of differences (i.e. increased or decreased) varies across studies and populations (particularly in prefrontal regions), the common implication of affected neural substrates during anxiety-relevant behavioral constructs as well as observations for similar dysfunctions in anxiety-prone or subclinically anxious samples (A. N. Simmons et al., 2010; A. Simmons et al., 2008; M. B. Stein et al., 2007) is strongly suggestive of a shared dysfunction in neural architecture/function across disorders. This dysfunction is most succinctly characterized as a hyperactivity of bottom-up neural substrates (i.e. amygdala/insula) with either hyperactivity or hypoactivity of top-down brain regions (i.e. PFC), suggesting a dual higher-order dysfunction characterized by: a) inefficient prefrontal regulation of exaggerated limbic reactivity to salient stimuli; and/or b) exaggerated compensatory top-down engagement which manifests in cognitive symptoms of anxiety such as worry and intolerance of uncertainty. The relative predominance of top-down hyperactivity or hypoactivity observed seems to depend upon predominance of relevant symptom manifestations in the sample of interest (e.g., hyperarousal, worry, panic attacks) as well as, to some extent, characteristics of the behavioral task (Felmingham et al., 2009; Kemp et al., 2009; Tuescher et al., 2011).

Childhood Maltreatment Effects on Brain Structure and Function

Childhood maltreatment and other early-life stressors have been demonstrated to relate to long-lasting and pervasive changes in neural structure and function which are detectable in adulthood. In this section, the brain changes associated with normative development will first be briefly reviewed in order to place the findings related to childhood maltreatment in the proper developmental context. Then, neuroimaging findings concerning childhood maltreatment effects on brain structure and function will be discussed. Finally, the relationship between mind-body states and endocrinological factors which may contribute to the biological instantiation of psychological states and experiences will be discussed.

Brain Development From Childhood to Adulthood

Structural Changes

Investigations of changes in brain structure across the lifespan have highlighted that the brain does not uniformly change either in time or in location. Rather, the timing and gradient of structural changes occurs depending upon the particular brain region, level of cytoarchitectural/functional complexity, and the particular phase of development. In brief, the major commonality of structural change across the brain regards the relative volumes of gray and white matter. Specifically, volumes of gray matter (composed of neuronal bodies and dendritic processes) and white matter (composed mainly of myelinated axons) can both be characterized by a growth curve with an initial increase in volume followed by a relative stabilization of varying length and then an eventual decline (Groeschel, Vollmer, King, & Connelly, 2010). For gray matter (GM), this growth curve is characterized by an initial level of sharp increase over the first 3-5 years of life followed by a stabilization and beginning of decline within the first decade (Gogtay et al., 2004). White matter (WM), in contrast, demonstrates a much more protracted range of volumetric development, beginning in early childhood and continuing until the sixth decade of life followed by a rapid decline in senescence. This volumetric trend is paralleled by a similar protracted increase in WM

fractional anisotropy (FA; a proxy measure for WM integrity) from early development into the fourth decade of life, followed by a steadily increasing decline in old age (Westlye et al., 2010).

These GM volumetric growth curves have been interpreted to indicate onset of regional maturation coinciding with the shift from increasing volume to stabilization and eventual decline, thought to reflect the cellular loss of neuronal cell bodies and synaptic pruning which characterize a period of functional stability (Gogtay et al., 2004). The age of relative maturation varies across different regions of the brain; in general, subcortical structures such as the amygdala and hippocampus are some of the earliest structures to reach volumetric stabilization and tend to display a relatively consistent maintenance of GM volumes until the last few decades of life (Grieve, Korgaonkar, Clark, & Williams, 2011). Cortical maturation proceeds along a tri-dimensional gradient, consisting of inferior-to-superior (or ventral-to-dorsal), posterior-to-anterior, and medial-to-lateral directionality (Gogtay et al., 2004; Shaw et al., 2008). Accordingly, inferior cortical structures such as the entorhinal cortex (important for memory processes) are some of the first cortical structures to stabilize volumetrically and show a protracted maintenance of GM volumes across the majority of the lifespan (Grieve et al., 2011). Primary sensory and motor cortices (located more posteriorly than higher-order association cortices) mature earlier than anterior prefrontal cortices while medial cortical structures such as the frontal and occipital poles (important for taste/smell and visual processing, respectively) mature earlier than lateral frontal and temporal cortices, consistent with the functional specialization of perceptual and sensorimotor behaviors early in life before the emergence of higher-order cognitive and heteromodal associative functions (Gogtay et al., 2004). The latest regions to mature include the dorsal and lateral prefrontal and temporal cortices, consistent with the relatively late developmental emergence

of associative functions dependent upon integration of perceptual, visceral, and cognitive data from disparate perceptual modalities (Gogtay et al., 2004).

Once a phase of GM volumetric maturation (stabilization of change) has been reached, brain structures tend to demonstrate progressive decreases in GM volume over the course of the lifespan of varying magnitudes. In general, brain regions which mature first tend to display the longest periods of relative stabilization with late GM loss, termed the "first in last out" pattern of aging (Grieve et al., 2011). This principle is convergent with observations of relative GM preservation in early-maturing limbic structures (Terribilli et al., 2011). Conversely, later-maturing structures such as the prefrontal cortex tend to show the steepest rates of decline in GM or cortical thickness over the course of adulthood and into old age, and this is particularly pronounced for frontal and parietal regions relative to lateral temporal and occipital regions (Thambisetty et al., 2010), consistent with the cognitive declines which accompany senescence and old age. Furthermore, these patterns of age-related volumetric changes are convergent with cytoarchitectural complexity of the specific cortical region, with lower-order and less complex three-layered allocortical structures (e.g., piriform cortex) tending to display simpler linear changes in cortical thickness while higher-order and more complex six-layered homotypical isocortical structures (e.g., prefrontal cortex) display more complex cubic growth trajectories; intermediately complex five-layered transition cortical structures (e.g., body of the insula and ventral ACC) tend to display quadratic growth curves (Shaw et al., 2008).

In aggregate, studies of structural brain changes across the lifespan have demonstrated that brain development and aging occurs in a heterogenous progression consistent with the developmental emergence of functionally localized cognitive, perceptual, and behavioral processes. Specifically, brain regions responsible for early-emerging functions such as stimulus salience (e.g., amygdala), memory (e.g., entorhinal cortex/hippocampus), sensory

perception (e.g., visual/primary sensory cortex), and motor control (e.g., primary motor cortex) tend to mature earlier and display less complex growth trajectories with a relative preservation of volumes across the majority of adulthood.   In contrast, brain regions responsible for higher-order cognitive (e.g., prefrontal cortex) and associative functions (e.g., lateral temporal cortices) mature later, display more complex growth trajectories, and tend to show the earliest onset of accelerated volumetric decline.

Functional Changes

One consistent finding which has emerged from studies of age-related changes in emotion-processing brain function is that children/adolescents tend to activate subcortical and core interoceptive (i.e., posterior insula) structures to a greater extent than adults, while adults tend to display greater activation of higher-order interoceptive (i.e. anterior insula) and prefrontal regions in response to emotional stimuli.   For example, adolescents were shown to display greater activation of the amygdala in response to passive viewing of fearful vs. neutral and masked sad faces compared to adults (A. E. Guyer et al., 2008a; Killgore & Yurgelun-Todd, 2007; Monk et al., 2003), while 5-6 year-old children displayed greater amygdala activation in response to emotional faces relative to adults (Hoehl, Brauer, Brasse, Striano, & Friederici, 2010).   Furthermore, amygdala responses were relatively more isolated from activity in other medial temporal structures, as demonstrated by greater amygdala-hippocampal connectivity in adults compared to adolescents for passive viewing of fearful vs. neutral faces (A. E. Guyer et al., 2008a).   In contrast, adults tend to show greater prefrontal cortex involvement during emotion processing tasks, as demonstrated by greater orbitofrontal cortex activation in adults compared to adolescents during processing of fearful and neutral faces across different attention conditions (Monk et al., 2003).   Furthermore, a study examining neural responses to empathy or sympathy-eliciting stimuli (i.e., visual animations depicting accidentally or purposefully-inflicted pain, respectively) in children, adolescents,

and adults observed that the younger the participants the greater the activation in the amygdala and the posterior insula while the older the participants the greater the activation in the prefrontal cortex and anterior insula (Decety & Michalska, 2010), illustrating a posterior-to-anterior developmental gradient in the context of insula function. A medial-to-lateral shift in prefrontal activity was also evident in this study, as during processing of sympathy-eliciting stimuli the younger the participants the greater the activation in the medial orbitfrontal cortex while the older the participants the greater the activity in the lateral orbitofrontal cortex.

Thus, the developmental transition from childhood/adolescence to adulthood seems to be characterized on the level of brain function by a decreased responsivity of subcortical and core interoceptive structures (e.g., amygdala and posterior insula) to emotional stimuli but an increased emotional responsivity of higher-order limbic (i.e., anterior insula) and prefrontal structures. This principle is convergent with age-related findings during cognitive tasks which demonstrate an increased spatial extent but decreased magnitude of prefrontal activation in children relative to adults (Durston et al., 2006) which has been suggested to be indicative of increasing efficiency of prefrontal control mechanisms from childhood to adulthood. Additionally, these functional patterns converge with structural studies demonstrating the later maturation of higher-order prefrontal regions relative to subcortical and limbic structures, also characterized by a medial-to-lateral gradient (Shaw et al., 2008).

In recent years, increasing attention has been focused on the assessment of resting-state brain function, i.e., how the brain functions during an inactive period in which participants are asked to lie still inside the scanner, using measures of resting-state functional connectivity MRI (rsfcMRI). In brief, the BOLD time course in a specific seed region of the brain is correlated with the time courses across all other regions of the brain, and those regions which display covarying spontaneous fluctuations in low-frequency BOLD signal are inferred to be functionally interconnected during the resting state (Fox et al., 2005). Investigations

using rsfcMRI have particularly focused on regions of the default-mode network (DMN), so-named due to frequent observations of task-induced deactivation in these regions for some active processing condition relative to a resting-state baseline. The DMN comprises portions of the ACC/mPFC, posterior cingulate/precuneus (PCC), inferolateral temporal cortex, parahippocampal gyrus, and lateral parietal lobes and is often inferred to play an important role in spontaneous self-focused attention, autobiographical memory retrieval, and reflection on one's mental state (Thomason et al., 2008), all of which have been reported by participants to occur during quiet resting states. Given the ecological validity of this brain state as well as the simple acquisition of data (requiring a brief five-minute scan with no stimuli or experimental probes), this paradigm has been increasingly applied to both healthy normal and anxious samples as well as both child and adult participants (Vogel, Power, Petersen, & Schlaggar, 2010).

As with emotion-processing brain function, resting-state brain function displays reliable shifts in patterns of connectivity from childhood into adulthood. In children, resting-state brain function has often been described using the term "small-world topology," meaning that interconnected "nodes" of the brain's functional networks tend to be spatially restricted to those regions which are close in distance. This phenomenon has often been interpreted in terms of "economic cost," meaning that in the early stages of development the functional nodes are interconnected in such a way as to minimize energy expenditure towards neuronal rewiring to support efficient synchronization of localized functions and rapid information transfer (Fan et al., 2011). This process allows for the formation of local interconnected "modules" of information transfer within the immature brain which are relatively segregated from other modules that are more spatially remote. For example, connectivity among the PCC, medial temporal lobes, and angular gyri (all of which are located in the posterior portion of the brain) was found to be similar across children and adults, but connectivity between the

PCC and mPFC (the most spatially remote nodes of the DMN) was found to be significantly weaker in children relative to adults; this weakened functional connectivity was also accompanied by weaker structural PCC-mPFC connectivity as indexed by diffusion tensor imaging and fiber tracking (Supekar et al., 2010). As maturation progresses, the functional connections among brain regions begin to shift from small-world modular topology to integration of greater long-distance connections and segregation from short-range connections, eventually resulting in the formation of distinct interconnected adult brain networks with spatially remote processing nodes (Fair et al., 2007). Such adult brain networks can generally be divided into: a) a cinguloopercular control network (comprising the dorsal ACC/mPFC, anterior insula/frontal operculum, thalamus, and anterior PFC) which is involved with stable-set maintenance of task control as well as assessment of a stimuli's motivational salience; b) a frontal-parietal/dorsal-attention network (comprising the dorsolateral PFC, intraparietal sulcus, inferior parietal lobule, precuneus, dorsal frontal cortex, and mid-cingulate cortex) which is involved with adaptive online control and deliberate behavioral adjustments in response to feedback; c) a default-mode network (previously described); d) a sensorimotor network (comprising the primary motor and sensory cortices) involved in tactile processing and body movement; e) an occipital network (comprising the visual cortex) involved in visual processing; and f) a cerebellar network involved in propriocetion and coordination of body movements (Dosenbach et al., 2010). Interestingly, this pattern of within-network strengthening and between-network weakening of functional connections is so reliable that rsfcMRI network measures can be used to predict individual level of brain maturity; in particular, the cinguloopercular control network was found to provide the greatest relative contribution towards prediction of brain maturity (Dosenbach et al., 2010), suggesting that the strengthening of connectivity among regions of this network (and weakening of connectivity to regions in other networks) is particularly indicative of maturational brain changes during

the resting state. In total, resting-state brain function is characterized by reliable shifts across development from an immature small-world topology and modular organization towards the incorporation of spatially remote processing nodes into a well-delineated and reliably-organized set of mature functional brain networks which occurs through segregation from local connections and integration of long-distance connections.

Neuroimaging Studies of Childhood Maltreatment

Numerous studies have demonstrated influences of childhood maltreatment and other early life stressors on child and adult brain structure and function of limbic and prefrontal regions known to be implicated in the pathophysiology of anxiety. The discussion of these studies will be organized by brain structure.

Amygdala

Recent studies have explored the relationship between amygdala volumes and early rearing environment by studying adolescents raised in orphanages characterized by mild-to-moderate levels of emotional and physical neglect. One study observed greater amygdala volumes in the institutionally-reared adolescents, controlling for smaller total gray and white matter volumes (Mehta et al., 2009). Another study in a larger sample of 38 institutionally-reared adolescents and 40 comparison subjects observed that amygdala volumes were not significantly different between the two groups, but within the institutionally-reared group larger cortex-corrected amygdala volumes were associated with longer time spent in the institution (Tottenham et al., 2010), even after controlling for adolescents with current anxiety disorders. Furthermore, there was a trend for larger amygdala volumes to be associated with greater percentage of errors on an emotional inhibition task and to predict greater parent-rated internalizing behavior and anxiety. In another study, adult participants exposed to high levels of early life stress demonstrated a greater negativity bias (i.e., an attributional bias towards expecting and perceiving negative events and outcomes) as well as increased heart rate

reactivity to nonconscious processing of fearful faces relative to those with low levels of early life stress. Furthermore, the high early life stress group displayed greater activation of the amygdala during nonconscious fear processing relative to the low early life stress group. Early life stress interacted with the short-allele genotype of the serotonin transporter promoter-region polymorphism, which has been heavily implicated as a potential genetic predisposition towards mood or anxiety disorders (Caspi et al., 2003; A. R. Hariri, Drabant, & Weinberger, 2006; M. B. Stein, Schork, & Gelernter, 2008), to promote the highest levels of negativity bias and amygdala activation during fear processing. Another study in a large sample of psychiatrically-healthy participants observed a strong positive association between amygdala activation to threat-related (i.e., angry and fearful) emotional faces and childhood maltreatment, with the strongest contributors being emotional abuse and emotional neglect (Dannlowski et al., 2012). Furthermore, this association was not confounded by trait anxiety, depression, age, intelligence, education, or recent stressful life events. A study using positron emission tomography to examine the neural correlates of fear conditioning in women with PTSD due to early childhood sexual abuse observed increased left amygdala activation during acquisition of fear responses (Bremner et al., 2005), but the definitive role of childhood maltreatment apart from the development of PTSD in influencing amygdala function in this study cannot be ascertained due to the absence of trauma-exposed comparison subjects. In aggregate, these findings indicate that childhood maltreatment and other forms of early life stress may cause a long-lasting sensitization of amygdala function in response to threat cues which persists into adulthood concomitant with structural alterations.

Insula

Several studies have also demonstrated insula abnormalities in maltreated samples. One study examining cognitive control in adolescents exposed to early-life stress observed increased insula activation during a Change task (a behavioral paradigm involving inhibition

of a prepotent response and switching to an alternative behavioral response) as well as longer latencies in inhibiting a prepotent response (Mueller et al., 2010), consistent with the role of the insula in attention and cognitive processes (Wager & Barrett, 2004). Similarly, greater levels of childhood maltreatment were associated with greater anterior insula activation during a shape-processing baseline of a face-processing task in women with PTSD due to intimate-partner violence, even while controlling for current levels of depression, PTSD symptom severity, and length of exposure to intimate-partner violence, which may relate to a childhood maltreatment-related increased attentional load necessitated by the paradigm (G. A. Fonzo et al., in submissionb). In this same study, greater childhood maltreatment was also associated with greater functional connectivity between the anterior insula and medial prefrontal cortex. Increased insula activation was also observed during fear acquisition and extinction in women exposed to childhood sexual abuse with PTSD (Bremner et al., 2005). Greater levels of childhood maltreatment were also related to smaller insula gray matter volumes in psychiatrically-healthy adults (Dannlowski et al., 2012). Taken together, there is a small but increasing evidence base suggesting childhood maltreatment and other forms of early life stress also exert an influence on insula function and structure in adulthood.

   Prefrontal Cortex

   Given the relatively late maturation and early plasticity of the prefrontal cortex (Shaw et al., 2008), this region might be expected to be extremely susceptible to detrimental developmental environmental influences such as childhood maltreatment. Consistent with this, there is a great deal of evidence demonstrating functional prefrontal abnormalities in maltreated samples. In a sample of adolescents exposed to early life stress, greater medial and lateral prefrontal activation was observed during a cognitive control paradigm along with less efficient behavior, suggesting a potential compensatory adaptation (Mueller et al., 2010). Another study also demonstrated increased recruitment of the medial frontal gyri and anterior

cingulate during completion of a cognitive-control task in maltreated children with posttraumatic stress symptoms (Carrion et al., 2008), suggesting that enhanced recruitment of midline prefrontal structures while exercising cognitive control also extends to more severe/symptomatic maltreated samples. In healthy adults, greater levels of early life stress were related to greater dorsal and ventral anterior cingulate activation during conscious processing of fearful faces, and this effect was potentiated by the presence of the short allele of the serotonin transporter polymorphism (Williams et al., 2009). A similar effect was observed in women with PTSD due to intimate-partner violence in which greater ventral ACC activation was related to greater levels of childhood maltreatment controlling for depression, PTSD symptoms severity, and length of exposure to intimate-partner violence (G. A. Fonzo et al., in submissionb). In another study, offspring from "risky family environments" (i.e., those with the highest levels of family stress) displayed increased functional connectivity between the amygdala and the ventrolateral prefrontal cortex during processing of threat-related emotional faces (Taylor, Eisenberger, Saxbe, Lehman, & Lieberman, 2006).

Similar prefrontal abnormalities have been observed in maltreated clinical samples, such as adults with PTSD due to childhood maltreatment. One study observed increased dorsal prefrontal activation in response to trauma scripts in women with PTSD due to childhood sexual abuse, but decreased activation in the anterior cingulate cortex (Bremner et al., 1999). This apparent divergence in directionality may relate to the role of the anterior cingulate in more implicit and automatic forms of emotion regulation (Etkin et al., 2010), while the dorsal prefrontal cortices are more heavily implicated in more explicit and deliberate forms of regulating emotions (Campbell-Sills et al., 2011). Similarly, during acquisition of fear responses in a fear conditioning paradigm women with PTSD due to childhood sexual abuse displayed increased activation of the lateral PFC, but they displayed decreased activation of the anterior cingulate during fear extinction (Bremner et al., 2005). Similar

results were observed in similar maltreated samples during retrieval of emotionally-valenced word pairs (Bremner et al., 2003) and during olfactory stimulation (Croy et al., 2010), suggesting this increased dorsal and lateral prefrontal activation with concomitant decreased anterior cingulate/medial prefrontal activation may be a reliable neural signature of maltreatment across behavioral paradigms.

There is also substantial evidence for prefrontal structural abnormalities related to maltreatment. In a large sample of psychiatrically-healthy adults, greater than two adverse childhood experiences was related to significantly smaller volumes of the anterior cingulate relative to those which experienced no adverse childhood events. Furthermore, regression analyses revealed these brain volumes were more strongly related to measures of early life stress than to measures of current emotional state (Cohen et al., 2006). Another study observed that greater early life stress was associated with diminished gray matter volumes in the right lateral prefrontal cortex, and in combination with a specific serotonin receptor type-3 gene allele conferred greater volumetric reductions in both the ventral and dorsal medial prefrontal cortex (Gatt et al., 2010). A study specifically examining childhood emotional maltreatment in psychiatric patients with depressive and/or anxiety disorders demonstrated that emotional maltreatment was associated with reduced left dorsal medial PFC volumes, irrespective of diagnosis, and greater reductions were associated with more severe maltreatment experiences (van Harmelen et al., 2010). Furthermore, adults exposed to corporal punishment as children displayed selective gray matter reductions in the right medial PFC as well as the right anterior cingulate (Tomoda et al., 2009). Several studies have observed abnormalities in prefrontal cortex volumes in pediatric samples with posttraumatic stress symptoms, such as larger volumes of the left frontal lobe and an attenuated frontal asymmetry (Carrion et al., 2001). Another study examining children with posttraumatic stress symptoms due to maltreatment observed significantly increased gray matter volumes in the

ventral half of the prefrontal cortex (Carrion et al., 2009; Richert et al., 2006). Prefrontal effects of childhood maltreatment may be especially robust, given evidence which suggests that dorsolateral prefrontal reductions in GM volume are specifically related to level of childhood maltreatment in women with PTSD due to intimate-partner violence while controlling for other relevant symptom dimensions (G. A. Fonzo et al., in submissionb). In aggregate, there is a large body of evidence indicating childhood maltreatment and other forms of early life stress exert robust effects on prefrontal structure and function that persist into adulthood, generally characterized by increased lateral prefrontal and decreased medial prefrontal activation to cognitive and emotional paradigms as well as decreased prefrontal structural volumes.

The Mind-Body Interface: A Potential Endocrinological Mechanism for Biological Effects

In understanding how early stressors contribute to lasting changes in biological structure and function, it is important to comprehend the relationship between stressful experiences and biological responses. The body's primary stress response system is known as the hypothalamic-pituitary-adrenal (HPA) axis, which is activated under environmental conditions necessitating quick, adaptive responses (Bremner & Vermetten, 2001). The HPA axis is responsible for triggering the release of the stress hormone cortisol, a glucocorticoid that is circulated throughout the bloodstream under conditions of sympathetic activation, effecting changes in a wide range of bodily functions to promote adaptive physiological responses to the metabolic demands of "fight-or-flight" (M. D. De Bellis et al., 1999). Since childhood maltreatment and anxiety have both been demonstrated to be associated with abnormalities of the HPA axis and cortisol response (Carpenter et al., 2009; Elzinga, Spinhoven, Berretty, de Jong, & Roelofs, 2010; MacMillan et al., 2009; McGowan et al., 2009; Tyrka et al., 2009), this mechanism has been identified as a potential common pathway through which chronic early life stressors may affect developmental changes in brain structure

and function which lead to the manifestation of anxiety. Excessive and chronic activation of the HPA-axis and cortisol stress response has been hypothesized to impact brain development through promoting increased susceptibility to glutamate-mediated neuronal excitotoxicity (Moghaddam, 2002), increasing atrophy of dendritic processes (Sapolsky, 2000), as well as inhibition of neurogenesis or gliogenesis through reduction in brain-derived neurotrophic factors (Duric & McCarson, 2005). However, the precise mechanism whereby stress hormones may directly influence brain structure has yet to be clearly elucidated.

Associations of cortisol function with hippocampal and prefrontal volumes (Carrion, Weems, & Reiss, 2007; Kremen et al., 2010; McGowan et al., 2009) suggests that the structure of these brain regions may be particularly malleable to stress-related effects. The hippocampus has received much attention as a potential regulator of the HPA-axis response, consistent with its abundant glucocorticoid receptors (McEwen, Weiss, & Schwartz, 1968) as well as its role in negative feedback inhibition of the cortisol response (Sapolsky, Zola-Morgan, & Squire, 1991). The hippocampus itself may be involved in initiating and regulating stress responses, as prominent theories suggest it plays a crucial role in stimulus evaluation pertaining to the frustration of goal-directed behavior (McNaughton, 2006). Given the involvement of the hippocampus in memory processes as well as its abundance of glucocorticoid receptors, stress-induced cortisol hypersecretion has been hypothesized as a mechanism linking memory dysfunction in survivors of childhood maltreatment to detrimental biological effects on hippocampal neuronal integrity (Bremner, 2006b). The prefrontal cortex, which is heavily implicated in fear and stress responses (Monk et al., 2006; A. Simmons et al., 2008), is involved with higher-order cognitive operations that serve an adaptive purpose under conditions of stress, and its structure is also malleable to the effects of stress-induced glucocorticoid secretion (Carrion et al., 2007; Kremen et al., 2010). Thus, chronic activation of the biological stress system seems to exert diffuse effects on brain structure and function

across the lifespan, and chronic stressors occurring early in the development of the central

nervous system may have particularly detrimental effects on later neuronal integrity and brain

function (Carrion et al., 2007).

The Shared Neural Substrates of Anxiety and Childhood Maltreatment

Given the existing evidence, it can be surmised the neural abnormalities implicated in

childhood maltreatment and clinical anxiety overlap to a great extent and are characterized by

a qualitatively similar pathology. More specifically, both populations demonstrate an

enhanced reactivity of limbic (e.g., amygdala and insula) and prefrontal substrates to threat

cues and negative emotional stimuli, perturbed corticolimbic interactions, and reductions in

prefrontal cortical volumes. In conjunction with the strong association between childhood

maltreatment and the later emergence of anxiety symptoms, it is possible to synthesize the

existing data into a tentative functional neuroanatomical model to illustrate a potential

neuroetiological pathway from childhood maltreatment to the emergence of anxiety in

adulthood.

A Proposed Neurodevelopmental Model to Link Childhood Maltreatment with Later Anxiety

The pattern of findings across studies broadly indicates that childhood maltreatment

seems to enhance limbic reactivity to salient stimuli and perturb cortical-limbic interactions

through promoting a cortical overmodulation of affective processing, especially under

conditions of perceived environmental threat. Specifically, across the studies reviewed

childhood maltreatment seems to impact reactivity of limbic brain regions (e.g., amygdala and

insula) to the processing of salient perceptual stimuli and associated emotional responses

while simultaneously increasing functional recruitment of higher-order brain regions such as

prefrontal cortical/paralimbic structures important for self-relevance processing,

contexualization of experience, and implicit/explicit emotion regulation (anterior cingulate,

medial prefrontal cortex, and dorsal/lateral prefrontal cortex). This outcome is proposed to occur as the end pathway of the following process.

First, childhood maltreatment will evoke increased activity of limbic structures involved in threat-detection and aversive emotional experience (primarily amygdala and insula). This increased activity will become paired with environmental threat cues through classical conditioning and evoke experience-dependent changes on the neuronal level such that certain environmental threat cues associated with maltreatment experiences come to reliably evoke increased activity in these structures over time.   Prefrontal structures such as the anterior cingulate and medial/lateral prefrontal cortex will be recruited in attempts to self-regulate emotional state in the maltreated child. However, given the relative immaturity of the prefrontal cortex in comparison to limbic brain structures (Tamnes et al., 2010) as well as the age-dependent potentiation of prefrontal inhibition of limbic activity (Van Leijenhorst et al., 2010), it is likely this perpetual recruitment of diffuse cortical regions due to early life stress will only be partially effective in downregulation of affective responses, resulting in prolonged states of hypervigilance and arousal which are only inefficiently modulated by the immature cerebral cortex. This ineffective prefrontal cortex regulation of stress responses may co-contribute to the dysregulation of psychoneuroendocrinological stress responses and cortisol hypersecretion, which may contribute to structural and volumetric brain changes in diffuse regions over the course of development. The repeated engagement of the prefrontal cortex in conjunction with limbic structures will lead to a greater propensity for coactivation to maltreatment-related threat cues, resulting in synaptic changes through long-term potentiation. Over time and with repetition, the prefrontal cortex will be conditioned to activate in conjunction with limbic structures, resulting in decreased cortical-limbic flexibility. With continuing development, the propensity for increased cortical-limbic engagement will generalize to threat-cues beyond those strictly related to maltreatment experiences, resulting in

increased bottom-up reactivity to any cue signaling a potential threat to the integrity of the self. This repeated overengagement of limbic structures and reduction in corticolimbic flexibility will tax prefrontal regulatory resources, leading to greater difficulties with emotion regulation and greater propensity towards sympathetic activation. This increased propensity towards sympathetic activation leads to excessive secretion of the stress hormone cortisol which, along with prefrontal overrecruitment, may then lead to structural prefrontal brain changes through use-dependent atrophication of dendritic processes or neuronal excitotoxicity. The accumulated effects of these processes will be observed on imaging measures as a reduction in gray matter volumes. In combination, this increased bottom-up reactivity to threat and decreased top-down resources necessary for successful regulation of emotional state will increase susceptibility to the development of excessive anxiety or fear responses to cognitive, social, emotional, or environmental stimuli indicating a potential threat to the integrity of the self. Over time and with repeated maladaptive learning experiences, the person will then develop a higher propensity towards manifesting anxiety symptoms. In conjunction with current life stressors, these symptoms of anxiety may then advance to the emergence of a clinically-significant anxiety disorder at some point in the lifespan.

To summarize, the main implication of this model is childhood maltreatment will: a) cause a sensitization of limbic reactivity to potential environmental threat cues; b) promote increased cortical modulation of affective states through necessitating cortical involvement in early attempts at regulation of emotional states; c) tax prefrontal regulatory resources which will eventually lead to a breakdown in effective emotion regulation mechanisms; and d) promote the development of anxiety symptoms through perturbing adaptive corticolimbic interactions and emotional regulatory mechanisms.

Design and Aims of Current Study

In order to test the above model, one would ideally prospectively follow individuals whom have experienced childhood maltreatment and those whom have not and examine them longitudinally for the development of anxiety disorders. However, this approach is impractical and time as well as cost-prohibitive. Instead, one can begin to examine the relationship between childhood maltreatment and anxiety disorders by retrospectively investigating brain processes in a cross-sectional sample of participants dimensionally encompassing various levels of anxiety and maltreatment experiences.

Study Design

A retrospective cross-sectional investigation of the effects of childhood maltreatment history on neural structure/function in a cross-sectional sample of clinically, subclinically, and normatively-anxious adult participants will be utilized. The rationale for utilizing a mixed sample of participants with and without anxiety disorders is threefold; first, prior investigations of the neural effects of childhood maltreatment/early life stress which have included both clinical (mood/anxiety) and non-clinical subjects as participants have not reported an effect of diagnostic status on childhood maltreatment effects (Dillon et al., 2009; Tomoda et al., 2009; Tomoda, Navalta, Polcari, Sadato, & Teicher, 2009; Tomoda et al., 2010; van Harmelen et al., 2010), suggesting there are reliable effects of childhood maltreatment on neural structure/function which persist into adulthood independent of the manifestation of psychiatric disorders. Second, studies investigating childhood maltreatment effects in both healthy normals and clinically anxious populations have observed qualitatively similar effects on several affected neural substrates, including anterior cingulate/medial prefrontal cortex function (G. A. Fonzo et al., in submissionb; Williams et al., 2009) and structure (Cohen et al., 2006; van Harmelen et al., 2010) and amygdala function (Bremner et al., 2005; Taylor et al., 2006; Williams et al., 2009), suggesting there is little theoretical basis for the expectation of maltreatment x diagnosis interaction effects in these regions. This observation is also

consistent with the developmental concept of hierarchical motility, such that any effects instantiated in childhood should be incorporated into the adult brain regardless of disorder development in adulthood. Third, as high levels of childhood maltreatment are often associated with the development of anxiety disorders, restricting the investigation of childhood maltreatment neural effects strictly to a clinical sample may reduce generalizability of findings to populations with less severe levels of childhood maltreatment or anxiety symptoms. Similarly, the exclusion of clinical participants and strict focus on non-clinical healthy normals would reduce generalizability of results to more severely maltreated samples and could potentially artificially restrict the range of maltreatment experiences to the low end of the spectrum. Therefore, given the substantial convergence of maltreatment effects in both clinical and non-clinical populations in prior studies, a combined sample of clinical and non-clinical participants will provide the optimum range of maltreatment experiences and statistical power necessary for identification of reliable maltreatment effects on neural structure/function which are maximally generalizable to the population.

In order to construct a sample maximally representative of childhood maltreatment neural effects in the general adult population, participants from three "classes" of anxiety manifestations which were collected as part of other ongoing research projects will be utilized: a) non-disordered young adults with normal levels of anxiety (as defined by a trait anxiety score in the 40th-60th percentile of an undergraduate mass-testing sample) and adults whom served as control participants for clinical samples; b) young adults with high levels of trait anxiety (i.e. trait anxiety score in the 85th percentile or above) and subclinical or non treatment-seeking manifestations of anxiety psychopathology; and c) treatment-seeking adults with a clinical diagnosis of GAD, SAD, PTSD, or PD. In accordance with the trandiagnostic conceptualization of anxiety utilized in this study, anxiety will be operationalized as a diagnosis-nonspecific dimensional construct rather than a discrete clinical variable.

Furthermore, given that emotional forms of childhood maltreatment (i.e., emotional abuse/neglect) are most reliably associated with the development or severity of anxiety in adulthood (Kuo et al., 2011; Mathews et al., 2008; Simon et al., 2009; Spinhoven et al., 2010; Teicher et al., 2010; Wright et al., 2009) and most reliably associated with brain structure and function relevant to the pathophysiology of anxiety (Dannlowski et al., 2012; Edmiston et al., 2011; van Harmelen et al., 2010), this investigation will be limited to the neural correlates of emotional maltreatment (abuse/neglect) in order to most effectively balance statistical power with risk for type I error.

The investigation of functional maltreatment effects will be implemented in the context of a threat-related contrast from a facial emotion processing paradigm which robustly activates limbic/paralimbic structures such as the amygdala, insula, and anterior cingulate which have been demonstrated to be sensitive to early life stressors (Dannlowski et al., 2012; Williams et al., 2009) and display functional abnormalities in clinically anxious samples (N. Amir et al., 2005; Etkin & Wager, 2007). Furthermore, a functional paradigm involving emotional face assessment, particularly of threat-related facial emotions (i.e., fear and angry) may be especially well-suited to the investigation of childhood maltreatment effects for several reasons. First, the recognition of emotions through facial expressions is an ability which develops early in the lifespan and continues to play an important role in socioemotional interactions throughout adulthood (Mondloch, Le Grand, & Maurer, 2010), suggesting that this construct may be particularly malleable to childhood maltreatment due to its early developmental emergence and ubiquitous usage throughout the lifespan. Second, childhood maltreatment is an early life stressor which occurs in the context of maladaptive familial interpersonal relationships, and these maladaptive social interactions are likely to be experienced concomitant with facial expressions of emotion; therefore, emotional facial expressions may serve as a useful functional probe of maltreatment neural effects which are

likely to become conditioned responses to the assessment of facial emotions. Third, prior studies have demonstrated behavioral abnormalities in maltreated samples during the processing of emotional faces (Gibb et al., 2009; Masten et al., 2008), suggesting that these behavioral abnormalities may be mediated by abnormal neural correlates of childhood maltreatment in face-processing neurocircuitry. Fourth, emotional faces are widely-utilized ecologically-valid experimental stimuli in neuroimaging studies of anxiety psychopathology (M. P. Paulus, 2008), thus providing for a level of consistency across studies and generalizability of findings.

Mediation analyses provide a powerful method for testing proposed causal pathways which link two variables. The basic mediation model involves an independent variable and dependent variable in which the relationship between the two is modeled as occurring through directional influences on a third mediating variable (independent variable $\rightarrow$ mediating variable $\rightarrow$ dependent variable). In the current case, the relationship between childhood emotional maltreatment and adulthood anxiety is proposed to occur through influences on brain structure and function which are instantiated in early life, maintained throughout the course of development, and result in the manifestation of anxiety in adulthood. Thus, this analytic pathway will be utilized in the current investigation in order to attempt to identify brain structure and function which underlies the relationship between childhood emotional maltreatment and anxiety in adulthood.

Specific Aims

The current study will address the following primary specific aims:

1. To investigate where brain function during the processing of threat-related emotional stimuli mediates the relationship between childhood emotional maltreatment and adulthood anxiety.

2. To investigate where brain structure (gray matter volume) mediates the relationship between childhood emotional maltreatment and adulthood anxiety.

The following secondary/exploratory aims will also be addressed:

3. To investigate how corticolimbic functional interactions impact the mediating role of activation in these structures on the relationship between childhood emotional maltreatment and anxiety in adulthood.

4. To investigate how the relationships between function and structure of a particular brain region influences the mediation of the relationship between childhood emotional maltreatment and anxiety in adulthood.

Hypotheses

Given the substantial relationship between childhood maltreatment and anxiety in adulthood as well as the substantial overlap of affected neural substrates, it is hypothesized that childhood maltreatment will instantiate a cascade of neural effects which serve as neural "risk/vulnerability" markers that are observable/measurable in adulthood and serve to predispose individuals to the later development of anxiety. More specifically, given that both anxiety and childhood maltreatment are associated with increased activation and connectivity of limbic and prefrontal regions (N. Amir et al., 2005; Dannlowski et al., 2012; Etkin & Wager, 2007; Etkin et al., 2009; Taylor et al., 2006; Williams et al., 2009), it is hypothesized that increasing activation in and connectivity between limbic (i.e., amygdala and insula) and prefrontal cortical regions will serve to mediate the relationship between childhood maltreatment and anxiety in adulthood (Aim 1). Second, as both childhood maltreatment and anxiety are associated with reductions in prefrontal cortical gray matter volumes (Uchida et al., 2008; van Harmelen et al., 2010; Woodward et al., 2009), it is hypothesized that smaller prefrontal cortical gray matter volumes will mediate the relationship between childhood maltreatment and anxiety in adulthood (Aim 2). Third, there is substantial evidence in the

literature that prefrontal regions appear to exert a regulatory role over activity in limbic structures, are implicated in emotion regulation, and that this relationship may be perturbed in those with anxiety (Campbell-Sills et al., 2011; Etkin et al., 2009; Etkin et al., 2010; Quirk et al., 2003; Shin et al., 2005). Therefore, it is reasonable to suspect that the interacting function of limbic and prefrontal regions may exert influences over the strength of the mediation effect of brain function in these regions on the relationship between childhood emotional maltreatment and adulthood anxiety. Consequently, it is predicted that in those analyses in which activity in prefrontal and limbic regions conjointly mediate the relationship between childhood emotional maltreatment and adulthood anxiety, the degree of mediating prefrontal activation will also moderate the mediation effect of limbic activation on the relationship between childhood emotional maltreatment and adulthood anxiety such that greater prefrontal activation will be associated with a weaker limbic mediation effect (Aim 3). Lastly, there is a relative paucity of existing research which examines the relationship between brain structure and function in the same sample of individuals, both within studies examining childhood maltreatment and those examining anxiety. However, there is some initial evidence which suggests that brain regions displaying functional abnormalities in anxious (Etkin et al., 2009) and maltreated samples (Dannlowski et al., 2012) also display concomitant structural abnormalities of gray matter volumes in the same participants. Therefore, it is predicted that in limbic and prefrontal structures there will be an interacting effect of brain structure and function in which gray matter volume will moderate the mediation effect of brain activation on the relationship between childhood emotional maltreatment and adulthood anxiety (Aim 4).

Methods

Participants

A total of one-hundred eighty-two participants ($n = 182$) were pooled from ongoing neuroimaging anxiety studies. Participants were recruited through local online and print advertisement and referral from university-affiliated primary care clinics. Of these, seventy-three ($n = 73$) were women recruited from a treatment study examining PTSD due to intimate-partner violence (IPV-PTSD). Of these women, thirty-two ($n = 32$) were health comparison subjects, thirty-five ($n = 35$) had PTSD, and six ($n = 6$) were exposed to IPV but did not develop PTSD. Sixty-nine participants ($n = 69$) were recruited from a treatment study for GAD, PD, or SAD. Of these, fifteen ($n = 15$, 12 females) had a primary diagnosis of GAD, nineteen ($n = 19$, 13 females) were healthy comparison subjects, fourteen ($n = 14$, 12 females) had a primary diagnosis of PD, and twenty-one ($n = 21$, 16 females) had a primary diagnosis of SAD. Forty ($n = 40$) participants were undergraduates recruited from San Diego State University as part of a study examining non-treatment seeking high trait-anxious young adults. Of these participants, twenty-one ($n = 21$, 16 females) were recruited due to scoring in the top 85th percentile of sampled students on trait anxiety measures, and nineteen ($n = 19$, 13 females) were recruited as healthy comparison subjects. Of those non-treatment seeking high trait-anxious participants, fourteen ($n = 14$) met subthreshold or full criteria for both GAD and SAD, two ($n = 2$) met full or subthreshold criteria only for GAD, four ($n = 4$) met full or subthreshold criteria only for SAD, two ($n = 2$) met full or subthreshold criteria only for OCD, and one ($n = 1$) met subthreshold criteria only for PD. The mean age of the participants was 30.71 years (+/- 11.27), and the mean number of years of education completed was 14.49 (+/-1.81). The sample was almost entirely female (148 females, 34 males) and the majority were of Caucasian ethnicity (101 participants). The remaining participants were of the following

ethnicities: African-American ($n = 13$), Asian ($n = 16$), Filipino ($n = 9$), Latino ($n = 14$), Native American ($n = 3$), and other ($n = 26$).

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, Weathers, Nagy, & Kaloupek, 1995) and the Structured Clinical Interview for Diagnosis-DSM IV (SCID-IV) (First, Spitzer, Gibbon, & Williams, 1998) administered by a doctoral-level clinical psychologist in an outpatient treatment center. For GAD, SAD, and PD treatment-seeking participants, DSM-IV psychiatric diagnoses were established by experienced clinicians using the structured diagnostic Mini International Neuropsychiatric Interview (Sheehan et al., 1998). Undergraduate participants were recruited as part of a mass-screening protocol at San Diego State University. Approximately 3,000 undergraduate students completed the Spielberger State-Trait Anxiety Inventory (STAI; (Spielberger, 1983)), and those whom were identified as anxiety-prone (scoring in the top 15th percentile of the distribution for trait anxiety (STAIT)) were selected to undergo further screening. All anxiety-prone subjects were administered the Structured Clinical Interview for DSM-IV Diagnosis (SCID; (First et al., 1998)).

Exclusion criteria across all studies included irremovable ferromagnetic bodily material; pregnancy; claustrophobia; DSM-IV lifetime diagnosis of psychotic disorder, bipolar disorder, organic mental disorder, any cognitive disorder, seizure disorder (other than febrile seizures in childhood), or learning disability having resulted in a failing grade and/or enrollment in special classes; head injury of any type resulting in a loss of consciousness for more than 5 minutes; and any concurrent (in the past six weeks) use of psychotropic or anti-epileptic medications. For women recruited as part of the IPV-PTSD study, exclusion criteria included substance abuse in the past year and history of greater than two years of alcohol

abuse. For GAD, PD, and SAD treatment-seeking participants, exclusion criteria included substance dependence in the past twelve months and current (past-month) substance abuse. For high trait-anxious undergraduate participants, exclusion criteria included lifetime diagnosis of substance dependence and current (within past 3 months) diagnosis of substance abuse. For all healthy comparison subjects across studies, additional exclusion criteria included lifetime diagnosis of mood or anxiety disorders, eating disorders, or substance dependence.   For treatment-seeking anxious participants, depressive and anxiety disorders comorbid with the primary diagnosis were permitted, but the primary diagnosis had to be judged by consensus of the research team to be clinically predominant (and subsequently became the focus of treatment). For non-treatment seeking undergraduate participants, those subjects meeting full or subthreshold (i.e. insufficient number of symptoms and/or not fulfilling impairment/distress criterion) diagnostic criteria for an anxiety or depressive disorder were allowed to participate as long as they were not and had never sought treatment for their psychiatric symptoms. After complete description of the study to subjects, they provided informed written consent according to University of California-San Diego Institutional Review Board guidelines.

Self-Report Measures

The emotional abuse (CTQEA) and emotional neglect (CTQEN) subscales from the 28-item Short Form version of the Childhood Trauma Questionnaire (CTQ-SF) (D. P. Bernstein et al., 2003) were used to assess extent of exposure to childhood emotional maltreatment. This measure encompasses 25 items rated on a five-point Likert scale (1= "Never true", 5 = "Very often true"; participant queried with "When I was growing up…") that assesses the subscale domains of emotional abuse, emotional neglect, physical abuse, physical neglect, and sexual abuse. Each subscale ranges in score from low (minimum score of 5) to high levels (maximum score of 25) of the maltreatment dimension, and the total score

ranges from 25 to 125. 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 (D. P. Bernstein, Fink, Handelsman, & Foote, 1994; Thombs, Lewis, Bernstein, Medrano, & Hatch, 2007). Anxiety symptoms were quantified using the score from the anxiety subscale (BSIAnx) of the Brief Symptom Inventory-18 (Derogatis & Fitzpatrick, 2004), a six-item subscale in which participants rate on a five-point Likert scale how often they were distressed by a list of symptoms within the past week. The subscale raw scores range from 0 to 24, and the t-scores range from 38 to 81, with a t-score of 63 indicating a suggested cutoff point to indicate significant distress on a given subscale (Derogatis, 2000). This subscale has been demonstrated to be reliable, valid, internally consistent, and display measurement equivalence across a wide range of populations (Galdón et al., 2008; Hoe & Brekke, 2009; Petkus et al., 2010; Recklitis et al., 2006; Ruz et al., 2010; Wang et al., 2010).

Emotion-Processing Task

Participants completed a modified version of the Emotion Face Assessment Task (A. R. Hariri et al., 2005; M. P. Paulus, Feinstein, Castillo, Simmons, & Stein, 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.

Image Acquisition

Data were collected during task completion using fMRI image parameters sensitive to BOLD contrast on a 3.0T GE Signa EXCITE (GE Healthcare, Milwaukee, Wisconsin) scanner (T2*-weighted echo planar imaging, TR = 2000 msec, TE= 32 msec, field of view (FOV) = 250 x 250 mm, 64 x 64 matrix, 30 2.6mm axial slices with 1.4mm gap, 256 repetitions). A high-resolution T1-weighted image (172 sagitally acquired spoiled gradient recalled 1mm thick slices, inversion time (TI) = 450 msec, TR = 8 msec, TE = 4 msec, flip angle = 12 degrees, FOV = 250 x 250 mm) was also collected from each participant for anatomical reference. Images were preprocessed by interpolating voxel time-series data to correct for non-simultaneous slice acquisition in each volume.

Activation Preprocessing and Individual Analysis

Data were processed using the AFNI software package (Cox, 1996). Voxel time-series data were first coregistered to an intra-run volume using a three-dimensional coregistration algorithm and then 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. As small motion corrections in translational and rotational dimensions are nearly collinear, only rotational parameters (roll, pitch, and yaw) were used as nuisance regressors for motion artifact. Each subject's timeseries 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 timeseries to account for individual variability in anatomical landmarks. A deconvolution analysis was conducted in which the 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 voxelwise activation magnitudes

for the within-subject contrasts of trials in which the subject engaged in emotion matching directed towards angry vs. happy and fearful vs. happy faces. Although usually analyzed with the sensorimotor condition as the comparator (M. P. Paulus et al., 2005), we have chosen to explore the direct contrast of emotion types for several reasons. First, our analyses of a large cohort of individuals with (n = 162) and without (n = 96) various anxiety disorders revealed contrasts between emotional face-types produced greater effect sizes in relevant limbic structures than contrasts with a sensorimotor control condition (mean voxelwise amygdala Cohen's D for fear vs. happy = 0.16, mean voxelwise amygdala Cohen's D for fear vs. oval = 0.07; unpublished data). Second, the contrast between emotional face-types provides greater specificity of emotion-related processing differences. Third, this contrast is most comparable with prior studies of anxiety and childhood maltreatment which have used happy or neutral faces for comparison (Shin et al., 2005; Williams et al., 2009). As the target emotional expression on each trial occurs in the presence of a non-congruent emotional expression, effects elicited by each contrast should be interpreted as occurring within the context of emotional appraisal directed towards the predominant (i.e. target) and away from the non-congruent emotional expression (i.e, distractor), hereafter referred to as targeting angry vs. happy or fearful vs. happy faces. These contrasts have proven useful elsewhere for eliciting anxiety-related hyperactivity in relevant limbic structures (G. A. Fonzo et al., 2010). 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.

Functional Connectivity Preprocessing and Individual Analysis

For each contrast, task-related activation clusters in the amygdala, anterior insula, and prefrontal cortex were chosen as seed regions for connectivity analyses in order to test *a-priori* hypotheses concerning connectivity among these regions. Functional connectivity analyses were conducted according to previously established methods (G. A. Fonzo et al., 2010) but slightly modified using a recently-published preprocessing pathway which maps and removes sources of artifact in scanner signal (Jo, Saad, Simmons, Milbury, & Cox, 2010). In brief, each participant's high-resolution anatomical was used to construct subject-specific gray matter (GM), white-matter (WM), and ventricular masks using FSL's FAST (fMRIB's Automated Segmentation Tool)(Smith, 2002; Smith et al., 2004; Woolrich et al., 2009). WM masks were then eroded by one voxel in each direction to prevent leakage of GM signal into the mask. Voxelwise local WM regressors for each subject were constructed by using a 30 mm sphere to average across voxels containing WM in the adjacent vicinity of each voxel, thus resulting in a region-specific WM time series at each voxel in the brain. Time series were also extracted from the lateral ventricles. Signal artifact arising from WM, ventricular cerebrospinal fluid, and six motion parameters was estimated using the AFNI program 3dTfitter, and the residual time series was calculated by removing these artifact effects from each subject's timeseries. The residual time series was then time-shifted, bandwidth filtered $(.009 < f < .08)$, and smoothed using a 4 mm FWHM Gaussian kernel within each tissue-type (i.e., GM and WM) separately. The timeseries from clusters displaying task-dependent activation in seed regions was extracted from this blurred and filtered residual timeseries, and the psychophysiological interaction (PPI) of the seed timeseries and the effects-coded contrast of interest (i.e., angry vs. happy or fearful vs. happy) was then entered into a deconvolution analysis along with regressors for the seed timeseries, task contrast, and two baseline polynomials. The outcome measure of interest was the voxelwise Fisher-Z transformed correlation-coefficient (rFz) for the PPI regressor.

Optimized Voxel-Based Morphometry

Gray matter (GM) volumes were assessed using FSL-VBM, a voxel-based morphometry style analysis (Ashburner & 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, Brady, & Smith, 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 & Smith, 2001; Jenkinson, Bannister, Brady, & Smith, 2002) followed by nonlinear registration with FNIRT (J. L. R. Andersson, Jenkinson, & Smith, 2007a; J. L. R. Andersson, Jenkinson, & Smith, 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.

Task Effect Activation and Connectivity

In order to identify significant activations and connectivity within each contrast, single-sample voxelwise t-tests against the null hypothesis were carried out on individual activation/connectivity maps across all participants.

Basic Mediation Analyses

Voxelwise basic mediation analyses were conducted using the MBESS package (Kelley & Lai, 2010) implemented in R (R Development Core Team, 2011). Childhood emotional abuse (CTQEA) and childhood emotional neglect (CTQEN) served as the independent variables (in separate models) and anxiety symptoms (BSIAnx) served as the dependent variable in the mediation model. For each activation contrast, connectivity seed region, and GM volumetric map, voxelwise %SCs, rFzs, and GM volumes served as the

respective mediating variable in the mediation model. Thus, these analyses identified on a voxelwise level brain function and structure which mediated the relationship between childhood emotional abuse/neglect and adulthood anxiety symptoms. The main outcome measure was the 95% confidence interval for the indirect effect (mediation effect). As the distribution of the indirect effect is often non-normal and therefore inappropriate and underpowered for statistical tests which assume normality (MacKinnon, Fairchild, & Fritz, 2007), bootstrapping of the indirect effect was utilized to determine the standard error and confidence intervals of the indirect effect. At each voxel, a minimum of 200 bootstrap samples were utilized to derive standard error estimates. The resulting statistical map(s) were thresholded by examining the bootstrapped lower bound of the confidence interval of the indirect effect for those which are greater than zero. If the lower bound of the confidence interval does not contain zero (i.e., is positive), the indirect effect is considered to be statistically significant.

Region of Interest and Whole Brain Analyses

Two types of analyses were conducted on the group level. In addition to a whole-brain (WB) exploratory analysis, *a-priori* region of interest (ROI) analyses were conducted on emotion-processing brain regions previously implicated in studies of anxiety and childhood maltreatment: bilateral insula, bilateral amygdala, and anterior cingulate/medial prefrontal cortex (ACC/mPFC). Boundaries of these ROIs were based upon both anatomical criteria and standardized locations taken from the Talairach atlas (Talairach & Tournoux, 1998). A threshold adjustment based upon Monte-Carlo simulations (using AFNI's program AlphaSim) was used to guard against false positives in the WB and ROI 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 and connectivity only, a more conservative voxelwise threshold of $p < 0.001$ 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 VBM analyses, ROI and WB analyses were also conducted. 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 ($p = 0.00003$).

Extended Mediation Analyses

In order to perform moderated mediation analyses (Aims 3 and 4) and mediation with covariates (extended mediation analyses), the average %SC, rFzs, and GM volumes were extracted from each participant from clusters displaying significant basic mediation effects in the voxelwise analyses. The PROCESS package (Hayes, In submission) implemented in IBM SPSS version 19.0 (SPSS Inc., an IBM company, 2010) was utilized for extended mediation analyses. In extended mediation analyses, bootstrapping of the confidence interval of the indirect effect (1000 bootstrap samples) was utilized to determine significance. Several extended mediation analyses were conducted. First, in order to determine the robustness of mediation effects and their specificity to the relationship between childhood emotional

maltreatment and anxiety, the depression subscale of the BSI (BSIDep) was utilized as a covariate in extended mediation analyses for clusters displaying significant effects in the basic mediation analysis. Thus, this will enable the determination of whether the mediation effect is specific to the relationship between childhood maltreatment and adulthood anxiety irrespective of adulthood symptoms of depression. Second, in order to determine if the mediating effects of brain function are significant irrespective of brain structure (and vice-versa), GM volume (or functional activation for significant structural mediators in regions also displaying significant functional mediation) was utilized as a covariate in mediation analyses for clusters displaying significant effects in the basic voxelwise mediation analysis. Third, in order to test the potential moderating effect of corticolimbic interactions on mediation effects (Aim 3), moderated mediation analyses were conducted for basic mediation analyses which yield significant mediation effects in both prefrontal and limbic regions. For these analyses, prefrontal activation was tested as a proposed moderator of the mediating effect of limbic activation on the relationship between childhood emotional maltreatment and anxiety. A significant interaction effect in one or both of the paths of the indirect effect (i.e., independent variable → mediating variable or mediating variable → dependent variable) indicates a significant moderation effect. Fourth, in order to test the potential moderating role of brain structure in the mediation effect of brain function (Aim 4), moderated mediation analyses were conducted on all activation clusters displaying significant mediation effects in the basic mediation analyses. For those clusters displaying functional mediation, the average GM volume in that cluster was extracted from each participant and was tested as a proposed moderator of the mediating effect of brain activation on the relationship between childhood emotional maltreatment and anxiety. A significant interaction effect in one or both of the paths of the indirect effect (i.e., independent variable → mediating variable or mediating variable → dependent variable) indicates a significant moderation effect.

Results

Demographics and Symptoms

The mean age of the participants was 30.71 years (+/- 11.27), and the mean number of years of education completed was 14.49 (+/- 1.81). The sample was almost entirely female (148 females, 34 males) and the majority were of Caucasian ethnicity (101 participants). The remaining participants were of the following ethnicities: African-American ($n = 13$), Asian ($n = 16$), Filipino ($n = 9$), Latino ($n = 14$), Native American ($n = 3$), and other ($n = 26$). The mean score on the CTQEA subscale was 9.50 (+/- 4.97) which indicates on average low-to-moderate levels of childhood emotional abuse (D. P. Bernstein & Fink, 1998). Scores on this subscale ranged from 5-24, indicating a range of emotional abuse from little to extreme across all participants. The mean score on the CTQEN subscale was 10.70 (+/- 5.25), also indicating on average low-to-moderate levels of childhood emotional neglect (D. P. Bernstein & Fink, 1998). The range on this subscale was from 5-25, also indicating a wide range of emotional neglect experiences from low to extreme. The mean score for the BSIAnx subscale was 5.41 (+/- 5.47) and the mean t-score was 54.19 (+/- 12.46), which corresponds to greater or equivalent anxiety symptoms of roughly 50-70% of the normative sample (Derogatis, 2000). The range of raw scores was from 0 to 24 and the range of t-scores was from 38 to 81, indicating a wide range of anxiety symptoms from none to severe. The mean score for the BSIDep subscale was 5.52 (+/- 5.40) and the mean t-score was 54.68 (+/- 11.38), which also corresponds to greater or equivalent depression symptoms of roughly 50-70% of the normative sample (Derogatis, 2000). The range of raw scores was from 0 to 24 and the range of t-scores was from 40 to 81, also indicating a wide range of depression symptoms from none to severe. See Table 1 for complete results.

Relationships Among Childhood Emotional Maltreatment and Anxiety Symptoms

Consistent with expectations, emotional abuse and neglect were both significantly positive correlated with anxiety scores from the BSI (CTQEA: Pearson's $r = 0.334$, $p < 0.001$; CTQEN: Pearson's $r = 0.265$, $p < 0.001$), indicating that greater levels of childhood emotional abuse and neglect are associated with greater symptoms of anxiety in adulthood. Emotional abuse and neglect were also significantly and highly positively correlated (Pearson's $r = 0.758$, $p < 0.001$), consistent with the frequent co-occurrence of multiple dimensions of childhood maltreatment (Teicher, Samson, Polcari, & McGreenery, 2006). Emotional abuse and neglect were also significantly positively correlated with depression scores from the BSI (CTQEA: Pearson's $r = 0.351$, $p < 0.001$; CTQEN: Pearson's $r = 0.322$, $p < 0.001$), indicating the expected nonspecific relationship between childhood maltreatment and worse mental health functioning in adulthood across several domains (Spinhoven et al., 2010). The anxiety and depression subscales of the BSI were also significant positively correlated (Pearson's $r = 0.694$, $p < 0.001$). These relationships between childhood emotional abuse and neglect and anxiety and depression symptoms continued to remain significant after controlling for age, gender, years of education, and presence of a current anxiety or depressive disorder using multiple regression.

Neuroimaging Results

Behavioral Data

All participants completed the emotional face matching task with high levels of accuracy, with the mean percentage of trials completed incorrectly ranging from 1 to 2.5%. Average reaction times ranged from 0.7 to 2.3 seconds per trial. A repeated measures ANOVA revealed a significant effect of trial type on both accuracy ($F = 10.981$, $p < 0.001$) and reaction time ($F = 256.584$, $p < 0.001$). Post-hoc pairwise comparisons with Bonferroni correction revealed that accuracy for angry was better than that for fear ($p = 0.002$) and for shapes ($p = 0.012$) and accuracy for happy was better than that for fear ($p < 0.001$) and for

shapes ($p < 0.001$). Accuracy of angry and happy did not differ, nor did accuracy of fear and shapes. For reaction time, pairwise comparisons demonstrated significant differences of each condition from each of the other three conditions (all p's < 0.001) such that reaction time for shapes < happy < angry < fear. There were no significant correlations between measures of accuracy and reaction time and measures of childhood emotional abuse/neglect, anxiety symptoms, or depressive symptoms (all p's > 0.05). See Table 1 for complete results.

Task Effects

Functional Activation

Limbic ROIs

For emotion processing directed towards fearful vs. happy faces, all participants displayed activation of the bilateral anterior insula and bilateral amygdala and deactivation of the perigenual and subgenual anterior cingulate (Table 2). For processing directed towards angry vs. happy faces, all participants displayed activation of the bilateral anterior insula (Table 3).

Whole Brain

For processing directed towards fearful vs. happy faces, all participants displayed activation of the bilateral inferior/superior temporoccipital cortex, precuneus, thalamus, dorsolateral PFC, anterior insula, dorsomedial PFC, and cerebellum and deactivation of the left middle frontal gyrus (dorsolateral PFC), posterior cingulate, and medial prefrontal cortex (Table 2). For processing directed towards angry vs. happy faces, all participants displayed activation of bilateral inferior/superior temporoccipital cortex, superior parietal lobule, precuneus, dorsolateral PFC, anterior insula, and dorsomedial PFC. There were no regions of significant deactivation in this contrast (Table 3).

Functional Connectivity

Limbic ROIs

Activity in a seed region in the right amygdala displaying task-dependent activation for processing directed towards fearful vs. happy faces displayed positive connectivity (i.e., significant positive covariation of timeseries) with the perigenual anterior cingulate and the right posterior insula. Activity in a seed region in the left anterior insula displaying task-dependent activation for processing directed towards fearful vs. happy faces displayed positive connectivity with the right anterior insula and left amygdala and negative connectivity (i.e., significant negative covariation of timeseries) with the bilateral middle/posterior insula. Activity in a seed region in the left middle frontal gyrus (dorsolateral PFC) displaying task-dependent activation for processing directed towards fearful vs. happy faces displayed positive connectivity with the bilateral anterior insula and bilateral amygdalae and negative connectivity with the dorsal/perigenual/subgenual anterior cingulate and the bilateral middle/posterior insula (Table 4).

Activity in a seed region in the right anterior insula displaying task-dependent activation for processing directed towards angry vs. happy faces displayed positive connectivity with the bilateral amygdalae and a more ventral portion of the right anterior insula and negative connectivity with the left middle insula. Activity in a seed region in the right middle frontal gyrus (dorsolateral PFC) displaying task-dependent activation for processing directed towards angry vs. happy faces displayed positive connectivity with the bilateral amygdalae and negative connectivity with the bilateral middle/posterior insula and perigenual anterior cingulate. Activity in a seed region in the dorsal medial frontal gyri displaying task-dependent activation for processing directed towards angry vs. happy faces displayed positive connectivity with the bilateral amygdalae and negative connectivity with the bilateral anterior/middle/posterior insula and perigenual anterior cingulate (Table 5).

Whole Brain

Activity in a seed region in the right amygdala displaying task-dependent activation for processing directed towards fearful vs. happy faces displayed positive connectivity with the left superior frontal gyrus (dorsomedial PFC); there were no regions of significant negative connectivity. Activity in a seed region in the left anterior insula displaying task-dependent activation for processing directed towards fearful vs. happy faces displayed positive connectivity with the bilateral fusiform gyri, bilateral middle frontal gyri (dorsolateral PFC), and right anterior insula; it displayed negative connectivity with the right precuneus, right posterior insula, right inferior parietal lobule, and right mid-cingulate gyrus. Activity in a seed region in the left middle frontal gyrus (dorsolateral PFC) displaying task-dependent activation for processing directed towards fearful vs. happy faces displayed positive connectivity with the bilateral fusiform gyri, inferior/superior temporoccipital cortex, right anterior insula and middle frontal gyrus (dorsolateral PFC), bilateral amygdala/globus pallidus, thalamus, bilateral superior parietal lobule/precuneus, cerebellum, and left precentral gyrus; it displayed negative connectivity with a large cluster encompassing the bilateral anterior/middle/posterior cingulate, dorsomedial and dorsolateral PFC, inferior parietal lobule, supramarginal gyri, angular gyri, precuneus, middle/superior temporal gyri, postcentral gyri, and parahippocampal gyri (Table 4).

Activity in a seed region in the right anterior insula displaying task-dependent activation for processing directed towards angry vs. happy faces displayed negative connectivity with the left precentral/postcentral gyri, left inferior parietal lobule, bilateral precuneus, and right superior frontal gyrus (supplementary motor area); there were no regions displaying significant positive connectivity. Activity in a seed region in the right middle frontal gyrus (dorsolateral PFC) displaying task-dependent activation for processing directed towards angry vs. happy faces displayed positive connectivity with the bilateral fusiform gyri, bilateral inferior/superior temporoccipital cortex, left superior and medial frontal gyri

(dorsomedial PFC), bilateral superior parietal lobule/precuneus, bilateral precentral gyrus, and right amygdala; it displayed negative connectivity with the bilateral posterior cingulate/precuneus, bilateral parahippocampal gyri, bilateral middle temporal gyrus, bilateral posterior insula, right transverse temporal gyrus, right thalamus, right caudate/nucleus accumbens, right supramarginal gyrus, and right inferior frontal gyrus (lateral PFC). Activity in a seed region in the dorsal medial frontal gyri displaying task-dependent activation for processing directed towards angry vs. happy faces displayed positive connectivity with the bilateral fusiform gyri, bilateral inferior/superior temporoccipital cortex, bilateral precentral gyri, bilateral superior parietal lobule/precuneus, bilateral amygdala, right inferior/middle frontal gyri (dorsolateral PFC), and right thalamus; it displayed negative connectivity with the bilateral posterior cingulate/precuneus, right claustrum/middle insula/superior temporal gyrus, bilateral parahippocampal gyri, bilateral middle temporal gyri, left claustrum/anterior insula, bilateral dorsal anterior cingulate, left inferior parietal lobule, right supramarginal gyrus, thalamus, left superior frontal gyrus (anterior PFC), left posterior insula, left postcentral gyrus, right caudate/nucleus accumbens, and bilateral perigenual anterior cingulate (Table 5).

<u>Basic Mediation Analyses</u>

Functional Activation

<u>Limbic ROIs</u>

For the contrast of processing targeted towards fearful vs. happy faces, greater activation in the left posterior insula partially mediated the relationship between childhood emotional abuse and anxiety symptoms (indirect effect = 0.0364, 95% CI: 0.0063-0.0908; Table 6 and Figure 1). This effect remained significant when controlling for depressive symptoms and GM volumes (indirect effect = 0.0241, 95% CI: 0.0028-0.0693). There were no significant clusters found in limbic ROIs which mediated the relationship between childhood emotional neglect and anxiety symptoms.

For the contrast of processing targeted towards angry vs. happy faces, there were no clusters found in limbic ROIs which mediated the relationship between childhood emotional abuse and anxiety symptoms. However, greater activation in the left amygdala partially mediated the relationship between childhood emotional neglect and anxiety symptoms (indirect effect = 0.0446, 95% CI: 0.0131-0.0895; Table 6 and Figure 3). This effect remained significant when controlling for depressive symptoms and gray matter volumes (indirect effect = 0.0226, 95% CI: 0.0011-0.0565).

Whole Brain

For the contrast of processing targeted towards fearful vs. happy faces, greater activation in the left temporal pole (middle/superior temporal gyri) partially mediated the relationship between childhood emotional abuse and anxiety symptoms (indirect effect = 0.0510, 95% CI: 0.0189-0.0996; Table 6). This effect remained significant when controlling for GM volumes (indirect effect = 0.0518, 95% CI: 0.0196-0.1034), but it did not remain significant when controlling for depressive symptoms (indirect effect = 0.0166, 95% CI: -0.0065-0.0477). Additionally, greater activation in the right fusiform gyrus partially mediated the relationship between childhood emotional neglect and anxiety symptoms (indirect effect = 0.0596, 95% CI: 0.0220-0.1176; Table 6). This effect remained significant when controlling for depressive symptoms and GM volumes (indirect effect = 0.0274, 95% CI: 0.0096-0.0642).

For the contrast of processing targeted towards angry vs. happy faces, decreasing activation in the right dorsolateral prefrontal cortex (inferior/middle frontal gyri; BA 10 and 46) partially mediated the relationship between childhood emotional abuse and anxiety symptoms (indirect effect = 0.0757, 95% CI: 0.0339-0.1405; Table 6 and Figure 2). This effect remained significant when controlling for depressive symptoms and GM volumes (indirect effect = 0.0563, 95% CI: 0.0223-0.1055). Likewise, decreasing activation in the right dorsolateral prefrontal cortex (inferior/middle frontal gyri; BA 10 and 46) also partially

mediated the relationship between childhood emotional neglect and anxiety symptoms (indirect effect = 0.0550, 95% CI: 0.0234-0.1026; Table 6). This effect also remained significant when controlling for depressive symptoms and GM volumes (indirect effect = 0.0368, 95% CI: 0.0109-0.0795).

Functional Connectivity

Limbic Seeds

For the contrast of processing directed towards fearful vs. happy faces, there were no regions of connectivity with task-dependent activity in the left anterior insula seed region or task-dependent activity in the right amygdala seed region which mediated the relationship between childhood emotional abuse or childhood emotional neglect and anxiety symptoms (Table 7).

For the contrast of processing directed towards angry vs. happy faces, there were no regions of connectivity with task-dependent activity in the right anterior insula seed region which mediated the relationship between childhood emotional abuse and anxiety symptoms. However, decreasing connectivity between task-dependent activity in the right anterior insula seed region and the posterior cingulate partially mediated the relationship between childhood emotional neglect and anxiety symptoms (indirect effect = 0.0484, 95% CI: 0.0111-0.1077; Table 8 and Figure 4). This effect remained significant when controlling for depressive symptoms and GM volumes (indirect effect = 0.0241, 95% CI: 0.0005-0.0652). Furthermore, decreasing connectivity between task-dependent activity in the right anterior insula seed region and the left medial prefrontal cortex (medial/superior frontal gyri; BA 9 and 10) partially mediated the relationship between childhood emotional neglect and anxiety symptoms (indirect effect = 0.0665, 95% CI: 0.0249-0.1305; Table 8). This effect also remained significant when controlling for depressive symptoms and GM volumes (indirect effect = 0.0289, 95% CI: 0.0079-0.0676).

Prefrontal Seeds

For the contrast of processing directed towards fearful vs. happy faces, decreasing connectivity between task-dependent activity in the left dorsolateral prefrontal cortex (left inferior/middle frontal gyrus) seed region and the left precentral/postcentral gyri partially mediated the relationship between childhood emotional abuse and anxiety symptoms (indirect effect = 0.0647, 95% CI: 0.0220-0.1399; Table 7 and Figure 5). This effect remained significant when controlling for depressive symptoms and GM volumes (indirect effect = 0.0370, 95% CI: 0.0032-0.0890). Furthermore, decreasing connectivity between these same two regions also partially mediated the relationship between childhood emotional neglect and anxiety symptoms (indirect effect = 0.0895, 95% CI: 0.0363-0.1666; Table 7). This effect also remained significant when controlling for depressive symptoms and GM volumes (indirect effect = 0.0587, 95% CI: 0.0186-0.1150).

For the contrast of processing directed towards angry vs. happy faces, decreasing connectivity between task-dependent activity in the right dorsolateral prefrontal cortex (right inferior/middle frontal gyrus) seed and activity in the left precentral/postcentral gyri partially mediated the relationship between childhood emotional abuse and anxiety symptoms (indirect effect = 0.0520, 95% CI: 0.0130-0.1200; Table 8). This effect remained significant when controlling for depressive symptoms and GM volumes (indirect effect = 0.0221, 95% CI: 0.0001-0.0661). Similarly, decreasing connectivity between task-dependent activity in the right dorsolateral prefrontal cortex seed and activity in the right precentral/postcentral gyri partially mediated the relationship between childhood emotional neglect and anxiety symptoms (indirect effect = 0.0690, 95% CI: 0.0345-0.1311; Table 8). This effect also remained significant when controlling for depressive symptoms and GM volumes (indirect effect = 0.0263, 95% CI: 0.0045-0.0687). Additionally, decreasing connectivity between task-dependent activity in the right dorsolateral prefrontal cortex seed and activity in the posterior

cingulate partially mediated the relationship between childhood emotional neglect and anxiety symptoms (indirect effect = 0.0475, 95% CI: 0.0144-0.0961; Table 8 and Figure 6). This relationship also remained significant when controlling for depressive symptoms and GM volumes (indirect effect = 0.0244, 95% CI: 0.0042-0.0567). There were no regions of connectivity with the dorsomedial prefrontal cortex (medial/superior frontal gyri) seed region which mediated the relationship between childhood emotional abuse and anxiety symptoms. However, decreasing connectivity between task-dependent activity in the dorsomedial prefrontal cortex and activity in the posterior cingulate/precuneus partially mediated the relationship between childhood emotional neglect and anxiety symptoms (indirect effect = 0.0601, 95% CI: 0.0189-0.1205; Table 8). This effect remained significant when controlling for depressive symptoms and GM volumes (indirect effect = 0.0259, 95% CI: 0.0021-0.0676).

Gray Matter Volumes

Limbic ROIs

There were no clusters in limbic ROIs in which GM volumes mediated the relationship between childhood emotional abuse or childhood emotional neglect and anxiety symptoms (Table 9).

Whole Brain

There were no clusters in the whole brain analysis which mediated the relationship between childhood emotional abuse and anxiety symptoms. However, decreasing GM volumes in the left precentral gyrus partially mediated the relationship between childhood emotional neglect and anxiety symptoms (indirect effect = 0.0444, 95% CI: 0.0140-0.1018; Table 9). However, this effect was no longer significant when controlling for depressive symptoms (indirect effect = 0.0130, 95% CI: -0.0078-0.0452). Furthermore, decreasing GM volumes in the right dorsolateral prefrontal cortex (inferior/middle frontal gyri; BA 10 and 46) partially mediated the relationship between childhood emotional neglect and anxiety

symptoms (indirect effect = 0.0400, 95% CI: 0.0098-0.0913; Table 9 and Figure 7). This effect continued to remain significant when controlling for depressive symptoms (indirect effect = 0.0335, 95% CI: 0.0070-0.0798). As this structural cluster partially overlapped a functional cluster which mediated the relationship between emotional neglect and anxiety symptoms during processing targeted towards angry vs. happy faces, this structural mediation effect was also tested for significance when controlling for brain activation in this cluster during the aforementioned contrast. This effect continued to remain significant when controlling for functional activation to angry vs. happy faces (indirect effect = 0.0416, 95% CI: 0.0113-0.0954) and when additionally controlling for symptoms of depression (indirect effect = 0.0318, 95% CI: 0.0065-0.0747).

Checking Anxiety Specificity of Mediation Effects

As an additional check to establish the specificity of these mediation effects to anxiety symptoms and not depression symptoms, all functional and structural clusters displaying significant mediation effects of the relationship between childhood emotional abuse/neglect and anxiety while controlling for depressive symptoms were also tested to see if they mediated the relationship between childhood emotional maltreatment and symptoms of depression. None of the aforementioned effects significantly mediated the relationship between childhood emotional abuse/neglect and symptoms of depression, suggesting they are relatively specific mediating effects for symptoms of anxiety.

Extended Mediation Analyses

Testing Moderation of Limbic Functional Activation by Prefrontal Cortical Activity

As the basic voxelwise mediation analysis for activation during processing targeted towards angry vs. happy faces on the relationship between childhood emotional neglect and anxiety symptoms yielded a cluster in the left amygdala and right dorsolateral prefrontal cortex, the potential moderating effect of prefrontal activation on the mediation effect of

amygdala activation was tested. The moderation effect of prefrontal activation on the amygdalar mediation of the childhood emotional neglect-anxiety symptom relationship was not significant on either the path from childhood emotional neglect to amgydala activation ($t = 0.2013$, $p = 0.8407$) or on the path from amygdala activation to anxiety symptoms ($t = 0.0771$, $p = 0.9386$). Additionally, the converse model was also tested (i.e., amygdala activation as a potential moderator of the meditation effect of right dorsolateral prefrontal cortical activation on the relationship between childhood emotional neglect and anxiety symptoms). Again, the moderation effect was not significant on either the path from childhood emotional neglect to prefrontal activation ($t = -0.836$, $p = 0.9335$) or on the path from prefrontal activation to anxiety symptoms ($t = 0.0771$, $p = 0.9386$). However, there was a marginally significant finding for an inverse correlation between activation magnitudes in these two mediating regions (Pearson's $r = -0.130$, $p = 0.079$), suggesting that individuals whom had greater activation in either the amygdala or prefrontal cortex tended to have less activation in the other region.

Testing Moderation of Functional Activation by Brain Structure

In order to test the potential interacting role of brain function and structure on the mediating effects of brain function on relationship between childhood emotional abuse/neglect and anxiety symptoms, GM volumes were explored as potential moderators of mediation effects for all functional activation clusters (left amygdala, right dorsolateral prefrontal cortex, left posterior insula, and right fusiform gyrus). The only cluster which displayed a significant moderated mediation effect was the left amygdala mediation of the relationship between childhood emotional neglect and anxiety symptoms for processing targeted towards angry vs. happy faces. Specifically, on the path from childhood emotional neglect to left amygdala activation there was a significant moderation by left amygdala GM volume ($t = -2.7252$, $p = 0.0071$; Figure 3) such that for increasing left amygdala GM volumes the mediation

relationship grew increasingly weak and was nonsignificant at +1 SD above the mean GM

volume (indirect effect at mean GM = 0.041, 95% CI: 0.0084-0.0906; indirect effect at 1 SD

below mean GM volume = 0.1057, 95% CI: 0.0383-0.1900; indirect effect at 1 SD above the

mean GM volume = -0.0046, 95% CI: -0.0674-0.0341). When the sample was split on median

amygdala GM volume, those individuals with GM volumes below the median displayed a

stonger positive relationship between childhood emotional neglect and amygdala activation

(standardized β = 0.290 vs. 0.043). There was no significant moderating effect of left

amygdala GM volumes on the path from left amygdala activation to anxiety symptoms (t = -

0.6460, p = 0.5191).

Discussion

The primary aims of this investigation were to determine if and where brain structure and function measured in adulthood might underlie the relationship between childhood emotional maltreatment and anxiety symptoms. Consistent with our hypotheses, increasing activation in limbic structures (i.e., amygdala and insula) during processing directed towards negative (angry and fear) vs. positive (happy) facial emotions mediated the relationship between childhood emotional maltreatment (abuse and neglect) and adulthood anxiety symptoms, and this effect in the amygdala was strongest for those with the smallest GM volumes. Furthermore, decreasing activation in a dorsolateral prefrontal region during processing directed towards angry vs. happy faces also mediated the relationship between childhood emotional maltreatment and anxiety symptoms. Connectivity analyses revealed that greater disconnect of function between prefrontal seed regions and posterior medial and sensorimotor brain structures mediated the relationship between childhood emotional maltreatment and anxiety symptoms. Finally, consistent with hypotheses structural analyses demonstrated that decreasing GM volumes in the right dorsolateral prefrontal cortex also mediated the relationship between childhood emotional neglect and aduldhood anxiety. All of these functional effects were significant irrespective of GM volumes and current depressive symptoms. Methodologically, these results demonstrate the utility of a retrospective cross-sectional neuroimaging investigation for elucidating a potential neuroetiological pathway which underlies the predisposing effects of childhood maltreatment towards the later development of anxiety in adulthood. Taken together, these findings suggest childhood maltreatment may predispose individuals to the eventual development of anxiety through long-lasting dysregulatory influences on limbic and prefrontal brain responses to threat cues which are characterized by exaggerated reactivity of structures implicated in affective

responses and attenuated function of higher-order frontal structures implicated in top-down control and affective regulation.

These results implicate increasing reactivity of limbic structures and decreasing engagement of frontal regions to negative or threatening socioemotional cues as a potential neural risk or vulnerability marker instantiated by early stressful life experiences which may promote the later manifestation of anxiety symptoms. This activation pattern is consistent with an *emotional dysregulation* mechanism of early life stress effects such that stressful experiences like childhood maltreatment early in development can disrupt normal socioemotional functioning by fostering enhanced states of fear and arousal in response to threatening interpersonal stimuli which cumulatively mount and ultimately result in a dysregulation of stress and fear responses and the emergence of anxiety disorder symptoms (Nolte, Guiney, Fonagy, Mayes, & Luyten, 2011). Consistent with this, the amygdala and insula are highly implicated in the expression of emotional responses and heightened states of arousal (Craig, 2004; Critchley et al., 2005), particularly the fear and stress responses (Feinstein et al., 2011; van Wingen, Geuze, Vermetten, & Fernandez, 2011). The mediation effects observed here suggest that childhood maltreatment promotes states of increased arousal and vigilance in response to socioemotional cues of threat (e.g., fearful or angry faces) through increased reactivity of limbic brain regions, consistent with convergent physiological and behavioral evidence (Gibb et al., 2009; Masten et al., 2008; Williams et al., 2009), which in turn than promote heightened expression of fear and anxiety manifestations.

Of note is that amygdala effects occurred only in the context of processing targeted towards angry vs. happy faces and only for emotional neglect, while insular effects occurred only in the context of processing targeted towards fearful vs. happy faces and only for emotional abuse. It can be difficult to establish maltreatment domain-specific effects due to the frequent cooccurrence and high intercorrelation of different types of maltreatment

(emotional abuse and emotional neglect correlated at nearly 0.8 in this sample). The amygdala, however, may be particularly responsive to forms of neglect given convergent evidence that amygdalar volumes were uniquely impacted by institutional deprivation (emotional/physical neglect) extremely early in development (Tottenham et al., 2010). The relationship between posterior insular activity and emotional abuse is also consistent with the role of this region in lower-order forms of interoceptive processing involving the instantiation of bodily states and sensations such as pain and heat (Craig, 2009), which makes sense given that emotional abuse denotes the deliberate commission of acts against the child by the caregiver that are likely to occur alongside strong powerfully felt emotions and sensations. Although angry faces are generally considered to be the probe of choice for eliciting abuse-related effects (Masten et al., 2008; Pollak, 2008), prior face-processing studies in maltreated samples have generally not been able to parse apart effects from different forms of abuse (e.g., emotional, physical, and sexual) in their analyses. Therefore, the relationships between angry face-processing abnormalities and abuse history may be stronger for abuse in one domain compared to another. In particular, one could hypothesize that the relationship between physical abuse and angry faces might be the strongest given that displays of violence frequently occur alongside expressions of anger (Eckhardt, Samper, & Murphy, 2008) as well as prior evidence for angry facial cue processing abnormalities in abused samples (Pollak, 2008), while other forms such as emotional or sexual abuse also occur in the form of teasing, taunting, and seduction that are likely to occur alongside displays of other emotions besides anger (Goodman, Quas, & Ogle, 2010). Consistent with this, we observed neural mediating effects for emotional abuse and anxiety in the context of emotion processing directed towards fearful vs. happy faces, which may have occurred due to the ability for fearful faces to signal a potential environmental threat from an ambiguous source (Whalen et al., 2001). In particular, it is plausible that fearful faces may elicit effects conditioned by maltreatment experiences

through witnessing fearful facial expressions from a sibling or parent also exposed to maltreatment in the person's early environment (Masten et al., 2008).

Regardless, both the amygdala and insula tend to be functionally important earlier in the lifespan, with developmental neuroscience studies indicating that children tend to display greater responsivity of the amygdala and posterior insula to emotional stimuli relative to adults (Decety & Michalska, 2010; Hoehl et al., 2010). Both regions also tend to show a protracted trajectory of gray matter development throughout the course of the lifespan (Grieve et al., 2011; Shaw et al., 2008), potentially indicating a prolonged period of neural plasticity and susceptibility to environmental influences. The current findings are therefore consistent with developmental studies and suggest that brain regions which are functionally important in childhood may be particularly sensitive to maladaptive environmental effects and these effects can persist into adulthood. It may be useful for future studies to attempt to disentangle the relative contributions of different types of emotional maltreatment (e.g., abuse vs. neglect) towards increased amygdala and insula activation as well as the practical significance of the potential segregation of distinct effects in response to particular emotional stimuli.

Of particular interest is the relationship of amygdala GM volumes to the strength of the functional mediation effect in this region, an interesting functional/structural interaction which to our knowledge is one of the first reported in the literature. Specifically, the smaller the GM volume in the portion of the left amygdala in which greater activation during processing targeted towards angry vs. happy faces underlied the relationship between childhood emotional neglect and anxiety symptoms, the stronger the mediation effect. Furthermore, this interaction was specific to the pathway from childhood emotional neglect to amygdala activation and did not occur on the pathway from amygdala activation to anxiety symptoms, suggesting this moderation effect is segregated to a maltreatment-related influence early in the lifespan. Reductions in amygdala structural volumes have been observed in

anxious samples (Asami et al., 2009; Hayano et al., 2009; Karl et al., 2006), suggesting that smaller amygdala volumes may be a marker for anxiety symptoms and/or involved in the underlying etiological process. Amygdala volumes have also been found to be abnormally large in adolescent survivors of institutional deprivation in early childhood (Mehta et al., 2009; Tottenham et al., 2010), which seems contradictory to the current findings. However, it is important to note that the amygdala may undergo developmental changes from adolescence to adulthood (Casey et al., 2010) and abnormally large amygdala volumes in adolescence may not necessarily carry over into adulthood. The relationship between brain structure (i.e., GM volumes) and function remains poorly understood in the neuroimaging literature, partly due to the fact that the majority of studies which investigate one or the other do not include analyses for both measures in the same sample of participants. There are two potential explanations for this finding, the first of which emphasizes a functional impact on structure and the second of which emphasize a structural impact on function. First, childhood emotional neglect promotes increasing activation of the amygdala to angry facial cues, and in those individuals in which this effect is the strongest there is a concomitant structural impact which results in atrophy of amygdalar GM. This may occur as a consequence of stress-induced neuronal excitotoxicity or enhanced neuronal pruning. Second, those individuals who have smaller amygdala GM volumes prior to experiencing maltreatment are more sensitive to the impact of childhood emotional neglect on increasing amygdala activation to angry facial cues. There may also be transactional (or a combination of the two aforementioned) effects between emotional neglect and amygdala function and structure such that the relationship of emotional neglect to amygdala function influences amygdalar structure while preexisting amygdalar structure also impacts the relationship between emotional neglect and amygdalar function. The cross-sectional retrospective design of this study, however, limits any inference concerning the causal relationships among these three variables. Regardless, the absence of any such

structural-functional interaction on the pathway from amygdala activation to adulthood anxiety symptoms suggests the moderating influence of amygdala structure on the relationship between amygdala function and environmental/behavioral variables is particularly important early in the course of life, consistent with the high levels of plasticity which characterize the brain in this stage of development (Stiles, 2008).

Consistent with prevailing theory concerning the role of prefrontal regions in regulating stress and fear responses (Campbell-Sills et al., 2011; A. N. Simmons et al., 2011), concomitant diminishment of dorsolateral prefrontal recruitment in response to angry facial cues due to the experience of both emotional abuse and neglect in childhood also appears to promote the emergence of anxiety symptoms. This likely occurs through diminishing prefrontal cortical flexibility and subsequent capability for effective regulation of affective states, consistent with the observed decrements in emotion regulation skills observed in survivors of childhood maltreatment (Tottenham et al., 2010) as well as the importance of the dorsolateral prefrontal cortex in deliberate mechanisms of emotion regulation (Campbell-Sills et al., 2011). Although greater prefrontal activation was expected to mediate the relationship between childhood emotional maltreatment and anxiety symptoms, the opposite relationship was actually observed. This suggests that frequent findings for increased medial and lateral prefrontal activation in those exposed to childhood maltreatment or early life stress (Croy et al., 2010; Mueller et al., 2010; Williams et al., 2009) most likely reflect a compensatory adaptation rather than an underlying aspect of the psychopathological mechanism responsible for the emergence of poor mental health outcomes, consistent with the results observed here. This particular region of the dorsolateral PFC (inferior/middle frontal gyri; BA 10 and 46) is highly implicated in studies of executive function, working memory, and cognitive control (Yarkoni, Poldrack, Nichols, Van Essen, & Wager, In press), consistent with its proposed regulatory role over affective responses and limbic brain function.

Convergent evidence was also found for a structural mediating effect of GM volumes in this same region on the relationship between childhood emotional neglect and adulthood anxiety symptoms, consistent with our hypotheses. Both anxiety and childhood maltreatment have been found to be associated with reduced GM volumes in the lateral prefrontal cortices (Eckart et al., 2010; Gatt et al., 2010; Woodward et al., 2009; Yoo et al., 2005), and a recent study also observed that reduced GM volumes in this same right dorsolateral prefrontal region were specifically associated with childhood maltreatment history in women with posttraumatic stress disorder while controlling for other relevant symptom dimensions ((G. A. Fonzo et al., in submissionb). This convergence of functional and structural effects across studies in the same brain region highly implicates the right dorsolateral prefrontal cortex (inferior/middle frontal gyri; BA 10 and 46) as a structure impacted by early maltreatment experiences which promotes an eventual susceptibility to the development of anxiety symptoms. This process may occur through a stress-hormone induced atrophy of GM volumes potentially through influences on neuronal pruning and excitotoxicity, consistent with recent evidence (Carrion et al., 2007; Kremen et al., 2010), and/or synergistically with maladaptive functional overrecruitment of this region for the purposes of regulating states of fear and arousal. The lateral portions of the PFC, in particular, are some of the latest regions to fully mature over the course of brain development (Shaw et al., 2008), which suggests the relative immaturity of this region in childhood may render this structure particularly prone to a reduced functional capacity from chronic fear and stress states. Given the cross-sectional design of this study, it is impossible to determine if dorsolateral prefrontal structural changes preceded functional changes or vice-versa. However, the observation that both structural and functional mediating effects remained significant when controlling for the other suggests that there may be dual effects on both brain structure and function which result in a synergistic detrimental influence.

We did not observe evidence for significant interactions of prefrontal and limbic structures through moderation of the mediation effects of activity in either region on the relationship between childhood emotional abuse/neglect and anxiety symptoms. The lack of such a moderated mediation effect is plausible given the relative immaturity of the prefrontal cortex in childhood in comparison to limbic structures (Tamnes et al., 2010; Van Leijenhorst et al., 2010), suggesting prefrontal regions involved in top-down control and affective regulation may be relatively ineffective at "buffering" the detrimental impact of childhood maltreatment on limbic structures. Furthermore, connectivity patterns in childhood and adolescence are characterized by a small-world topology and are relatively segregated from functional networks in distant portions of the brain (Fan et al., 2011; Supekar et al., 2010), suggesting that prefrontal-limbic connections are immature and may be relatively absent during the experience of childhood maltreatment--thus limiting potential for adaptive prefrontal-limbic regulatory interactions. Alternatively, the current study may not have been adequately powered to detect such a moderated mediation effect, which requires greater sample sizes that those necessary for detecting basic mediation effects (MacKinnon et al., 2007). There was, however, a marginally significant finding for an inverse correlation between activation magnitudes in these two mediating regions (amygdala and right dorsolateral PFC), consistent with the hypothesis of an inverse relationship between function in the prefrontal cortex and the amygdala and a regulatory role for the PFC over affective responses. However, future studies are needed to determine if the functioning of prefrontal and/or limbic regions has the potential to buffer or potentiate the mediating effects of the other region on the relationship between childhood emotional maltreatment and anxiety symptoms in adulthood.

There were also no significant mediation effects of limbic-prefrontal connectivity on the relationship between childhood emotional maltreatment and anxiety in adulthood, contrary

to expectations. Alterations in limbic-prefrontal connectivity are quite prevalent in anxious populations (Etkin et al., 2009; G. A. Fonzo et al., 2010; A. E. Guyer et al., 2008b; Klumpp, Angstadt, & Phan, 2012), although less evidence for alterations in limbic-prefrontal connectivity is present in samples exposed to childhood maltreatment (G. A. Fonzo et al., in submissionb; Taylor et al., 2006). Instead, we observed several findings for decreased connectivity between limbic seed regions such as the anterior insula and dorsal prefrontal seed regions such as the medial and middle frontal gyri with activity in posterior medial (i.e., posterior cingulate/precuneus) and sensory/motor cortices (i.e., precentral/postcentral gyri) as mediators of the relationship between childhood emotional maltreatment and anxiety symptoms. Although not expected *a-priori*, there are other findings in the literature which relate a similar disconnect between posterior medial and prefrontal regions as a functional impact of childhood maltreatment and anxiety (Bluhm et al., 2009; Lanius et al., 2009).

The posterior medial cortices—along with the medial prefrontal cortex, angular gyri, and medial temporal lobes--are heavily implicated in the brain's default-mode network, frequently characterized by self-relevant and autobiographical forms of cognition (Gusnard, Akbudak, Shulman, & Raichle, 2001) and so-named due to frequent observations for increased function in these regions while at rest compared to completion of some active task (Dosenbach et al., 2010). Furthermore, the posterior cingulate/precuneus is also heavily implicated in self-referential mental activity, autobiographical memory, and social cognition (Yarkoni et al., In press). The precentral and postcentral gyri are the brain's primary motor and sensory cortices, respectively, and as such are implicated in a sensory-motor neural network (Dosenbach et al., 2010)involved in initiation and coordination of movements with sensory feedback (Yarkoni et al., In press). Dorsal prefrontal regions are implicated in a frontoparietal executive control network involved in adaptive online control of behavior, while the anterior insula is implicated in a cinguloopercular salience network involved in the

detection and response to salient environmental stimuli (Dosenbach et al., 2010). Posterior and sensory/motor cortical regions are some of the first to reach peak levels of GM volumes in the course of development (Gogtay et al., 2004; Shaw et al., 2008) before beginning a gradual decline which characterizes the processes of neuronal pruning and integration of long-distance functional networks (Vogel et al., 2010), while dorsal prefrontal regions tend to have a longer period of protracted development and reach peak GM volumes in late childhood/early adolescence (Gogtay et al., 2004; Shaw et al., 2008). Furthermore, the network interactions of posterior medial and sensory/motor regions of the brain are relatively segregated from frontal networks early in development, and the functional integration of these two networks parallels similar neurodevelopmental changes such as increased integrity of long-range white-matter connections and greater coherence of functional connectivity (Supekar et al., 2010).

Taken together, these findings suggest that childhood emotional maltreatment may disrupt long-distance coherent functioning between frontal-posterior and frontal-sensory/motor functional networks during the processing of negative or threat-related socioemotional cues, and this disrupted coherence between frontal-posterior and frontal-sensory/motor cortical networks may increase susceptibility to the later development of anxiety. This disruption of network coherence may occur as a consequence of maltreatment-related maladaptive influences on brain development which differentially impact the functioning of frontal and posterior cortical networks due to their disparate developmental trajectories. Given the functional implications of these networks, these findings may practically implicate an etiological psychological process from childhood maltreatment to anxiety symptoms in which top-down executive control and salience processing of socioemotional cues is unable to be brought into coherent functioning with resting-state self-relevant thought processes and basic sensory/motor functions, consistent with evidence for impaired cognitive control of behavior in maltreated adolescents (Mueller et al., 2010) and the

mediating role of maladaptive self-relevant cognitive schemas on the relationship between childhood emotional maltreatment and symptoms of anxiety (Wright et al., 2009). Longitudinal studies in maltreated populations will be useful in delineating the developmental characteristics of this process (i.e., how this disconnect among networks changes over development and relates to the emergence of anxiety symptoms) as well as the associated psychological effects which may occur as a concomitant process.

There are several limitations to the current study. First, the design of this study was cross-sectional and retrospective and the results were correlational in nature. Thus, one cannot draw any firm conclusions as to the causal effects of childhood emotional maltreatment on brain function/structure or how any such effects may influence susceptibility to development or manifestation of anxiety. Although informed by theory and prior evidence, longitudinal studies are necessary to establish that childhood emotional maltreatment exerts effects on brain structure and function which promote susceptibility to the emergence of later anxiety symptoms. Second, the sample utilized was relatively heterogenous and composed of healthy participants as well as several clinical and non-clinical manifestations of anxiety. Given power constraints, we are unable to determine whether mediation effects are specific to a particular syndromal manifestation or whether diagnostic status moderated the strength of mediation effects. Third, many of the clinical anxiety participants met criteria for additional depressive disorders and this may reduce specificity of the results to the relationship between childhood emotional maltreatment and anxiety. However, statistical methods were employed to attempt to control for any confounding effects of depressive symptoms. Additionally, the index anxiety disorder was established as the basis for study enrollment and experienced clinical researchers confirmed the principality of the index disorder as the most debilitating condition. Inclusion of these subjects is also most consistent with the high comorbidity among anxiety/depressive disorders in the population (Kessler et al., 2005). Fourth, the

majority of the sample was composed of adult Caucasian females. Thus, these results may not generalize well to male populations, populations of predominantly non-Caucasian ethnicity, or child/adolescent populations. Fifth, self-report measures of childhood maltreatment are susceptible to reporting biases or inaccuracies. Furthermore, maltreatment experiences may have occurred outside the time range queried by the self-report measure (e.g.., at a later stage of development). Sixth, the emotion-processing task used here does not directly isolate effects related to the target emotional expression due to the presence of a non-congruent face (i.e., the distractor) on each trial. Accordingly, participants must engage in several mental computations for matching, and group differences may arise due to the assessment of the target/matching face, inhibition of the distractor, or both. Thus, the results of this study are not directly comparable to those presenting single faces.

In summary, this study produced initial evidence for a neuroetiological mechanism linking childhood emotional maltreatment to anxiety in adulthood through a potentiation of limbic and an attenuation of prefrontal responses to socioemotional threat cues, consistent with existing evidence for emotional dysregulation as a psychological characteristic in survivors of childhood maltreatment (Pechtel & Pizzagalli, 2010; Tottenham et al., 2010; Wright et al., 2009) as well as those with anxiety (Cornwell, Johnson, Berardi, & Grillon, 2006; Larson, Nitschke, & Davidson, 2007; Tsunoda et al., 2008). Currently, functional neuroanatomical models of clinical anxiety focus almost exclusively on neural abnormalities manifested in the psychopathological state with little attention towards etiological pathways which may underlie these manifestations. Ultimately, the retrospective elucidation of neural effects which underlie the relationship between childhood emotional maltreatment and adulthood anxiety demonstrated here may provide an initial impetus for the consideration of developmental characteristics such as early life experiences in systems neuroscience etiological models of anxiety. Although childhood maltreatment or early-life stress likely

represents only a subset of the potential developmental pathways which converge in the emergence of pathological anxiety in adulthood, the demonstration of the potential to successfully identify neural functional/structural effects in adulthood through retrospective investigation of the relationship of past experiences to the current brain state and symptom profile may encourage the use of a similar methodology for investigation of other distal anxiety risk factors. Such a technique may ultimately lead to the identification of several distinct developmental pathways and circumscribed neural effects which predispose persons to develop clinical anxiety as adults. The identification of these pathways could then be used to refine existing theory, inform the development of specialized/targeted treatments, identify at-risk individuals, and modify existing treatments for distinct sub-groups of anxious individuals.

Tables

Table 1. Participant Demographics and Clinical Characteristics

Measure	Mean/Frequency	Standard Deviation
Age (years)	30.71	11.27
Years of Education	14.49	1.81
Gender	148 Female	--
	34 Male	
Ethnicity	101 Caucasian	
	13 African-American	
	16 Asian	
	9 Filipino	--
	14 Latino	
	3 Native American	
	26 Other	
Primary Diagnoses	70 Healthy Control	
	15 GAD	
	14 PD	
	35 IPV-PTSD+	--
	6 IPV-PTSD-	
	21 SAD	
	21 HTA	
CTQ Total Score	41.38	17.37
CTQ Emotional Abuse	9.50	4.97
CTQ Emotional Neglect	10.70	5.25
CTQ Physical Abuse	7.03	3.52
CTQ Physical Neglect	7.47	3.47
CTQ Sexual Abuse	6.63	4.04
BSI Total	14.36	13.41
BSI Anxiety	5.45	5.48
BSI Depression	5.49	5.38
Angry RT (ms)	1477.18	290.03
Fear RT (ms)	1632.48	353.13
Happy RT (ms)	1238.78	279.13
Shapes RT (ms)	1003.99	239.95
Angry % Incorrect	1.11	3.17
Fear % Incorrect	2.78	4.16
Happy % Incorrect	0.53	1.95
Shapes % Incorrect	2.40	3.92

Notes: BSI=Brief Symptom Inventory-18; CTQ=Childhood Trauma Questionnaire; GAD=generalized anxiety disorder; HTA=high trait-anxious; IPV-PTSD+=posttraumatic stress disorder due to intimate-partner violence; IPV-PTSD-=exposure to intimate-partner violence but no posttraumatic stress disorder; ms=milliseconds; PD=panic disorder; SAD=social anxiety disorder

Table 2. Task-Evoked Activation for Emotion Processing Targeted Towards Fear vs. Happy

Mask	H	Region	Vol. (µl)	X	Y	Z	Voxelwise Stats Mean (sd)	
							t	p
		Activation						
ROI	R	Insula (a)	5248	38	15	4	5.05 (1.84)	0.003 (0.008)
ROI	L	Insula (a)	4992	-37	15	4	4.72 (1.79)	0.004 (0.009)
WB	L/R	Fusiform Gyrus/Middle Occipital Gyrus/Lingual Gyrus/Inferior, Middle, & Superior Temporal Gyri/Posterior Cingulate/Precuneus/Supramaringal Gyrus/Angular Gyrus/Inferior & Superior Parietal Lobule	85376	7	-56	18	4.76 (1.19)	<0.001 (<0.001)
WB	R	Thalamus/Claustrum/Globus Pallidus/Putamen/Caudate/Insula (a)/Inferior, Middle, & Superior Frontal Gyri (dl)/Precentral Gyrus	64128	43	-2	28	4.99 (1.46)	<0.001 (<0.001)
WB	L	Claustrum/Globus Pallidus/Putamen/Caudate/Insula (a)/Inferior, Middle, & Superior Frontal Gyri (dl)/Precentral Gyrus	30208	-40	15	8	5.20 (1.50)	<0.001 (<0.001)
WB	L/R	Cingulate Gyrus/Medial & Superior Frontal Gyri (dm)	11264	1	19	42	5.00 (1.27)	<0.001 (<0.001)
WB	L/R	Lingual Gyrus/Cuneus/Posterior Cingulate	2176	1	-69	8	3.77 (0.36)	<0.001 (<0.001)
WB	L/R	Culmen	1344	-1	-50	-4	3.84 (0.39)	<0.001 (<0.001)
WB	L/R	Pyramis/Declive of Vermis	576	-2	-75	-21	3.78 (0.30)	<0.001 (<0.001)
		Deactivation						
ROI	L/R	Anterior Cingulate (pg)	1344	-1	39	9	-2.61 (0.43)	0.015 (0.012)
ROI	R	Anterior Cingulate (pg)	576	9	43	4	-2.90 (0.70)	0.013 (0.014)
ROI	L/R	Anterior Cingulate (sg)	384	-2	18	-4	-2.52 (0.21)	0.014 (0.006)
ROI	R	Insula (p)	320	45	-17	16	-2.16 (0.11)	0.033 (0.009)
WB	L	Middle Frontal Gyrus (dl)	1920	-22	23	39	-3.95 (0.44)	<0.001 (<0.001)
WB	L	Cingulate Gyrus	512	-6	-37	34	-3.81 (0.19)	<0.001 (<0.001)
WB	L	Medial Frontal Gyrus (am)	448	-1	54	7	-3.58 (0.33)	<0.001 (<0.001)
WB	L	Posterior Cingulate	448	-7	-52	20	-3.76 (0.31)	<0.001 (<0.001)
WB	L	Angular Gyrus	320	-44	-64	33	-3.98 (0.27)	<0.001 (<0.001)

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; a=anterior; am=anteromedial; dl=dorsolateral; 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.

Table 3. Task-Evoked Activation for Emotion Processing Targeted Towards Angry vs. Happy

Mask	H	Region	Vol. (μl)	X	Y	Z	Voxelwise Stats Mean (sd)	
							t	p
		Activation						
ROI	R	Insula (a)	3712	39	15	3	3.50 (0.98)	0.007 (0.010)
ROI	L	Insula (a)	3008	-35	17	4	3.21 (0.78)	0.008 (0.011)
ROI	L	Insula (a/m)	320	-45	7	10	2.40 (0.36)	0.023 (0.015)
ROI	R	Anterior Cingulate (d)	320	5	30	21	2.20 (0.19)	0.031 (0.013)
WB	R	Fusiform Gyrus/Middle Occipital Gyrus/Middle & Superior Temporal Gyri/Precuneus/Angular Gyrus/Supramarginal Gyrus/Inferior & Superior Parietal Lobule	27968	39	-54	20	4.16 (0.61)	<0.001 (<0.001)
WB	R	Inferior & Middle Frontal Gyri (dl)/Precentral Gyrus	15680	43	13	29	4.38 (0.81)	<0.001 (<0.001)
WB	L	Fusiform Gyrus/Middle Occipital Gyrus/Middle & Superior Temporal Gyri	9664	-45	-58	0	3.92 (0.50)	<0.001 (<0.001)
WB	L	Middle Temporal Gyrus/Precuneus/Angular Gyrus/Supramarginal Gyrus/Inferior & Superior Parietal Lobule	8704	-31	-51	39	4.16 (0.61)	<0.001 (<0.001)
WB	L	Inferior & Middle Frontal Gyri (dl)/Precentral Gyrus	7488	-40	4	33	4.36 (0.87)	<0.001 (<0.001)
WB	L/R	Cingulate Gyrus/Medial & Superior Frontal Gyri (dm)	4032	3	18	42	4.12 (0.61)	<0.001 (<0.001)
WB	R	Claustrum/Insula (a)/Inferior Frontal Gyrus	3264	40	17	3	4.17 (0.58)	<0.001 <0.001)
WB	L	Claustrum/Insula (a)	1984	-32	19	4	3.96 (0.38)	<0.001 (<0.001)
WB	L	Middle Frontal Gyrus (dl)	1728	-41	23	19	4.24 (0.49)	<0.001 (<0.001)
WB	R	Superior Frontal Gyrus (am)	448	29	56	3	3.57 (0.18)	0.001 (<0.001)
WB	L	Middle Occipital Gyrus	384	-35	-75	12	3.86 (0.33)	<0.001 (<0.001)
		Deactivation						
ROI	R	Anterior Cingulate (v)	320	5	38	-8	-2.23 (0.18)	0.029 (0.012)

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; a=anterior; am=anteromedial; d=dorsal; dl=dorsolateral; dm=dorsomedial; H=hemisphere; L=left; m=middle; R=right; ROI=region of interest masks; sd=standard deviation; Vol. = volume; WB=whole-brain masks.

Table 4. Task-Evoked Connectivity for Emotion Processing Targeted Towards Fearful vs. Happy

Seed	Mask	H	Region	Vol. (µl)	X	Y	Z	Voxelwise Stats Mean (sd)	
								t	p
			Positive Connectivity						
RAmyg	ROI	L/R	Anterior Cingulate (d)	960	5	38	15	2.46 (0.37)	0.020 (0.015)
RAmyg	ROI	R	Insula (p)	384	41	-17	10	2.37 (0.36)	0.024 (0.016)
RAmyg	WB	L	Superior Frontal Gyrus (dm)	448	-16	48	21	3.82 (0.32)	<0.001 (<0.001)
LAntIns	ROI	R	Insula (a)	1408	34	18	4	2.88 (0.71)	0.013 (0.014)
LAntIns	ROI	L	Amygdala	384	-20	-4	-12	2.22 (0.19)	0.030 (0.012)
LAntIns	WB	L	Lingual Gyrus/Middle Occipital Gyrus	3136	-34	-74	-1	3.91 (0.49)	<0.001 (<0.001)
LAntIns	WB	R	Inferior Frontal Gyrus (dl)/Precentral Gyrus	1856	39	5	29	3.81 (0.35)	<0.001 (<0.001)
LAntIns	WB	R	Inferior Occipital Gyrus	1600	38	-67	-4	3.75 (0.40)	<0.001 (<0.001)
LAntIns	WB	R	Middle Frontal Gyrus (dl)	512	46	23	21	4.05 (0.43)	<0.001 (<0.001)
LAntIns	WB	L	Fusiform Gyrus	448	-40	-46	-11	3.73 (0.38)	<0.001 (<0.001)
LAntIns	WB	L	Precentral Gyrus	384	-39	-2	31	3.49 (0.12)	0.001 (<0.001)
LAntIns	WB	R	Insula (a)	320	32	18	4	3.93 (0.37)	<0.001 (<0.001)
LPFC	ROI	R	Insula (a)	3136	35	16	5	3.49 (0.88)	0.005 (0.009)
LPFC	ROI	R	Amygdala	1344	24	-5	-11	3.85 (1.10)	0.006 (0.012)
LPFC	ROI	L	Insula (a)	1280	-32	17	7	2.96 (0.86)	0.014 (0.017)
LPFC	ROI	L	Amygdala	896	-23	-5	-10	3.42 (0.75)	0.004 (0.008)
LPFC	WB	L	Declive/Fusiform Gyrus/Inferior & Middle Occipital Gyri/Lingual Gyrus/Inferior & Middle Temporal Gyri/Cuneus	39808	-26	-71	-7	5.40 (1.61)	<0.001 (<0.001)
LPFC	WB	R	Declive/Fusiform Gyrus/Inferior & Middle Occipital Gyri/Lingual Gyrus/Inferior & Middle Temporal Gyri/Cuneus	38912	31	-70	-3	5.96 (1.93)	<0.001 (<0.001)
LPFC	WB	R	Insula (a)/Inferior & Middle Frontal Gyri (dl)/Precentral Gyrus	8640	39	12	22	4.69 (1.10)	<0.001 (<0.001)
LPFC	WB	R	Amygdala/Globus Pallidus	1984	22	-7	-8	4.36 (0.72)	<0.001 (<0.001)
LPFC	WB	R	Thalamus/Pulvinar	1792	23	-28	3	4.81 (1.20)	<0.001 (<0.001)
LPFC	WB	L/R	Thalamus	1408	2	-29	-1	3.92 (0.43)	<0.001 (<0.001)
LPFC	WB	L	Insula (a)/Inferior Frontal Gyrus (dl)	1344	-29	20	11	4.04 (0.59)	<0.001 (<0.001)
LPFC	WB	R	Superior Parietal Lobule	1344	27	-52	40	4.00 (0.35)	<0.001 (<0.001)
LPFC	WB	L	Amygdala/Globus Pallidus	1280	-22	-5	-7	4.04 (0.54)	<0.001 (<0.001)
LPFC	WB	L	Pyramis/Uvula	768	-20	-73	-33	3.81 (0.40)	<0.001 (<0.001)
LPFC	WB	L	Inferior Frontal Gyrus (dl)	704	-39	-1	32	4.21 (0.62)	<0.001 <0.001

Table 4. Task-Evoked Connectivity for Emotion Processing Targeted Towards Fearful vs. Happy, Continued

Seed	Mask	H	Region	Vol. (µl)	X	Y	Z	Voxelwise Stats Mean (sd)	
								t	p
			Positive Connectivity						
LPFC	WB	L	Thalamus	512	-15	-14	8	4.24 (0.54)	<0.001 (<0.001)
LPFC	WB	L	Precuneus/Inferior Parietal Lobule	512	-25	-53	40	4.24 (0.63)	<0.001 (<0.001)
LPFC	WB	L	Thalamus	448	-22	-27	1	4.74 (0.58)	<0.001 (<0.001)
LPFC	WB	L	Cerebellar Tonsil	320	-19	-43	-28	3.60 (0.20)	<0.001 (<0.001)
			Negative Connectivity						
LAntIns	ROI	R	Insula (m/p)	3840	40	-8	9	-2.61 (0.49)	0.017 (0.014)
LAntIns	ROI	L	Insula (m/p)	3392	-39	-1	5	-2.52 (0.38)	0.018 (0.014)
LAntIns	ROI	R	Insula (p)	896	39	-23	16	-2.71 (0.42)	0.012 (0.012)
LAntIns	ROI	L	Insula (p)	448	-33	-20	11	-2.59 (0.48)	0.017 (0.014)
LAntIns	ROI	L	Insula (p)	448	-50	-24	19	-2.54 (0.33)	0.016 (0.013)
LAntIns	WB	R	Cuneus	768	10	-75	29	-3.79 (0.30)	<0.001 (<0.001)
LAntIns	WB	R	Precentral Gyrus	384	49	-5	6	-3.69 (0.20)	<0.001 (<0.001)
LAntIns	WB	R	Inferior Parietal Lobule	384	50	-29	24	-3.74 (0.31)	<0.001 (<0.001)
LAntIns	WB	R	Cingulate Gyrus	320	10	-32	41	-4.01 (0.55)	<0.001 (<0.001)
LPFC	ROI	L/R	Anterior Cingulate (v/pg/d)	12864	1	37	8	-3.57 (0.98)	0.006 (0.011)
LPFC	ROI	R	Insula (m/p)	8768	41	-17	13	-3.27 (1.12)	0.008 (0.012)
LPFC	ROI	L	Insula (m/p)	7360	-41	-17	12	-2.91 (0.73)	0.012 (0.013)
LPFC	ROI	L	Insula (m)	448	-35	8	-4	-2.59 (0.74)	0.023 (0.016)
LPFC	WB	L/R	Cuneus/Precuneus/Posterior Cingulate/Cingulate Gyrus/Supramarginal Gyrus/Angular Gyrus/Inferior Parietal Lobule/Postcentral Gyrus/Precentral Gyrus/Paracentral Lobule/Middle, Medial, & Superior Frontal Gyri (dm/dl)	196352	-1	-16	37	-4.83 (1.11)	<0.001 (<0.001)
LPFC	WB	R	Precuneus/Angular Gyrus/Supramarginal Gyrus	5696	47	-57	31	-3.89 (0.44)	<0.001 (<0.001)
LPFC	WB	L	Middle Temporal Gyrus	1792	-51	-31	-4	-3.88 (0.35)	<0.001 (<0.001)
LPFC	WB	R	Superior Temporal Gyrus	1408	59	-25	0	-3.93 (0.51)	<0.001 (<0.001)
LPFC	WB	L	Middle Temporal Gyrus	1344	-57	-49	-2	-3.88 (0.46)	<0.001 (<0.001)
LPFC	WB	L	Precentral Gyrus	1024	-41	-13	32	-3.67 (0.30)	<0.001 (<0.001)
LPFC	WB	L	Parahippocampal Gyrus	960	-25	-39	-6	-4.18 (0.79)	<0.001 (<0.001)
LPFC	WB	L	Middle Temporal Gyrus	576	-58	-21	-7	-3.69 (0.35)	<0.001 (<0.001)

Table 4. Task-Evoked Connectivity for Emotion Processing Targeted Towards Fearful vs. Happy, Continued

Seed	Mask	H	Region	Vol. (µl)	X	Y	Z	Voxelwise Stats Mean (sd)	
								t	p
			Negative Connectivity						
LPFC	WB	L	Precentral Gyrus	512	-51	-6	25	-4.04 (0.50)	<0.001 (<0.001)
LPFC	WB	L	Parahippocampal Gyrus	384	-28	-24	-12	-3.65 (0.28)	<0.001 (<0.001)
LPFC	WB	L	Insula (p)	384	-35	-22	12	-4.24 (0.72)	<0.001 (<0.001)
LPFC	WB	R	Middle Temporal Gyrus	320	50	-24	-8	-3.85 (0.36)	<0.001 (<0.001)
LPFC	WB	R	Parahippocampal Gyrus	320	23	-38	-6	-3.80 (0.50)	<0.001 (<0.001)

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; a=anterior; am=anteromedial; dl=dorsolateral; dm=dorsomedial; H=hemisphere; L=left; LAntIns=left anterior insula seed region; LPFC=left dorsolateral prefrontal seed region; p=posterior; pg=perigenual; R=right; RAmyg=right amygdala seed region; ROI=region of interest masks; sd=standard deviation; sg=subgenual; Vol. = volume; WB=whole-brain masks.

Table 5. Task-Evoked Connectivity for Emotion Processing Targeted Towards Angry vs. Happy

Seed	Mask	H	Region	Vol. (µl)	X	Y	Z	t	Mean (sd) p
			Positive Connectivity						
RAntIns	ROI	L	Amygdala	512	-20	-5	-15	2.24 (0.23)	0.029 (0.014)
RAntIns	ROI	L	Insula (m)	512	-44	2	-3	2.39 (0.27)	0.026 (0.018)
RAntIns	ROI	R	Insula (a)	384	32	16	-1	2.51 (0.46)	0.020 (0.017)
RAntIns	ROI	R	Amygdala	320	23	-5	-11	2.70 (0.47)	0.013 (0.014)
RAntIns	ROI	L	Amygdala	320	-23	-8	-8	2.47 (0.53)	0.024 (0.019)
RPFC	ROI	R	Amygdala	1024	23	-5	-12	2.96 (0.75)	0.011 (0.010)
RPFC	ROI	L	Amygdala	256	-18	-5	-14	2.17 (0.07)	0.032 (0.006)
RPFC	WB	R	Fusiform Gyrus/Inferior & Middle Occipital Gyri/Lingual Gyrus/Inferior & Middle Temporal Gyri/Cuneus	21760	30	-76	-1	4.87 (1.20)	<0.001 (<0.001)
RPFC	WB	L	Fusiform Gyrus/Inferior & Middle Occipital Gyri/Lingual Gyrus/Inferior & Middle Temporal Gyri/Cuneus	12608	-29	-77	-2	4.55 (0.94)	<0.001 (<0.001)
RPFC	WB	L/R	Medial & Superior Frontal Gyri (dm)	1472	0	5	49	3.81 (0.44)	<0.001 (<0.001)
RPFC	WB	R	Precuneus/Superior Parietal Lobule	1408	26	-51	45	4.12 (0.54)	<0.001 (<0.001)
RPFC	WB	L	Precentral Gyrus	1216	-38	-9	44	3.98 (0.53)	<0.001 (<0.001)
RPFC	WB	R	Middle Frontal Gyrus (SMA)	768	34	-7	45	3.81 (0.25)	<0.001 (<0.001)
RPFC	WB	L	Precuneus/Superior Parietal Lobule	768	-25	-49	46	3.83 (0.36)	<0.001 (<0.001)
RPFC	WB	L	Superior Frontal Gyrus (dm)	704	-11	45	36	3.71 (0.27)	<0.001 (<0.001)
RPFC	WB	R	Amygdala/Globus Pallidus	576	19	-8	-8	3.90 (0.38)	<0.001 (<0.001)
RPFC	WB	L	Superior Frontal Gyrus (dm)	512	-7	30	46	3.66 (0.20)	<0.001 (<0.001)
DMedFG	ROI	R	Amygdala	1664	23	-5	-12	4.38 (1.24)	0.002 (0.006)
DMedFG	ROI	L	Amygdala	1408	-22	-5	-12	3.29 (0.89)	0.006 (0.008)
DMedFG	WB	R	Declive/Fusiform Gyrus/Inferior & Middle Occipital Gyri/Lingual Gyrus/Inferior & Middle Temporal Gyri/Cuneus	29504	31	-74	-1	6.04 (1.93)	<0.001 (<0.001)
DMedFG	WB	L	Declive/Fusiform Gyrus/Inferior & Middle Occipital Gyri/Lingual Gyrus/Inferior & Middle Temporal Gyri/Cuneus	21440	-30	-75	-2	5.40 (1.53)	<0.001 (<0.001)
DMedFG	WB	R	Middle Frontal Gyrus (dl)/Precentral Gyrus	4608	39	1	34	4.15 (0.61)	<0.001 (<0.001)
DMedFG	WB	R	Superior Parietal Lobule/Precuneus	4096	26	-54	43	4.74 (1.17)	<0.001 (<0.001)
DMedFG	WB	R	Amygdala/Globus Pallidus	2624	22	-5	-12	4.58 (0.99)	<0.001 (<0.001)
DMedFG	WB	L	Superior Parietal Lobule/Precuneus	1536	-25	-54	45	4.06 (0.60)	<0.001 (<0.001)

Table 5. Task-Evoked Connectivity for Emotion Processing Targeted Towards Angry vs. Happy, Continued

Seed	Mask	H	Region	Vol. (µl)	X	Y	Z	Voxelwise Stats Mean (sd)	
								t	p
			Positive Connectivity						
DMedFG	WB	R	Middle Frontal Gyrus (dl)	1408	46	22	25	4.10 (0.46)	<0.001 (<0.001)
DMedFG	WB	L	Amygdala/Globus Pallidus	1152	-23	-5	-12	3.93 (0.63)	<0.001 (<0.001)
DMedFG	WB	L	Middle Frontal Gyrus (SMA)	832	-31	-7	43	3.84 (0.27)	<0.001 (<0.001)
DMedFG	WB	R	Thalamus/Pulvinar	512	22	-30	2	3.86 (0.71)	<0.001 (<0.001)
DMedFG	WB	R	Precuneus	448	28	-65	24	3.91 (0.5)	<0.001 (<0.001)
			Negative Connectivity						
RAntIns	WB	L	Precentral and Postcentral Gyri	2432	-33	-23	54	-3.74 (0.34)	<0.001 (<0.001)
RAntIns	WB	R	Precuneus	704	15	-53	55	-3.82 (0.41)	<0.001 (<0.001)
RAntIns	WB	L	Middle Frontal Gyrus (SMA)	512	-33	-4	50	-3.73 (0.35)	<0.001 (<0.001)
RAntIns	WB	L	Precuneus	512	-16	-57	54	-3.60 (0.15)	<0.001 (<0.001)
RAntIns	WB	L	Inferior Parietal Lobule	384	-39	-56	43	-3.44 (0.09)	0.001 (<0.001)
RAntIns	WB	R	Superior Frontal Gyrus (SMA)	320	9	-6	63	-3.97 (0.36)	<0.001 (<0.001)
RPFC	ROI	L	Insula (m/p)	8256	-38	-4	8	-2.68 (0.51)	0.015 (0.013)
RPFC	ROI	R	Insula (m/p)	5376	40	-11	7	-2.93 (0.68)	0.011 (0.013)
RPFC	ROI	R	Insula (a)	2560	36	15	5	-2.69 (0.47)	0.014 (0.013)
RPFC	ROI	R	Anterior Cingulate (pg)	576	10	41	2	-2.43 (0.24)	0.019 (0.011)
RPFC	ROI	R	Anterior Cingulate (v)	320	16	44	-6	-2.77 (0.52)	0.011 (0.011)
RPFC	WB	L/R	Cingulate Gyrus	4544	1	-33	28	-4.33 (0.77)	<0.001 (<0.001)
RPFC	WB	L	Culmen/Parahippocampal Gyrus	3200	-23	-39	-8	-4.31 (0.81)	<0.001 (<0.001)
RPFC	WB	R	Posterior Cingulate/Precuneus	2624	14	-59	27	-4.24 (0.66)	<0.001 (<0.001)
RPFC	WB	L	Posterior Cingulate/Precuneus	2560	-12	-61	28	-4.11 (0.60)	<0.001 (<0.001)
RPFC	WB	L	Middle Temporal Gyrus	2368	-49	-51	-2	-3.99 (0.47)	<0.001 (<0.001)
RPFC	WB	R	Parahippocampal Gyrus	2112	22	-43	-5	-4.25 (0.60)	<0.001 (<0.001)
RPFC	WB	R	Claustrum/Insula (p)/Putamen	1920	37	-12	4	-4.04 (0.62)	<0.001 (<0.001)
RPFC	WB	R	Middle Temporal Gyrus	1664	53	-49	-2	-4.20 (0.52)	<0.001 (<0.001)
RPFC	WB	R	Superior Temporal Gyrus	1216	50	-20	7	-3.75 (0.37)	<0.001 (<0.001)
RPFC	WB	R	Precuneus	1152	36	-67	35	-4.12 (0.70)	<0.001 (<0.001)
RPFC	WB	R	Thalamus	1024	10	-26	10	-4.12 (0.76)	<0.001 (<0.001)
RPFC	WB	L	Claustrum/Insula (p)	768	-36	-11	3	-3.70 (0.28)	<0.001 (<0.001)

Table 5. Task-Evoked Connectivity for Emotion Processing Targeted Towards Angry vs. Happy, Continued

Seed	Mask	H	Region	Vol. (µl)	X	Y	Z	Voxelwise Stats Mean (sd)	
								t	p
			Negative Connectivity						
RPFC	WB	R	Lentiform Nucleus/Putamen	512	16	10	-1	-3.77 (0.22)	<0.001 (<0.001)
RPFC	WB	R	Posterior Cingulate	512	6	-46	13	-3.84 (0.41)	<0.001 (<0.001)
RPFC	WB	R	Supramarginal Gyrus	448	46	-45	31	-4.53 (1.22)	<0.001 (<0.001)
RPFC	WB	R	Cuneus	320	3	-76	22	-4.07 (0.64)	<0.001 (<0.001)
DMedFG	ROI	R	Insula (a/m/p)	13824	40	-5	8	-3.30 (0.89)	0.008 (0.013)
DMedFG	ROI	L	Insula (a/m/p)	12416	-39	-3	7	-3.00 (0.73)	0.011 (0.013)
DMedFG	ROI	L/R	Anterior Cingulate (pg/d)	7424	1	38	7	-2.70 (0.86)	0.013 (0.013)
DMedFG	WB	L/R	Cuneus/Precuneus/Posterior Cingulate/Cingulate Gyrus	29248	0	-48	29	-4.59 (0.90)	<0.001 (<0.001)
DMedFG	WB	R	Claustrum/Insula/Putamen/Precentral Gyrus/Superior Temporal Gyrus	13888	44	-11	8	-4.11 (0.69)	<0.001 (<0.001)
DMedFG	WB	L	Culmen/Parahippocampal Gyrus	5056	-20	-43	-6	-4.50 (0.92)	<0.001 (<0.001)
DMedFG	WB	L	Middle Temporal Gyrus	3200	-51	-50	-1	-4.03 (0.53)	<0.001 (<0.001)
DMedFG	WB	R	Culmen/Parahippocampal Gyrus	2752	21	-42	-5	-4.40 (0.83)	<0.001 (<0.001)
DMedFG	WB	L	Insula (a)	2752	-33	14	1	-3.93 (0.49)	<0.001 (<0.001)
DMedFG	WB	L/R	Anterior Cingulate (d)/Cingulate Gyrus	2240	2	29	26	-3.99 (0.49)	<0.001 (<0.001)
DMedFG	WB	L	Inferior Parietal Lobule/Supramarginal Gyrus	1984	-52	-38	32	-3.84 (0.48)	<0.001 (<0.001)
DMedFG	WB	R	Supramarginal Gyrus	1728	50	-47	34	-4.31 (0.68)	<0.001 (<0.001)
DMedFG	WB	L	Thalamus/Pulvinar	1664	-7	-27	9	-3.95 (0.70)	<0.001 (<0.001)
DMedFG	WB	L	Middle & Superior Frontal Gyri	1280	-29	47	13	-4.09 (0.63)	<0.001 (<0.001)
DMedFG	WB	L	Claustrum/Insula (p)	1216	-36	-15	4	-4.09 (0.53)	<0.001 (<0.001)
DMedFG	WB	L	Postcentral Gyrus	1216	-55	-25	15	-3.83 (0.32)	<0.001 (<0.001)
DMedFG	WB	R	Thalamus/Pulvinar	1088	10	-25	11	-4.38 (0.94)	<0.001 (<0.001)
DMedFG	WB	R	Middle Temporal Gyrus	832	54	-52	-2	-3.91 (0.29)	<0.001 (<0.001)
DMedFG	WB	L	Angular Gyrus	704	-35	-72	32	-3.83 (0.42)	<0.001 (<0.001)
DMedFG	WB	L	Middle Frontal Gyrus (dl)	576	-30	31	32	-3.84 (0.53)	<0.001 (<0.001)
DMedFG	WB	R	Anterior Cingulate (pg)	512	5	48	3	-3.72 (0.32)	<0.001 (<0.001)
DMedFG	WB	L	Superior Temporal Gyrus	448	-46	-6	0	-3.67 (0.30)	<0.001 (<0.001)
DMedFG	WB	R	Caudate Head	384	13	12	0	-3.79 (0.38)	<0.001 (<0.001)
DMedFG	WB	R	Angular Gyrus	384	36	-70	32	-3.95 (0.44)	<0.001 (<0.001)

Table 5. Task-Evoked Connectivity for Emotion Processing Targeted Towards Angry vs. Happy, Continued

							Voxelwise Stats Mean (sd)	
Seed	Mask	H	Region	Vol. (µl)	X	Y	Z	t	p
			Negative Connectivity						
DMedFG	WB	L	Anterior Cingulate (pg)	320	-8	41	2	-3.89 (0.56)	<0.001 (<0.001)

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; a=anterior; d=dorsal; dl=dorsolateral; dm=dorsomedial; DMedFG=dorsal medial frontal gyri seed region; H=hemisphere; L=left; m=middle; p=posterior; pg=perigenual; R=right; RAntIns=right anterior insula seed region; RPFC=right dorsolateral prefrontal seed region; ROI=region of interest masks; sd=standard deviation; sg=subgenual; SMA=supplementary motor area; Vol. = volume; WB=whole-brain masks.

Table 6. Activation Mediating the Relationship Between Childhood Emotional Maltreatment and Adulthood Anxiety

CTQ Scale	Mask	H	Region	Vol. (µl)	X	Y	Z	Voxelwise Stats Mean (sd)			With GM & Depression Covariates
								Indirect Effect	Lower CI	Upper CI	Extracted Indirect Effect (CI)
						Fear vs. Happy					
EA	ROI	L	Insula (p)	576	-36	-21	13	0.023 (0.006)	0.003 (0.004)	0.075 (0.018)	0.024 (0.003, 0.069)
EA	WB	L	Middle & Superior Temporal Gyri	1088	-57	10	-11	0.021 (0.004)	0.003 (0.003)	0.063 (0.019)	0.012 (-0.002, 0.039)
EN	ROI	--	No sig. effects	--	--	--	--	--	--	--	--
EN	WB	R	Fusiform Gyrus	1280	41	-40	-17	0.022 (0.006)	0.003 (0.003)	0.071 (0.021)	0.027 (0.010, 0.064)
						Angry vs. Happy					
EA	ROI	--	No sig. effects	--	--	--	--	--	--	--	--
EA	WB	R	Inferior & Middle Frontal Gyri (dl)	1088	40	34	15	0.029 (0.010)	0.005 (0.006)	0.083 (0.018)	0.056 (0.022, 0.106)
EN	ROI	L	Amygdala	256	-19	-13	-9	0.031 (0.013)	0.008 (0.009)	0.073 (0.021)	0.023 (0.001, 0.057)
EN	WB	R	Inferior & Middle Frontal Gyri (dl)	768	39	31	15	0.028 (0.011)	0.006 (0.006)	0.077 (0.021)	0.037 (0.011, 0.080)

Notes: X, Y, and Z are the Talairach coordinates for the cluster center of mass; Voxelwise stats report mean statistical value with standard deviations in parentheses; Column with GM & depression covariates indicates indirect mediation effect for extracted cluster values after controlling for cluster gray matter volume and BSI depression subscale score, with lower and upper bounds of 95% confidence interval 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; EA=emotional abuse; EN=emotional neglect; GM=gray matter; H=hemisphere; L=left; p=posterior; R=right; ROI=region of interest masks; sd=standard deviation; sig.=significant; Vol. = volume; WB=whole-brain masks.

Table 7. Connectivity Mediating the Relationship Between Childhood Emotional Maltreatment and Adulthood Anxiety for Processing Targeted Towards Fearful vs. Happy

CTQ Scale	Mask	H	Region	Vol. (µl)	X	Y	Z	Voxelwise Stats Mean (sd)			With GM & Depression Covariates
								Indirect Effect	Lower CI	Upper CI	Extracted Indirect Effect (CI)
			Right Amygdala Seed Region								
EA	ROI	--	No sig. effects	--	--	--	--	--	--	--	--
EA	WB	--	No sig. effects	--	--	--	--	--	--	--	--
EN	ROI	--	No sig. effects	--	--	--	--	--	--	--	--
EN	WB	--	No sig. effects	--	--	--	--	--	--	--	--
			Left Anterior Insula Seed Region								
EA	ROI	--	No sig. effects	--	--	--	--	--	--	--	--
EA	WB	--	No sig. effects	--	--	--	--	--	--	--	--
EN	ROI	--	No sig. effects	--	--	--	--	--	--	--	--
EN	WB	--	No sig. effects	--	--	--	--	--	--	--	--
			Left Dorsolateral Prefrontal Seed Region								
EA	ROI	--	No sig. effects	--	--	--	--	--	--	--	--
EA	WB	L	Precentral & Postcentral Gyri	768	-37	-16	42	0.031 (0.010)	0.005 (0.003)	0.094 (0.025)	0.037 (0.003, 0.089)
EN	ROI	--	No sig. effects	--	--	--	--	--	--	--	--
EN	WB	L	Precentral & Postcentral Gyri	1024	-37	-17	41	0.039 (0.009)	0.005 (0.005)	0.096 (0.019)	0.059 (0.019, 0.115)

Notes: X, Y, and Z are the Talairach coordinates for the cluster center of mass; Voxelwise stats report mean statistical value with standard deviations in parentheses; Column with GM & depression covariates indicates indirect mediation effect for extracted cluster values after controlling for cluster gray matter volume and BSI depression subscale score, with lower and upper bounds of 95% confidence interval in parentheses; EA=emotional abuse; EN=emotional neglect; GM=gray matter; H=hemisphere; L=left; R=right; ROI=region of interest masks; sd=standard deviation; sig.=significant; Vol. = volume; WB=whole-brain masks.

Table 8. Connectivity Mediating the Relationship Between Childhood Emotional Maltreatment and Adulthood Anxiety for Processing Targeted Towards Angry vs. Happy

CTQ Scale	Mask	H	Region	Vol. (µl)	X	Y	Z	Voxelwise Stats Mean (sd)			With GM & Depression Covariates
								Indirect Effect	Lower CI	Upper CI	Extracted Indirect Effect (CI)
			Right Anterior Insula Seed Region								
EA	ROI	--	No sig. effects	--	--	--	--	--	--	--	--
EA	WB	--	No sig. effects	--	--	--	--	--	--	--	--
EN	ROI	--	No sig. effects	--	--	--	--	--	--	--	--
EN	WB	L/R	Posterior Cingulate	1216	2	-52	25	0.024 (0.006)	0.003 (0.004)	0.072 (0.015)	0.024 (0.001, 0.065)
EN	WB	L	Medial & Superior Frontal Gyri (dm)	832	-12	53	15	0.024 (0.005)	0.002 (0.002)	0.076 (0.011)	0.029 (0.008, 0.068)
			Right Dorsolateral Prefrontal Seed Region								
EA	ROI	--	No sig. effects	--	--	--	--	--	--	--	--
EA	WB	L	Precentral & Postcentral Gyri	1088	-27	-23	56	0.028 (0.007)	0.002 (0.002)	0.080 (0.012)	0.022 (0.001, 0.066)
EN	ROI	--	No sig. effects	--	--	--	--	--	--	--	--
EN	WB	L/R	Posterior Cingulate	704	1	-45	22	0.028 (0.004)	0.005 (0.003)	0.079 (0.014)	0.022 (0.004, 0.057)
EN	WB	R	Precentral & Postcentral Gyri	704	25	-22	56	0.033 (0.009)	0.005 (0.005)	0.090 (0.016)	0.026 (0.005, 0.069)
			Dorsal Medial Frontal Gyri Seed Region								
EA	ROI	--	No sig. effects	--	--	--	--	--	--	--	--
EA	WB	L	No sig. effects	--	--	--	--	--	--	--	--
EN	ROI	--	No sig. effects	--	--	--	--	--	--	--	--
EN	WB	L/R	Cingulate Gyrus/Precuneus	704	1	-44	46	0.027 (0.006)	0.002 (0.002)	0.077 (0.011)	0.026 (0.002, 0.068)

Notes: X, Y, and Z are the Talairach coordinates for the cluster center of mass; Voxelwise stats report mean statistical value with standard deviations in parentheses; Column with GM & depression covariates indicates indirect mediation effect for extracted cluster values after controlling for cluster gray matter volume and BSI depression subscale score, with lower and upper bounds of 95% confidence interval 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; dm=dorsomedial; EA=emotional abuse; EN=emotional neglect; GM=gray matter; H=hemisphere; L=left; R=right; ROI=region of interest masks; sd=standard deviation; sig.=significant; Vol. = volume; WB=whole-brain masks.

Table 9. Gray Matter Volumes Mediating the Relationship Between Childhood Emotional Maltreatment and Adulthood Anxiety

CTQ Scale	Mask	H	Region	Vol. (µl)	X	Y	Z	Voxelwise Stats Mean (sd)			With Depression Covariates
								Indirect Effect	Lower CI	Upper CI	Extracted Indirect Effect (CI)
EA	ROI	--	No sig. effects	--	--	--	--	--	--	--	--
EA	WB	--	No sig. effects	--	--	--	--	--	--	--	--
EN	ROI	--	No sig. effects	--	--	--	--	--	--	--	--
EN	WB	L	Precentral Gyrus	888	-47	-4	40	0.026 (0.006)	0.003 (0.003)	0.075 (0.014)	0.013 (-0.008, 0.045)
EN	WB	R	Inferior & Middle Frontal Gyri (dl)	824	42	38	12	0.022 (0.004)	0.002 (0.002)	0.067 (0.011)	0.034 (0.007, 0.080)

Notes: X, Y, and Z are the Talairach coordinates for the cluster center of mass; Voxelwise stats report mean statistical value with standard deviations in parentheses; Column with depression covariates indicates indirect mediation effect for extracted cluster values after controlling for BSI depression subscale score, with lower and upper bounds of 95% confidence interval 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; EA=emotional abuse; EN=emotional neglect; H=hemisphere; L=left; R=right; ROI=region of interest masks; sd=standard deviation; sig.=significant; Vol. = volume; WB=whole-brain masks.
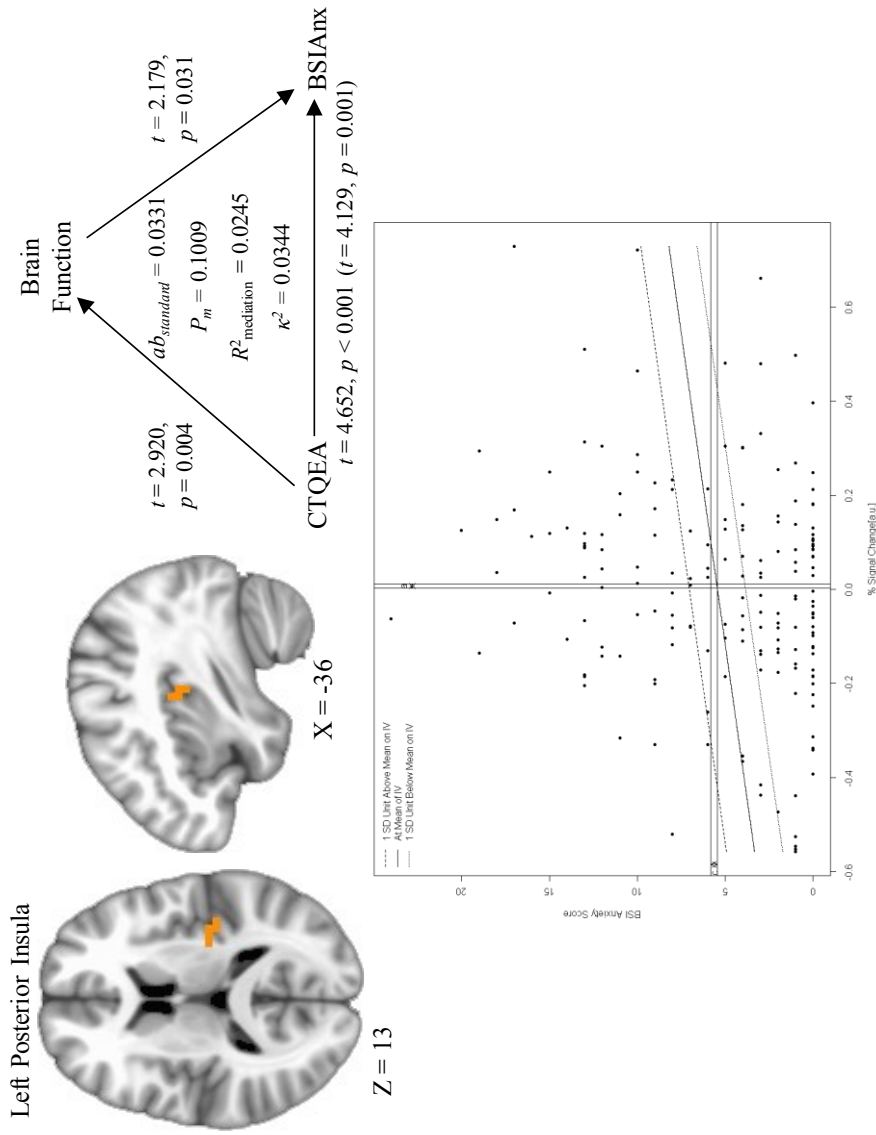
Figures

Figure 1. Left posterior insula activation to fear vs. happy mediating relationship between emotional abuse and anxiety. Horizontal lines on scatter plot indicate predicted level of brain activation at mean level of emotional abuse and increase in predicted brain activation per unit increase of emotional abuse. Vertical lines on scatter plot indicate predicted level of anxiety symptoms at mean level of emotional abuse and increase in predicted anxiety symptoms per unit increase of emotional abuse. Diagonal lines on scatter plot indicate relationship between brain activation and anxiety symptoms at mean level of emotional abuse and at 1 standard deviation above and below the mean. $ab_{standard}$ = standardized indirect mediation effect; BSIAnx = anxiety subscale of the Brief Symptom Inventory-18; CTQEA = Childhood Trauma Questionnaire emotional abuse subscale; κ^2 = kappa squared statistic, or the proportion of the maximum possible indirect effect that could have occurred, had the constituent effects been as large as the design and data permitted; P_m = mediation ratio, i.e. proportion of total effect mediated; $R^2_{mediation}$ = variance in anxiety symptoms that is common to both emotional abuse and brain activation but can be attributed to neither alone.
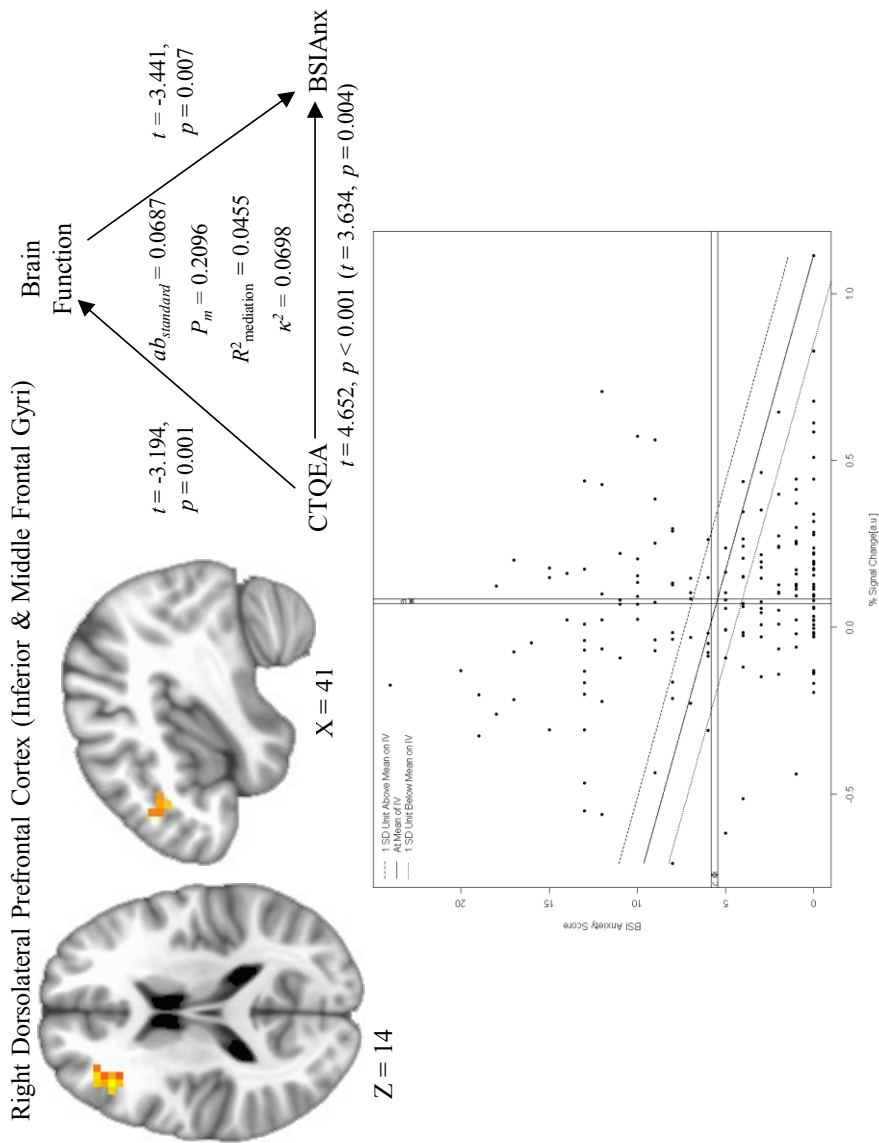
Figure 2. Right dorsolateral prefrontal activation to angry *vs.* happy mediating relationship between emotional abuse and anxiety. Horizontal lines on scatter plot indicate predicted level of brain activation at mean level of emotional abuse and increase in predicted brain activation per unit increase of emotional abuse. Vertical lines on scatter plot indicate predicted level of anxiety symptoms at mean level of emotional abuse and increase in predicted anxiety symptoms per unit increase of emotional abuse. Diagonal lines on scatter plot indicate relationship between brain activation and anxiety symptoms at mean level of emotional abuse and at 1 standard deviation above and below the mean. $ab_{standard}$ = standardized indirect mediation effect; BSIAnx = anxiety subscale of the Brief Symptom Inventory-18; CTQEA = Childhood Trauma Questionnaire emotional abuse subscale; κ^2 = kappa squared statistic, or the proportion of the maximum possible indirect effect that could have occurred, had the constituent effects been as large as the design and data permitted; P_m = mediation ratio, i.e. proportion of total effect mediated; $R^2_{mediation}$ = variance in anxiety symptoms that is common to both emotional abuse and brain activation but can be attributed to neither alone.
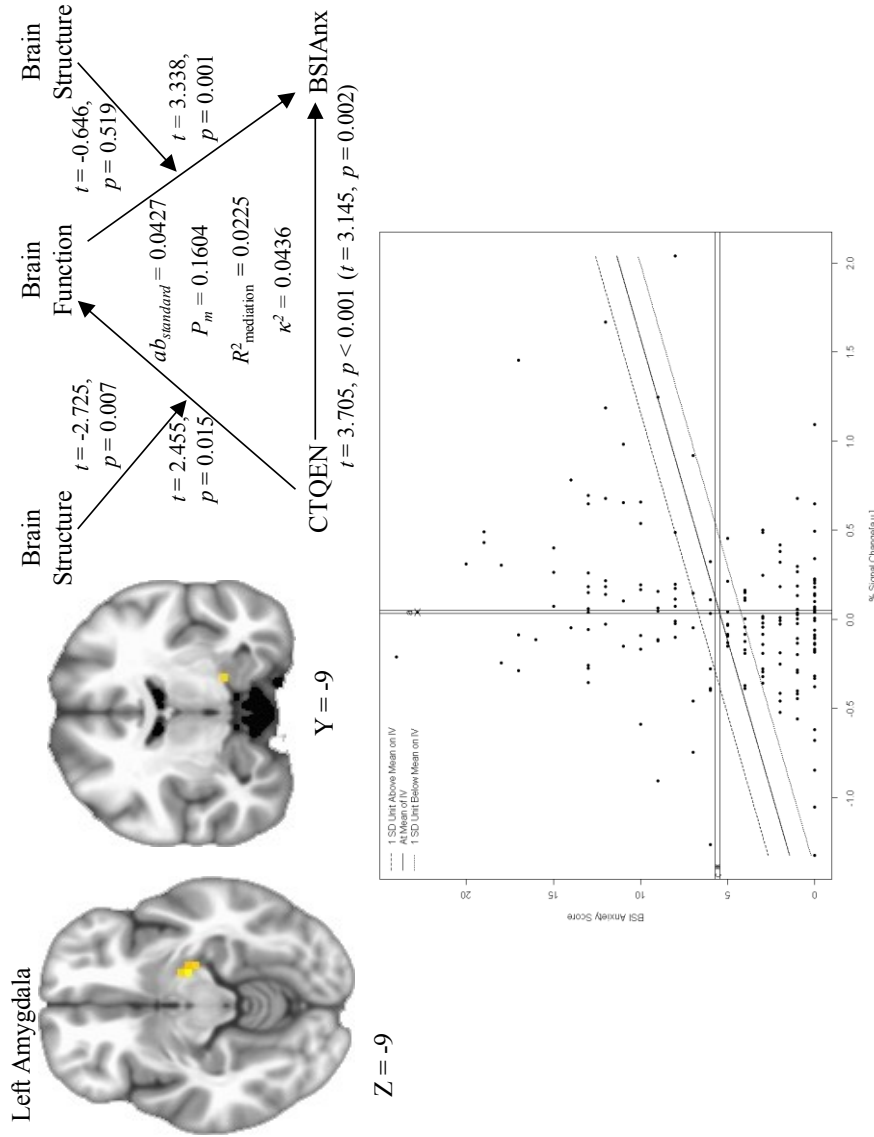
Figure 3. Left amygdala activation to angry vs. happy mediating relationship between emotional neglect and anxiety and moderation by gray matter volume.

Horizontal lines on scatter plot indicate predicted level of brain activation at mean level of emotional neglect and increase in predicted brain activation per unit increase of emotional neglect. Vertical lines on scatter plot indicate predicted level of anxiety symptoms at mean level of emotional neglect and increase in predicted anxiety symptoms per unit increase of emotional neglect. Diagonal lines on scatter plot indicate relationship between brain activation and anxiety symptoms at mean level of emotional neglect and at 1 standard deviation above and below the mean. $ab_{standard}$ = standardized indirect mediation effect; BSIAnx = anxiety subscale of the Brief Symptom Inventory-18; CTQEN = Childhood Trauma Questionnaire emotional neglect subscale; κ^2 = kappa squared statistic, or the proportion of the maximum possible indirect effect that could have occurred, had the constituent effects been as large as the design and data permitted; P_m = mediation ratio, i.e. proportion of total effect mediated; $R^2_{mediation}$ = variance in anxiety symptoms that is common to both emotional neglect and brain activation but can be attributed to neither alone.
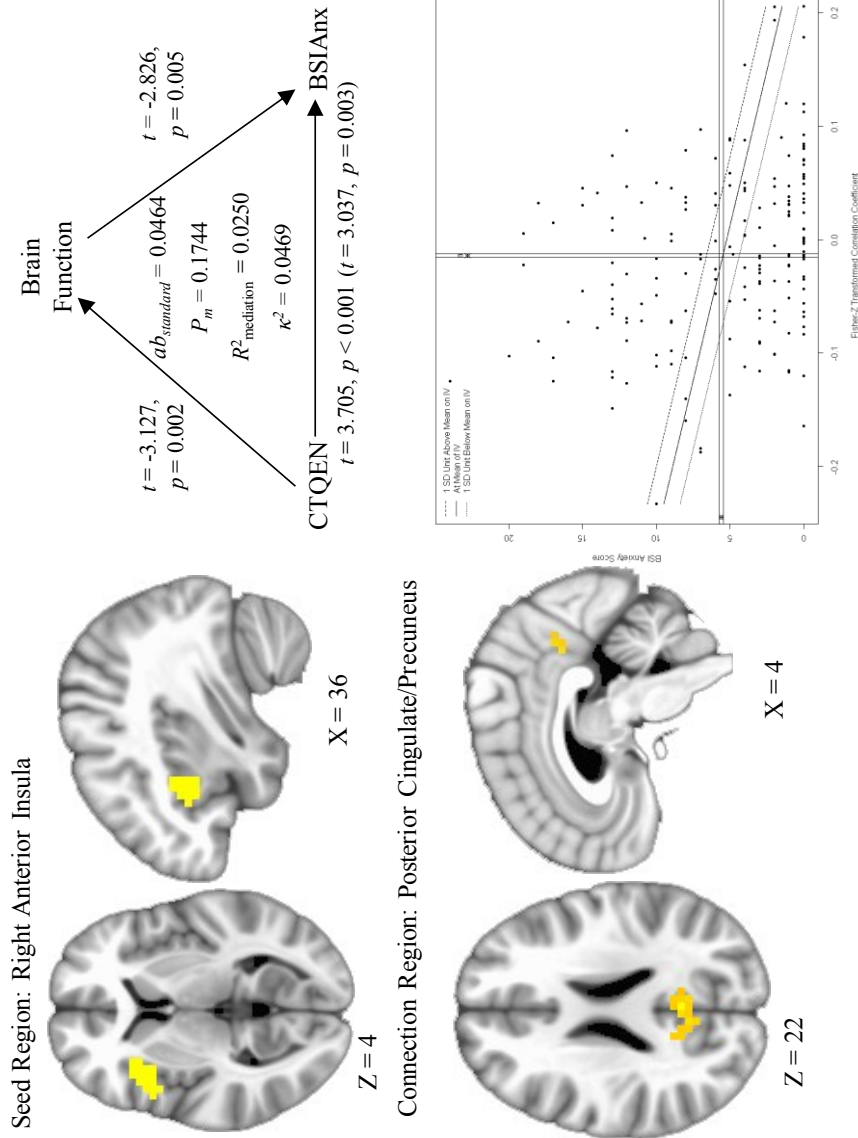
Seed Region: Right Anterior Insula

X = 36

Z = 4

Connection Region: Posterior Cingulate/Precuneus

X = 4

Z = 22

Brain
Function

BSIAnx

$t = -2.826$,
$p = 0.005$

$t = -3.127$,
$p = 0.002$

$ab_{standard} = 0.0464$
$P_m = 0.1744$
$R^2_{mediation} = 0.0250$
$\kappa^2 = 0.0469$

CTQEN
$t = 3.705, p < 0.001$ ($t = 3.037, p = 0.003$)

1 SD Unit Above Mean on IV
At Mean of IV
1 SD Unit Below Mean on IV

BSI Anxiety Score

Fisher-Z Transformed Correlation Coefficient

Figure 4. Anterior insula-posterior medial connectivity to angry vs. happy mediating relationship between emotional neglect and anxiety. Horizontal lines on scatter plot indicate predicted level of brain connectivity at mean level of emotional neglect and increase in predicted brain connectivity per unit increase of emotional neglect. Vertical lines on scatter plot indicate predicted level of anxiety symptoms at mean level of emotional neglect and increase in predicted anxiety symptoms per unit increase of emotional neglect. Diagonal lines on scatter plot indicate relationship between brain connectivity and anxiety symptoms at mean level of emotional neglect and at 1 standard deviation above and below the mean. $ab_{standard}$= standardized indirect mediation effect; BSIAnx = anxiety subscale of the Brief Symptom Inventory-18; CTQEN = Childhood Trauma Questionnaire emotional neglect subscale; κ^2= kappa squared statistic, or the proportion of the maximum possible indirect effect that could have occurred, had the constituent effects been as large as the design and data permitted; P_m = mediation ratio, i.e. proportion of total effect mediated; $R^2_{mediation}$ = variance in anxiety symptoms that is common to both emotional neglect and brain connectivity but can be attributed to neither alone.
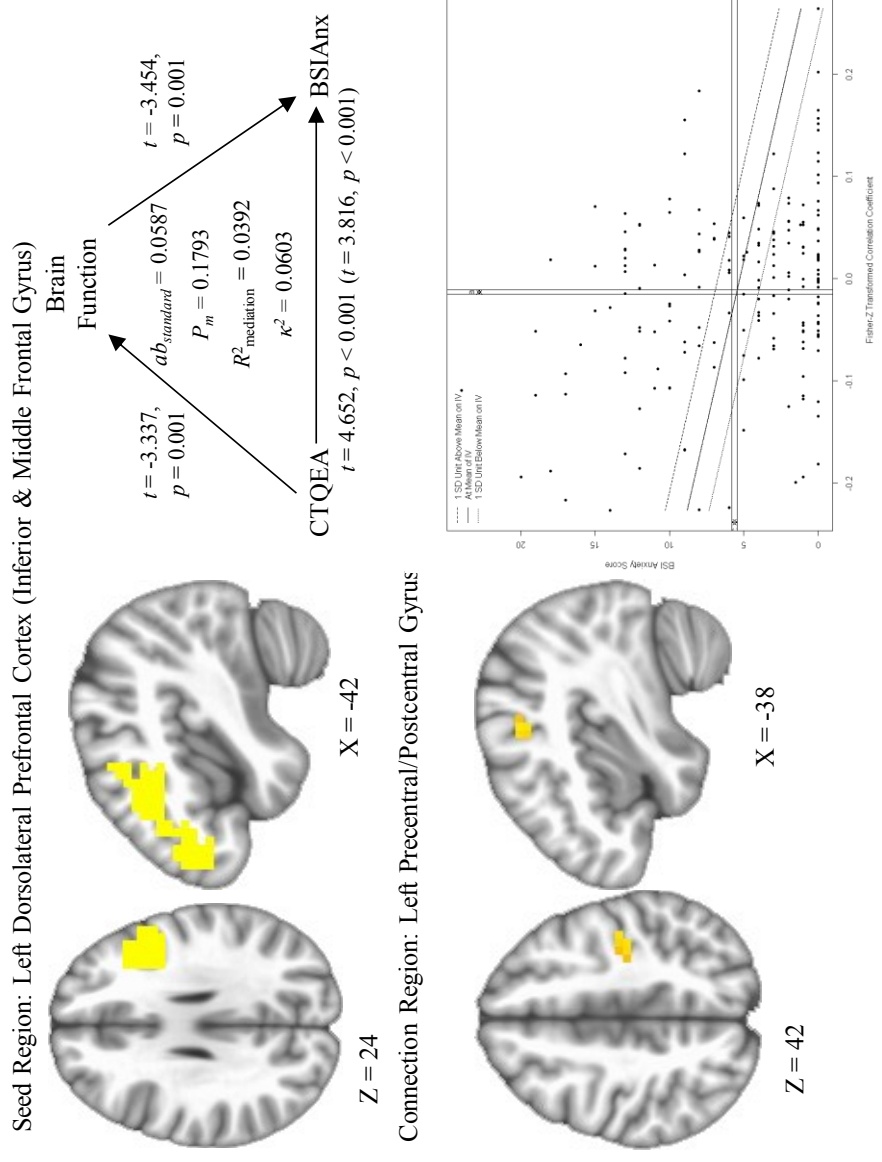
Figure 5. Dorsolateral prefrontal-pre/postcentral connectivity to fear vs. happy mediating relationship between emotional abuse and anxiety. Horizontal lines on scatter plot indicate predicted level of brain connectivity at mean level of emotional abuse and increase in predicted brain connectivity per unit increase of emotional abuse. Vertical lines on scatter plot indicate predicted level of anxiety symptoms at mean level of emotional abuse and increase in predicted anxiety symptoms per unit increase of emotional abuse and at 1 standard deviation above and below the mean. $ab_{standard}$ = standardized indirect mediation effect; BSIAnx = anxiety subscale of the Brief Symptom Inventory-18; CTQEA = Childhood Trauma Questionnaire emotional abuse subscale; κ^2 = kappa squared statistic, or the proportion of the maximum possible indirect effect that could have occurred, had the constituent effects been as large as the design and data permitted; P_m = mediation ratio, i.e. proportion of total effect mediated; $R^2_{mediation}$ = variance in anxiety symptoms that is common to both emotional abuse and brain connectivity but can be attributed to neither alone.
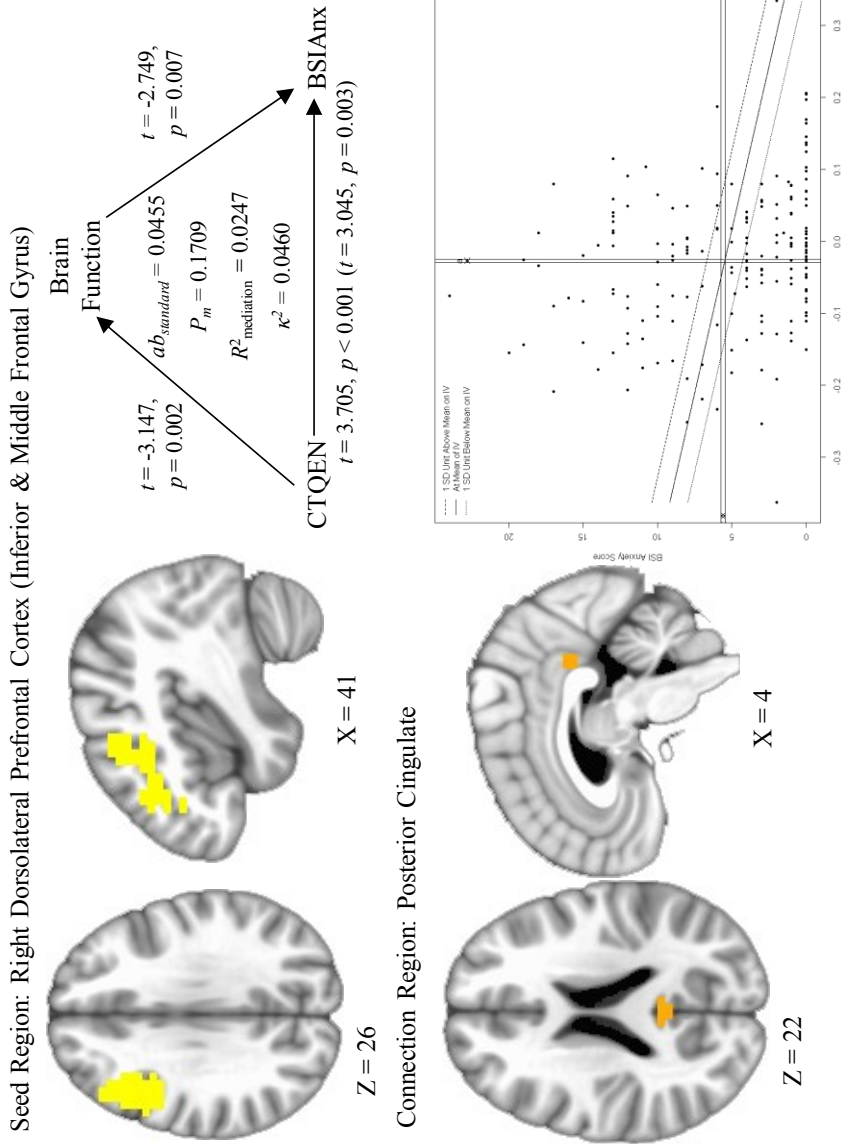
Seed Region: Right Dorsolateral Prefrontal Cortex (Inferior & Middle Frontal Gyrus)

X = 41

Z = 26

Connection Region: Posterior Cingulate

X = 4

Z = 22

Brain Function

CTQEN

BSIAnx

$t = -3.147$, $p = 0.002$

$t = -2.749$, $p = 0.007$

$ab_{standard} = 0.0455$
$P_m = 0.1709$
$R^2_{mediation} = 0.0247$
$\kappa^2 = 0.0460$

$t = 3.705$, $p < 0.001$ ($t = 3.045$, $p = 0.003$)

Figure 6. Dorsolateral prefrontal-posterior medial connectivity to angry vs. happy mediating relationship between emotional neglect and anxiety.

Horizontal lines on scatter plot indicate predicted level of brain connectivity at mean level of emotional neglect and increase in predicted brain connectivity per unit increase of emotional neglect. Vertical lines on scatter plot indicate predicted level of anxiety symptoms at mean level of emotional neglect and increase in predicted anxiety symptoms per unit increase of emotional neglect. Diagonal lines on scatter plot indicate relationship between brain connectivity and anxiety symptoms at mean level of emotional neglect and at 1 standard deviation above and below the mean. $ab_{standard}$ = standardized indirect mediation effect; BSIAnx = anxiety subscale of the Brief Symptom Inventory-18; CTQEN = Childhood Trauma Questionnaire emotional neglect subscale; κ^2 = kappa squared statistic, or the proportion of the maximum possible indirect effect that could have occurred, had the constituent effects been as large as the design and data permitted; P_m = mediation ratio, i.e. proportion of total effect mediated; $R^2_{mediation}$ = variance in anxiety symptoms that is common to both emotional neglect and brain connectivity but can be attributed to neither alone.

Right Dorsolateral Prefrontal Cortex (Inferior & Middle Frontal Gyri)

X = 41

Z = 11

Brain
Structure

BSIAnx

$t = -2.598,$
$p = 0.010$

$ab_{standard} = 0.0383$
$P_m = 0.1455$
$R^2_{mediation} = 0.0205$
$\kappa^2 = 0.0390$

$t = -2.784,$
$p = 0.006$
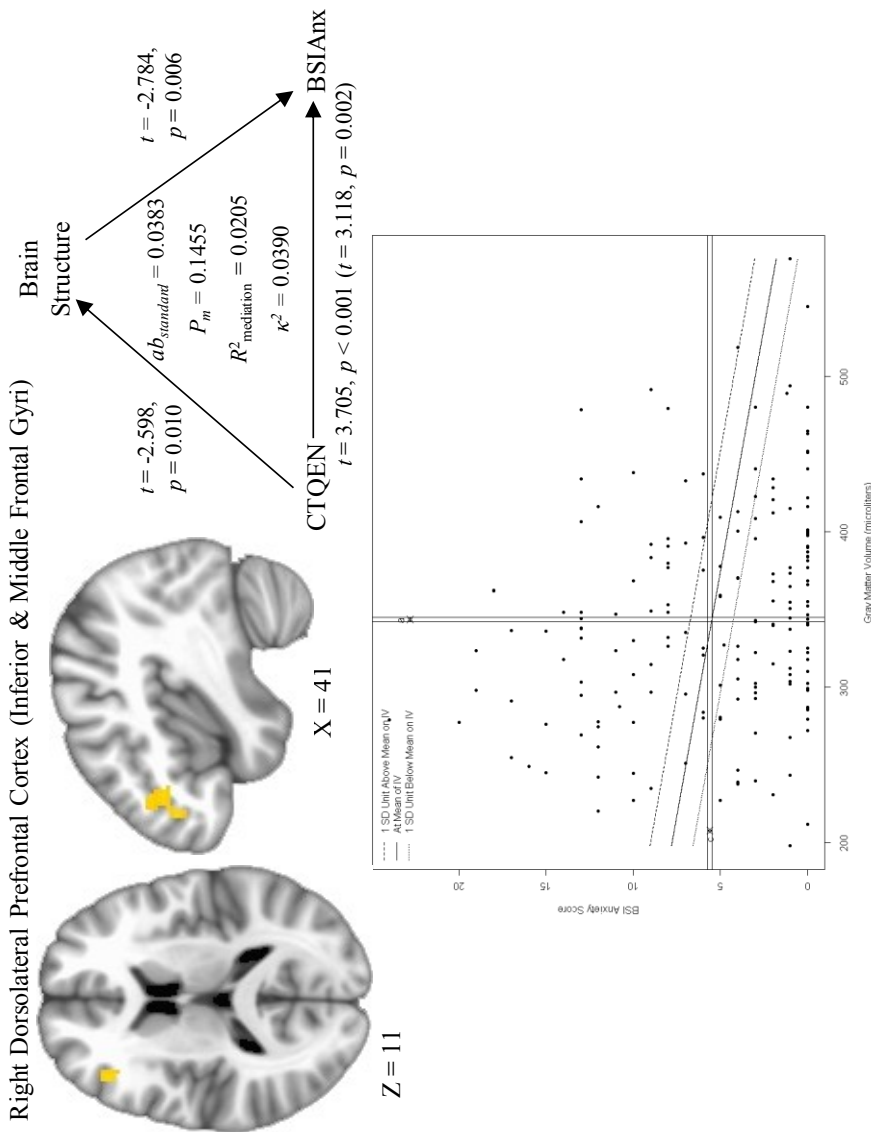
CTQEN
$t = 3.705, p < 0.001$ ($t = 3.118, p = 0.002$)

Figure 7. Right dorsolateral prefrontal gray matter volume mediating relationship between emotional neglect and anxiety.
Horizontal lines on scatter plot indicate predicted level of gray matter volume at mean level of emotional neglect and increase in predicted gray matter volume per unit increase of emotional neglect. Vertical lines on scatter plot indicate predicted level of anxiety symptoms at mean level of emotional neglect and increase in predicted anxiety symptoms per unit increase of emotional neglect. Diagonal lines on scatter plot indicate predicted level of anxiety symptoms at mean level of emotional neglect and at 1 standard deviation above and below the mean. $ab_{standard}$ = standardized indirect mediation effect; BSIAnx = anxiety subscale of the Brief Symptom Inventory-18; CTQEN = Childhood Trauma Questionnaire emotional neglect subscale; κ^2 = kappa squared statistic, or the proportion of the maximum possible indirect effect that could have occurred, had the constituent effects been as large as the design and data permitted; P_m = mediation ratio, i.e. proportion of total effect mediated; $R^2_{mediation}$ = variance in anxiety symptoms that is common to both emotional neglect and gray matter volume but can be attributed to neither alone.

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