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ORIGINAL ARTICLE

Early life stress and the anxious brain: evidence for a neural mechanism linking childhood emotional maltreatment to anxiety in adulthood

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Background. Childhood emotional maltreatment (CEM) increases the likelihood of developing an anxiety disorder in adulthood, but the neural processes underlying conferment of this risk have not been established. Here, we test the potential for neuroimaging the adult brain to inform understanding of the mechanism linking CEM to adult anxiety symptoms.

Method. One hundred eighty-two adults (148 females, 34 males) with a normal-to-clinical range of anxiety symptoms underwent structural and functional magnetic resonance imaging while completing an emotion-processing paradigm with facial expressions of fear, anger, and happiness. Participants completed self-report measures of CEM and current anxiety symptoms. Voxelwise mediation analyses on gray-matter volumes and activation to each emotion condition were used to identify candidate brain mechanisms relating CEM to anxiety in adulthood.

Results. During processing of fear and anger faces, greater amygdala and less right dorsolateral prefrontal (dlPFC) activation partially mediated the positive relationship between CEM and anxiety symptoms. Greater right posterior insula activation to fear also partially mediated this relationship, as did greater ventral anterior cingulate (ACC) and less dorsal ACC activation to anger. Responses to happy faces in these regions did not mediate the CEM-anxiety relationship. Smaller right dlPFC gray-matter volumes also partially mediated the CEM-anxiety relationship.

Conclusions. Activation patterns of the adult brain demonstrate the potential to inform mechanistic accounts of the CEM conferment of anxiety symptoms. Results support the hypothesis that exaggerated limbic activation to negative valence facial emotions links CEM to anxiety symptoms, which may be consequent to a breakdown of cortical regulatory processes.

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Key words: Amygdala, anxiety, childhood maltreatment, early life stress, imaging.

Introduction

Anxiety disorders are an insidious public health problem with a high prevalence and a substantial burden of suffering (Mendlowicz & Stein, 2000; Kessler *et al.* 2005), and great effort has been directed towards identifying and probing neural substrates responsible for the development of excessive anxiety. The majority of studies have focused on descriptive characterization of dysfunctional brain substrates in participants already manifesting anxiety disorders (Paulus, 2008). Although such studies are useful in directing the focus of research towards relevant brain regions, they are unable to drive inference concerning neural mechanisms which underlie the etiology of clinical anxiety. Understanding the mechanisms by which mental illness manifests has emerged as a major focus of scientific interest, and particularly so in the framework of the Research Domain Criteria (RDoC; Insel *et al.* 2010; Insel, 2014), which emphasizes the establishment of mechanistic relationships by which disruptions in one or more specified constructs results in symptoms or impairment (Cuthbert, 2014). To address

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this critically important issue, it is crucial to move beyond a descriptive focus on end-state neural abnormalities towards testing hypothesized models of neural mechanisms that putatively lead to the manifestation of anxiety disorders.

A useful method to facilitate mechanistic inference is through study of developmental risk factors known to predispose individuals to the later manifestation of clinical anxiety. As many mental illnesses can be viewed as neurodevelopmental disorders (Cuthbert, 2014), understanding how particular known risk factors interact with the developing brain to result in intermediate phenotypes and eventual full manifestation of pathology can provide a mechanistic view of an etiological pathway. A potent risk factor for adult anxiety (amongst other psychopathology) is childhood emotional maltreatment (CEM), a prevalent and damaging form of early life stress broadly defined as the intentional or unintentional commission of acts (e.g. verbal abuse, taunting, belittling) or withholding of emotional resources (e.g. emotional neglect, unavailability, or dismissiveness) by caregivers that adversely influence the emotional health, growth, or adaptation of the child (Egeland, 2009). CEM is not only reliably associated with more severe anxiety in adulthood (Zlotnick *et al.* 2008; Simon *et al.* 2009; Spinhoven *et al.* 2010; Kuo *et al.* 2011) but both anxious and maltreated populations display altered processing of emotional stimuli, particularly those that are negative in valence and convey potential threat, i.e. fear and anger (Masten *et al.* 2008; Amir *et al.* 2009; Gibb *et al.* 2009; Klumpp & Amir, 2009; Waters *et al.* 2014). From a developmental perspective, the ability to accurately identify facial emotions is a crucial skill that facilitates a child's ability to read non-verbal cues, anticipate another's mental state, and adaptively respond to human interaction. In a childhood environment saturated with constant threats to emotional well-being via criticism, teasing, or verbal abuse, an increased sensitivity to facial emotions signaling a potential threat to emotional well-being is likely to convey an adaptive advantage, facilitating early detection and avoidance of a potentially emotionally harmful interaction with the caregiver (Masten *et al.* 2008; Gibb *et al.* 2009).

Over the course of development, however, this initially adaptive sensitivity may become maladaptive, rendering the individual prone to hypervigilance for potential threats to emotional stability in the environment and fostering heightened stress responses and poorer overall mental health (Herringa *et al.* 2013). The neurocircuitry underlying facial emotion processing encompasses both limbic and prefrontal regions responsive to emotion, such as the amygdala, insula, anterior cingulate/medial prefrontal cortex (ACC/mPFC), dorsolateral (dlPFC) and ventrolateral prefrontal cortex (vlPFC), as well as specialized visual cortical face-processing regions such as the fusiform gyrus (Sabatinelli *et al.* 2011). Imaging studies have revealed that adult participants with anxiety disorders as well as those exposed to CEM display similar alterations distributed across this affective corticolimbic network in response to stimuli conveying threat or negative emotionality (Etkin & Wager, 2007; Williams *et al.* 2009; Dannlowski *et al.* 2012). Particularly relevant evidence comes from a series of studies investigating the neural 'imprinting' of CEM in the context of healthy individuals and outpatients with anxiety and depressive disorders. These studies reveal CEM is associated with reduced structural integrity and engagement of the mPFC to emotional and neutral word pair encoding and recognition (van Harmelen *et al.* 2010, 2014), as well as enhanced amygdala engagement to emotional and neutral faces (van Harmelen *et al.* 2013). Importantly, these findings did not vary as a function of psychopathology, suggesting such effects may be instantiated early in life and confer vulnerability to development of anxiety and depression. This aggregate evidence suggests CEM-related alterations in neural structure and neural responses to facial emotions may serve as one mechanism through which CEM promotes the propensity towards the manifestation of anxiety symptoms. However, the nature of this mechanism and relationships among its constituent neural components remains unknown. Ideally, one would prospectively follow individuals whom have experienced CEM and examine them longitudinally. Indeed, such an approach has already yielded promising results in adolescents (Burghy *et al.* 2012; Herringa *et al.* 2013). However, for examining such mechanisms into adulthood, this approach is time and cost prohibitive. Before such investments are made, it is prudent to first identify if neural characteristics in a cross-sectional sample of adults encompassing various levels of anxiety and retrospectively reported CEM can be leveraged towards informing future longitudinal investigations.

Here, we employ a transdiagnostic, mechanistically focused analytic approach across neural data from a large, primarily female sample of adults, both healthy and anxiety and mood-disordered. Consistent with a neurodevelopmental perspective on the RDoC initiative (Insel *et al.* 2010; Simpson, 2012; Casey *et al.* 2014; Insel, 2014), we utilize a dimensional approach to assessing a candidate neural mechanism that links a potent developmental risk factor to mental health outcomes. To do this, we employed a voxelwise mediation analysis mapping approach. To our knowledge, it is the first such application of this statistical technique to facilitate inference on neural mechanisms linking CEM to anxiety in adulthood. Mediation analysis provides a powerful statistical framework to test a

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proposed mechanism linking two related variables (MacKinnon *et al.* 2007). In the current investigation, CEM served as the independent (causal) variable, adult anxiety symptoms as the outcome, and neural function and structure as the mechanism (indirect path) through which CEM conveys risk for anxiety symptoms in adulthood. We sought to answer the following questions: (*a*) Can a plausible neural mechanism relating CEM to anxiety be identified retrospectively from brain function and structure assessed in adulthood?; and (*b*) What is the nature of this neural mechanism?, i.e. which component brain structures are involved and what can we infer about the process(es) occurring in the brain from existing knowledge of neurocircuitry? Neural function was probed using separate emotion contrasts (fear, anger, and happy, each *v.* a sensorimotor baseline condition) from a widely employed facial emotion-processing paradigm. This task reliably activates conceptually relevant limbic and cortical regions (Bertolino *et al.* 2005; Hariri *et al.* 2005) and elicits neural abnormalities in anxious populations (Stein *et al.* 2007; Fonzo *et al.* 2010, 2013, 2015).

On the basis of existing findings (van Harmelen *et al.* 2010, 2013, 2014; Dannlowski *et al.* 2012), we expected to detect evidence consistent with the following hypothesized mechanism. We believe CEM provokes increased reactivity of affective processing regions to facial emotions, particularly those conveying negative valence and/or potential threat (e.g. fear and anger), which in turn initially promote a compensatory engagement of prefrontal substrates for affective regulation. Some individuals will be successful in regulating emotional state via cortical engagement, but in vulnerable individuals this compensatory mechanism likely breaks down with repeated overuse and leads to prefrontal hypoactivity and insufficient emotional regulation. In CEM-exposed adults with significant levels of anxiety symptoms, this compensatory engagement was likely ineffective at adequately regulating emotional state, leading to a dysregulation of emotional reactivity, hypofrontality, increased limbic engagement, and the emergence of symptoms. We also predict this *threat-priming* mechanism will interact with developmental brain processes to confer abnormal structure of implicated substrates, most notably in the PFC and hippocampus due to their prominent stress hormone structural sensitivity (Carrion *et al.* 2007; Kremen *et al.* 2010). Specifically, we hypothesized that increasing activation in limbic structures (i.e. amygdala and insula) across all emotion types would serve as an indirect path linking CEM to anxiety symptoms. In the context of negative valence facial emotions conveying potential threat, i.e. fear and anger, we also predicted decreasing activation in medial and lateral prefrontal cortical regulatory regions would serve as an indirect path. Finally, due to considerable evidence demonstrating decreased prefrontal cortical and hippocampal gray matter volumes in individuals exposed to childhood maltreatment (Woon & Hedges, 2008; van Harmelen *et al.* 2010; Dannlowski *et al.* 2012; Fonzo *et al.* 2013; Kelly *et al.* 2013) and those with anxiety (Bonne *et al.* 2008; Uchida *et al.* 2008; Asami *et al.* 2009; Sobanski *et al.* 2010; Thomaes *et al.* 2010; Hettema *et al.* 2012), we also predicted decreasing prefrontal and hippocampal gray matter volumes would serve as an indirect path linking CEM to anxiety symptoms.

Method

Participants

One hundred eighty-two participants (148 females, 34 males) were recruited through online and print advertisements and referral from university-affiliated primary-care and mental health clinics. Participants were pooled from ongoing research studies investigating the neurobiology of anxiety disorders, post-traumatic stress disorder (PTSD), and anxiety disorder-proneness (high levels of trait anxiety). These participants encompassed a wide range of anxiety psychopathology, consisting of psychiatrically healthy individuals as well as those with clinical and subclinical anxiety manifestations. Clinical participants were recruited on the basis of 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: (*a*) the Clinician-Administered PTSD Scale (CAPS; Blake *et al.* 1995) for those patients recruited into a PTSD study and their matched healthy controls; (*b*) Structured Clinical Interview for Diagnosis-DSM IV (SCID-IV; First *et al.* 1998) for individuals recruited for a primary diagnosis GAD, PD, or for high levels of trait anxiety, and their matched healthy controls; and (*c*) Mini International Neuropsychiatric Interview (Sheehan *et al.* 1998) for individuals recruited into an SAD study. Exclusion criteria included lifetime diagnosis of psychotic disorder, organic mental disorder, mental retardation, bipolar disorder, substance dependence in the past year, and substance abuse in the past month. All participants were medication-free for a minimum of 30 days prior to study enrollment and not undergoing current psychotherapy for anxiety or related 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 (see Table 1 for more information).

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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, Bernstein *et al.* 2003) were additively combined to create a composite measure of CEM. Scores on CTQ subscales range from 5 to 25 and assess EA, EN, physical abuse (PA), physical neglect (PN), and sexual abuse (SA). Given their high intercorrelation ($r = 0.76$) in this sample, EA and EN scores were combined to yield a single measure of CEM; thus, the CEM composite measure ranged from 10 to 50. Anxiety symptoms were quantified using the score from the 6-item anxiety subscale (BSI-Anx) of the Brief Symptom Inventory-18 (Derogatis & Fitzpatrick, 2004) in which participants rate, on a 5-point Likert scale, how often they were distressed by a list of symptoms within the past week. Symptoms of depression were quantified using the depression subscale of this same measure (BSI-Dep).

Emotion-processing task

Participants completed a modified version of the Emotion Face Assessment Task (Hariri *et al.* 2005; Paulus *et al.* 2005) with angry, happy, or fearful faces. On each trial, participants viewed a trio of faces and were instructed to match the facial expression of the top face to one of the two bottom faces through key press of a button box (see Supplementary method for further details).

Image acquisition

Data were collected during task completion using fMRI image parameters sensitive to BOLD contrast on a 3 T GE Signa EXCITE (GE Healthcare, USA) scanner [T2*-weighted echo planar imaging, repetition time (TR) = 2000 ms, echo time (TE) = 32 ms, field of view (FOV) = 250 × 250 mm, 64 × 64 matrix, 30 2.6 mm axial slices with 1.4 mm gap, 256 repetitions]. A high-resolution T1-weighted image [172 sagitally acquired spoiled gradient recalled 1 mm thick slices, inversion time (TI) = 450 ms, TR = 8 ms, TE = 4 ms, flip angle = 12°, FOV = 250 × 250 mm] was also collected from each participant for anatomical reference. Echo-planar 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). 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, fearful, or happy faces *v.* the shape-matching baseline condition (see Supplementary method for details).

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) (see Supplementary method for details).

Task effect activation

In order to identify significant task-evoked activation within each contrast, *t* tests against the null hypothesis were carried out on individual activation maps across all participants.

Basic mediation analyses

Voxelwise basic mediation analyses were conducted using the MBESS package (Kelley, 2007*a*,*b*; Kelley & Lai, 2012) implemented in R (R Core Team, 2013). Mediation models provide a statistical framework for testing a proposed variable as an indirect path (brain function/structure) for conveying an effect of an independent variable (CEM) on a dependent variable (adult anxiety symptoms) (MacKinnon *et al.* 2007). CEM served as the independent variable and anxiety symptoms served as the dependent variable in the mediation model. For each activation contrast and GM volumetric map, voxelwise percent signal change (% SC) or GM volumes served as the respective mediating variable in the mediation model. The main outcome measure was the 95% confidence interval (CI) for the indirect effect (mediation effect). Bootstrapping of the indirect effect was utilized to determine the standard error (S.E.) and CIs of the indirect effect (MacKinnon *et al.* 2007). At each voxel, 500 bootstrap samples were utilized to derive S.E. estimates.

Region of interest (ROI) and whole-brain analyses

Two types of analyses were conducted on the group level. For functional data, in addition to a whole-brain exploratory analysis, *a-priori* ROI analyses were conducted on emotion-processing brain regions previously implicated in studies of anxiety and CEM: bilateral insula, bilateral amygdala, and ACC/mPFC. Boundaries of these ROIs were based upon both anatomical criteria and standardized locations taken from the Talairach atlas (Talairach & Tournoux, 1998). For structural data, these regions were also investigated in ROI analyses, with the addition of the bilateral hippocampus. A threshold adjustment based upon Monte-Carlo simulations (using AFNI's program

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Table 1. *Participant demographics and clinical characteristics*

Measure	Mean (S.D.)	Frequency/range
Age (years)	30.71 (11.27)	
Education (years)	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/mixed
Primary diagnoses		76 Healthy controls
		26 GAD
		14 PD
		35 PTSD
		28 SAD
		2 Anxiety NOS
CTQ		
Total score	41.38 (17.37)	25–111
Emotional abuse	9.52 (4.97)	5–24
Emotional neglect	10.70 (5.25)	5–25
Physical abuse	7.04 (3.52)	5–22
Physical neglect	7.49 (3.47)	5–23
Sexual abuse	6.63 (4.04)	5–25
BSI		
Total (*T* score)	54.41 (12.60)	33–81
Anxiety (raw score)	5.45 (5.47)	0–24
Depression (raw score)	5.49 (5.38)	0–24
Somatitization (raw score)	3.41 (4.43)	0–22
Reaction time (s)		
Angry	1.48 (0.29)	1.05–3.08
Fear	1.63 (0.35)	1.13–2.61
Happy	1.24 (0.28)	1.07–2.23
Shapes	1.00 (0.24)	0.69–2.13
% Incorrect		
Angry	1.11 (3.17)	0–11.11
Fear	2.78 (4.16)	0–14.29
Happy	0.53 (1.95)	0–11.00
Shapes	2.40 (3.92)	0–14.29

BSI, Brief Symptom Inventory-18; CTQ, Childhood Trauma Questionnaire; GAD, generalized anxiety disorder; NOS, not otherwise specified; PTSD, posttraumatic stress disorder; PD, panic disorder; SAD, social anxiety disorder.

AlphaSim) was used to guard against false positives in the whole-brain and ROI analyses (see Supplementary method for details).

Extended mediation analyses

We performed moderated mediation analyses to test if the strength of mediation relationships were conditional on another variable – that is, if identifiable subject characteristics could influence the strength of mechanistic effects. In particular, we were interested whether structural brain characteristics influenced the mediation relationship of specific functional brain activation patterns between CEM and anxiety. Moderated mediation tests whether the strength of a mediating variable's effect on the relationship between the independent and dependent variables is conditional upon a fourth variable. In this context, we conducted exploratory analyses to test whether the strength of the effect of a particular cluster of brain activation on mediating the

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CEM-anxiety symptom relationship was moderated by brain structure (GM volumes). We also performed additional mediation analysis on brain activation identified in the voxelwise mediation analysis to test if the mediating effect of brain function on the CEM-anxiety symptom relationship remained significant when controlling for current regional GM volumes. In order to perform moderated mediation analyses and mediation with covariates, the average %SCs and GM volumes were extracted from each participant from clusters displaying significant basic mediation effects in the voxelwise analyses. The PROCESS package (Hayes, 2013) implemented in IBM SPSS version 19.0 (IBM SPSS Inc., 2010) was utilized for extended mediation analyses. Bootstrapping of the CI of the indirect effect was utilized to determine significance. To describe the robustness of mediation effects and their adequacy in supporting our proposed threat-priming model, we also tested the indirect effect of an alternative model (anxiety symptoms mediating the effect of CEM on brain function/structure). To examine the degree to which the indirect effect accounted for the relationship between the independent and dependent variables in each model, we constrained the direct path between the variables to zero to test the adequacy of a fully mediated relationship, i.e. if the effects of the independent variable on the dependent variable are conveyed entirely via the mediator. We report the χ^2 for each model with the direct path constrained to zero, as well as root mean square error of approximation (RMSEA), the Comparative Fit Index (CFI), and the standardized root mean square residual (SRMR). These model fit indices were derived using MPlus version 7.3.1 (Muthén & Muthén, 1998–2012). Good model fit indices with the direct path constrained to zero (e.g. non-significant χ^2, RSMEA and SRMR < 0.1, CFI > 0.93) in combination with a significant indirect effect suggest a fully mediated relationship between the independent and dependent variable, while poor model fit statistics with a significant indirect effect indicate a partially mediated relationship.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Results

Demographics and symptoms

The sample was almost entirely female (~81%) and displayed low levels of CEM and anxiety symptoms, on average, though the full spectrum observed ranged from low to severe (Table 1).

Relationships among CEM and anxiety symptoms

As expected, CEM was significantly positively correlated with BSI-Anx scores (Pearson's $r = 0.317$, $p < 0.001$) and BSI-Dep scores (Pearson's $r = 0.347$, $p < 0.001$). The BSI-Anx and BSI-Dep subscales were also significant positively correlated (Pearson's $r = 0.694$, $p < 0.001$). The associations between CEM 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.

Task-related behavior

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 CEM, anxiety symptoms, or depressive symptoms (all p's > 0.05) (see Table 1).

Task-related activation

In brief, all emotion contrasts activated the bilateral amygdala, bilateral posterior insula, subgenual ACC, and visual cortices, and deactivated the perigenual ACC. For fear and anger, additional activation was observed in the bilateral dlPFC and bilateral anterior insula (see Supplementary Tables S1–S3).

Threat-related limbic activation and maltreatment-priming effects

To test our hypothesis that CEM will prime affective processing regions for exaggerated reactivity to threatening facial cues, we examined two threat-contrasts of interest: anger *v.* shapes and fear *v.* shapes. For the contrast of fear *v.* shapes, greater activation in the right posterior insula [indirect effect = 0.009, 95% bootstrapped CI 0.001–0.016; $\chi^2(1) = 17.36$, $p < 0.0001$; RMSEA = 0.30, 90% CI 0.187–0.431; CFI = 0.27; SRMR = 0.101] and the right amygdala [indirect effect = 0.028, 95% bootstrapped CI 0.001–0.057; $\chi^2(1) = 15.27$, $p = 0.0001$; RMSEA = 0.280, 90% CI 0.168–0.412; CFI = 0.552; SRMR = 0.09] partially mediated the relationship between CEM and anxiety (Table 2, Fig. 1). Note that model fit indices when constraining the direct effect to zero were poor in both regions, indicating that although the indirect effect is significant it does not fully account for the relationship between CEM and anxiety, i.e. partial mediation. The alternative model indirect effect was non-significant for both the

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Table 2. *Activation mediating the relationship between childhood emotional maltreatment and adulthood anxiety*

							Voxelwise statistics, mean (S.D.)			With GM covariate
Mask	H	Region	Vol. (μl)	x	y	z	Indirect effect	Lower CI	Upper CI	Extracted indirect effect (CI)
Fear *v.* shapes										
ROI	R	Insula (p)	512	44	−21	2	0.008 (0.001)	0.0006 (0.0002)	0.025 (0.003)	0.0087 (0.0004–0.025)
ROI	R	Amygdala	256	22	0	−14	0.018 (0.002)	0.002 (0.0011)	0.029 (0.006)	0.0278 (0.002–0.039)
WB	L	Fusiform gyrus	1088	−46	−36	−18	0.012 (0.001)	0.0008 (0.0002)	0.046 (0.007)	0.0227 (0.0068–0.0538)
WB	R	Middle/superior frontal gyri (dl)	768	22	37	37	0.011 (0.001)	0.0005 (0.0002)	0.035 (0.008)	0.0135 (0.0022–0.0325)
Anger *v.* shapes										
ROI	L/R	Anterior cingulate (v)	640	4	33	−2	0.010 (0.002)	0.002 (0.0011)	0.027 (0.002)	0.0175 (0.0068–0.0339)
ROI	R	Anterior cingulate (d)	640	10	21	26	0.014 (0.003)	0.002 (0.0013)	0.041 (0.005)	0.0247 (0.0061–0.0537)
ROI	L	Amygdala	192	−25	−5	−12	0.019 (0.002)	0.002 (0.0008)	0.030 (0.004)	0.029 (0.003–0.0417)
WB	R	Inferior/middle frontal gyri (dl)	1024	46	16	15	0.012 (0.001)	0.002 (0.0003)	0.042 (0.008)	0.018 (0.002–0.0411)
Happy *v.* shapes										
ROI	–	No significant effects	–	–	–	–	–	–	–	–
WB	L/R	Lentiform Nucleus/hypothalamus/caudate	896	8	−2	−7	0.011 (0.002)	0.0005 (0.0001)	0.032 (0.006)	0.009 (0.0007–0.0310)
WB	R	Lingual gyrus	832	11	−64	4	0.011 (0.002)	0.001 (0.0009)	0.031 (0.006)	0.011 (0.004–0.0314)

d, Dorsal; dl, dorsolateral; EA, emotional abuse; EN, emotional neglect; GM, gray matter; H, hemisphere; L, left; p, posterior; R, right; ROI, region of interest masks; S.D., standard deviation; v, ventral; Vol., volume; WB, whole-brain masks.

x, y, z are the Talairach coordinates for the cluster center of mass. Voxelwise statistics report mean statistical value with standard deviations in parentheses; Column with GM and depression covariates indicates indirect mediation effect for extracted cluster values after controlling for cluster gray matter volume, 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.

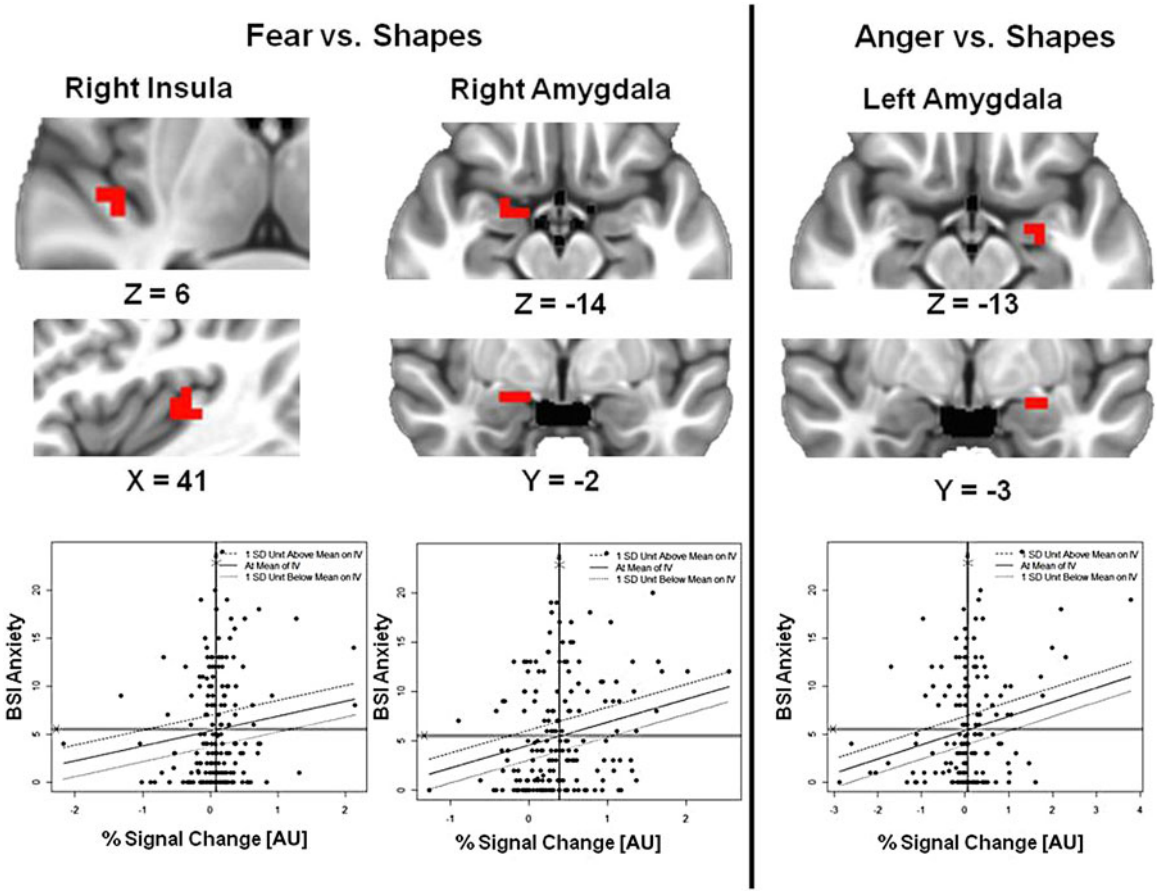

Fig. 1. Increasing limbic activation to anger and fear partially mediates the relationship between childhood emotional maltreatment (CEM) and anxiety. Graphs depict the relationship between regional brain activation and anxiety symptoms at different levels of CEM (the additive combination of the Childhood Trauma Questionnaire Short Form emotional abuse and emotional neglect subscales), with the center fitted line indicating the activation anxiety relationship at the CEM sample mean and each line above or below representing one standard deviation above or below the CEM mean, respectively. AU, Arbitrary units; BSI, Brief Symptom Inventory.

posterior insula [indirect effect = 0.002, 95% bootstrapped CI −0.001 to 0.005; $\chi^2(1) = 29.78$, $p < 0.0001$; RMSEA = 0.276, 90% CI 0.194–0.456; CFI = 0.167; SRMR = 0.141] and right amygdala [indirect effect = 0.004, 95% bootstrapped CI −0.001 to 0.009; $\chi^2(1) = 18.448$, $p < 0.0001$; RMSEA = 0.319, 90% CI 0.188–0.462; CFI = 0.162; SRMR = 0.138], and model fit indices were also poor. For the contrast of anger *v.* shapes, greater activation in the left amygdala partially mediated the relationship between CEM and anxiety [indirect effect = 0.019, 95% bootstrapped CI 0.005–0.033; $\chi^2(1) = 15.015$, $p = 0.0001$; RMSEA = 0.277, 90% CI 0.165–0.409; CFI = 0.539; SRMR = 0.089; Table 2, Fig. 1]. Although the indirect effect was significant, the overall model fit was poor, indicating a partial mediation effect. The indirect effect of the alternative mediation model was also not significant [indirect effect = 0.006, 95% bootstrapped CI −0.001 to 0.013; $\chi^2(1) = 25.87$, $p < 0.0001$; RMSEA = 0.301, 90% CI 0.194–0.408; CFI = 0.215; SRMR = 0.132] and model fit statistics were also poor. Indirect effects remained significant when controlling for structural characteristics (i.e. GM volume).

Threat-related prefrontal activation and maltreatment-related engagement

We next examined prefrontal substrates using an ROI mask for the ACC/mPFC and a whole-brain mask for the remaining portions to test the hypothesis that CEM-related priming of affective processing regions would tax prefrontal affective control regions and result in diminished prefrontal cortical responses. For the contrast of fear *v.* shapes, we observed that less activation in the right dlPFC (middle/superior frontal gyri; BA 8 and 9) partially mediated the relationship between CEM and anxiety symptoms [indirect effect = 0.014, 95% bootstrapped CI 0.001–0.029; $\chi^2(1) = 16.53$, $p < 0.0001$; RMSEA = 0.292, 90% CI 0.179–0.423; CFI = 0.498; SRMR = 0.095; Table 2, Fig. 2]. Again, the indirect effect was significant but model fit statistics were generally

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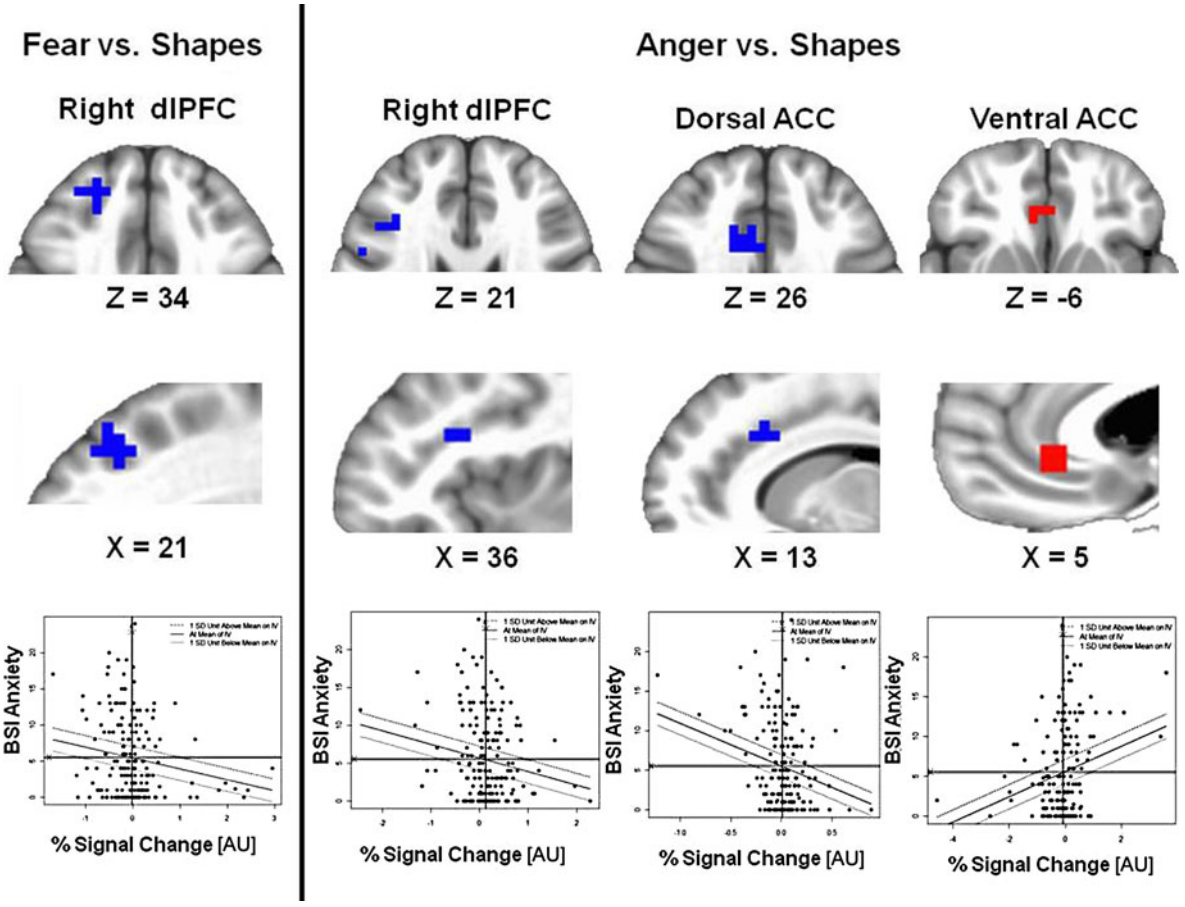

Fig. 2. Prefrontal activation to anger and fear partially mediates the relationship between childhood emotional maltreatment (CEM) and anxiety. Graphs depict the relationship between regional brain activation and anxiety symptoms at different levels of CEM (the additive combination of the Childhood Trauma Questionnaire Short Form emotional abuse and emotional neglect subscales), with the center fitted line indicating the activation-anxiety relationship at the CEM sample mean and each line above or below representing one standard deviation above or below the CEM mean, respectively. AU, Arbitrary units; BSI, Brief Symptom Inventory.

poor, indicating the mediation effect was partial. The mediation effect was non-significant for the alternative model [indirect effect = −0.003, 95% bootstrapped CI −0.007 to 0.001; $\chi^2(1) = 24.78$, $p < 0.0001$; RMSEA = 0.350, 90% CI 0.268–0.443; CFI = 0.116; SRMR = 0.127] and model fit statistics were also poor. We also observed effects in other non-hypothesized regions (see Supplementary Results). For the contrast of anger *v.* shapes, we observed that decreasing activation in the right dlPFC (inferior/middle frontal gyri; BA 10 and 46) also partially mediated the relationship between CEM and anxiety [indirect effect = 0.018, 95% bootstrapped CI 0.001–0.035; $\chi^2(1) = 15.644$, $p = 0.0001$; RMSEA = 0.284, 90% CI 0.171–0.415; CFI = 0.479; SRMR = 0.092; Table 2, Fig. 2]. Model fit statistics were poor, indicating the mediation effect was partial. The mediation effect was non-significant for the alternative model [indirect effect = −0.002, 95% bootstrapped CI −0.005 to 0.001; $\chi^2(1) = 25.23$, $p < 0.0001$; RMSEA = 0.324, 90% CI 0.194–0.454; CFI = 0.213; SRMR = 0.138] and model fit statistics were also poor. We additionally observed mediation effects in medial prefrontal regions for anger, with greater activation in the ventral ACC [indirect effect = 0.020, 95% bootstrapped CI 0.001–0.039; $\chi^2(1) = 15.962$, $p = 0.0001$; RMSEA = 0.287, 90% CI 0.174–0.415; CFI = 0.451; SRMR = 0.093] and decreasing activation in the dorsal ACC partially mediating this relationship [indirect effect = 0.028, 95% bootstrapped CI 0.004–0.053; $\chi^2(1) = 13.835$, $p = 0.0002$; RMSEA = 0.266, 90% CI 0.154–0.398; CFI = 0.634; SRMR = 0.084; Table 2, Fig. 2]. Indirect effects were significant but model fit statistics were also poor for both ACC effects, indicating the mediation effects were partial. The mediation effect was non-significant for the alternative model in both the ventral ACC [indirect effect = 0.006, 95% bootstrapped CI −0.001 to 0.013; $\chi^2(1) = 23.41$, $p < 0.0001$; RMSEA = 0.318, 90% CI 0.215–0.421; CFI = 0.263; SRMR = 0.142] and dorsal ACC [indirect effect = −0.002, 95% bootstrapped CI −0.005 to 0.001; $\chi^2(1) = 21.398$, $p < 0.0001$; RMSEA = 0.342, 90% CI 0.274–0.410; CFI = 0.389;

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SRMR = 0.112] and model fit statistics for both were also poor. Indirect effects remained significant when controlling for structural characteristics.

Ventral striatal engagement to happy faces and maltreatment effects

We then examined brain responses to happy faces *v.* shapes to examine if limbic activation mediated the relationship between CEM and anxiety symptoms. We did not observe any significant mediation effects in *a-priori* hypothesized regions. An exploratory whole brain analysis did, however, identify additional effects of interest. Decreasing activation in a cluster encompassing the ventral striatum/pallidum (lentiform nucleus and caudate head) and hypothalamus partially mediated the relationship between CEM and anxiety [indirect effect = 0.015, 95% bootstrapped CI 0.001–0.029; $\chi^2(1) = 17.115$, $p < 0.0001$; RMSEA = 0.298, 90% CI 0.185–0.429; CFI = 0.385; SRMR = 0.090; Table 2, Supplementary Fig. S1]. This was also a partial mediation effect, as indicated by the significant indirect effect but poor model fit statistics when constraining the direct path from CEM to anxiety. The indirect effect for the alternative model was non-significant [indirect effect = −0.001, 95% bootstrapped CI −0.003 to 0.001; $\chi^2(1) = 20.732$, $p < 0.0001$; RMSEA = 0.334, 90% CI 0.214–0.454; CFI = 0.302; SRMR = 0.142] and model fit was also poor. An additional similar effect was observed in the right visual cortex [lingual gyrus; indirect effect = 0.011, 95% bootstrapped CI 0.002–0.020; $\chi^2(1) = 16.737$, $p < 0.0001$; RMSEA = 0.294, 90% CI 0.181–0.425; CFI = 0.329; SRMR = 0.091]. The indirect effect for the alternative model was non-significant [indirect effect = −0.002, 95% bootstrapped CI −0.005 to 0.001; $\chi^2(1) = 19.484$, $p < 0.0001$; RMSEA = 0.387, 90% CI 0.294–0.480; CFI = 0.284; SRMR = 0.122] and model fit was also poor. Indirect effects remained significant when controlling for structural characteristics. Given the role of the ventral striatum in reward and positive affect, we expected the mediation effect seen in this region for the CEM-anxiety relationship might be better accounted for by concurrent symptoms of diminished positive affect (e.g. anhedonia) observed in depression. We therefore also tested extracted %SCs as a mediator of the relationship between CEM and BSI-Dep scores. However, activation in this region to happy facial expressions did not significantly mediate the CEM-depression relationship (lower bound of 95% CI for indirect effect = −0.003).

Maltreatment effects on prefrontal brain structure

We also predicted our hypothesized functional mechanism would interact with brain development to result in abnormal structure of affective processing and control substrates in adulthood. In support of this, we examined GM volumes in limbic regions first, including the amygdala, hippocampus, and insula. There were no limbic structures in which GM volumes mediated the relationship between CEM and anxiety.

Next, we used an ROI analysis for the ACC/mPFC and a whole-brain analysis for the lateral PFC to examine how prefrontal structure might be implicated in our proposed model. We observed that smaller GM volumes in the right dlPFC (inferior/middle frontal gyri; BA 10 and 46) partially mediated the relationship between CEM and anxiety [indirect effect = 0.020, 95% bootstrapped 95% CI 0.001–0.039; $\chi^2(1) = 13.551$, $p = 0.0002$; RMSEA = 0.263, 90% CI 0.151–0.395; CFI = 0.556; SRMR = 0.085; Table 3, Fig. 3]. The indirect effect was significant though model fit was poor when constraining the direct effect, indicating a partial mediation. The indirect effect for the alternative model was non-significant [indirect effect = 0.001, 95% bootstrapped CI −0.009 to 0.011; $\chi^2(1) = 19.101$, $p < 0.0001$; RMSEA = 0.365, 90% CI 0.283–0.447; CFI = 0.313; SRMR = 0.115] and model fit was also poor. Moreover, this structural effect partially overlapped the functional effect seen in this same affective control region for processing anger expressions. To determine if this effect may be attributed entirely to the functional process implicated in this region, this structural mediation effect was also tested for significance when controlling for brain activation to anger *v.* shapes in this cluster. This effect continued to remain significant when controlling for functional activation (see Table 3 for details). We also observed additional structural effects in non-hypothesized regions (see Supplementary Results).

Structural independence of functional mediation effects

In order to explore whether the strength of a functional mediation effects was conditional upon the structure of that particular region, structural characteristics of regions (i.e. GM volumes of clusters) displaying functional mediation effects were explored as potential moderators of the mediation effect in limbic and prefrontal regions relevant to our hypotheses (bilateral amygdala, right posterior insula, dorsal and ventral ACC, and right dlPFC). We did not observe any significant moderation effects of structural characteristics on strength of functional mediation.

Discussion

We utilized functional activation patterns to facial emotions across a large, primarily female adult sample

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Table 3. *Gray-matter volumes mediating the relationship between childhood emotional maltreatment and adulthood anxiety*

							Voxelwise statistics, mean (S.D.)		
Mask	H	Region	Vol. (μl)	x	y	z	Indirect effect	Lower CI	Upper CI
ROI	–	No significant effects	–	–	–	–	–	–	–
WB	L	Precentral gyrus	960	−47	−6	43	0.0142 (0.004)	0.0019 (0.0018)	0.041 (0.008)
WB	R	Inferior/middle frontal gyri (dl)	880	42	38	15	0.0107 (0.003)	0.0009 (0.0008)	0.036 (0.005)

dl, Dorsolateral; H, hemisphere; L, left; R, right; ROI, region of interest masks; S.D., standard deviation; Vol., volume; WB, whole-brain masks.

x, y, z are the Talairach coordinates for the cluster center of mass. Voxelwise statistics report mean statistical 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.

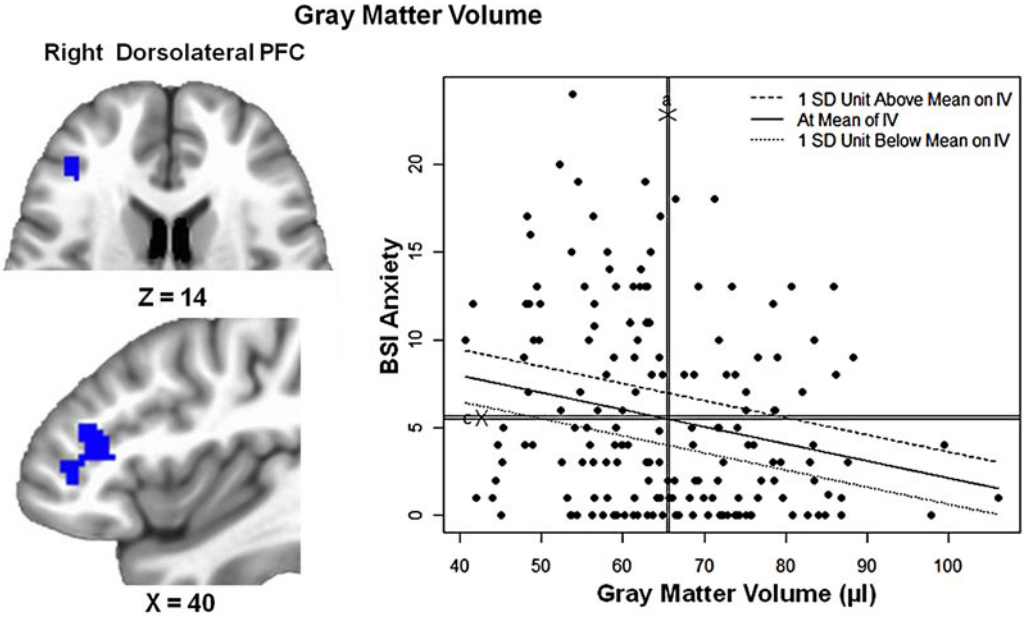

Fig. 3. Decreasing right dorsolateral prefrontal gray matter volumes partially mediates the childhood emotional maltreatment (CEM)-anxiety relationship. Graphs depict the relationship between regional gray-matter volume and anxiety symptoms at different levels of CEM (the additive combination of the Childhood Trauma Questionnaire Short Form emotional abuse and emotional neglect subscales), with the center fitted line indicating the gray-matter volume-anxiety relationship at the CEM sample mean and each line above or below representing one standard deviation above or below the CEM mean, respectively. AU, Arbitrary units; BSI, Brief Symptom Inventory.

with a wide range of CEM and transdiagnostic anxiety symptoms to identify candidate neural mechanisms that may underlie the CEM conferment of risk for anxiety disorders. We tested a hypothesized corticolimbic threat priming model as a potential neural mechanism linking these two constructs. This study produced three primary findings consistent with this model. First, greater amygdala engagement to both fear and anger partially mediated the relationship between CEM and anxiety symptoms. Second, decreasing recruitment of the right dlPFC to fear and anger also partially mediated the relationship between CEM and anxiety symptoms. Third, diminished structural integrity (lower GM volumes) of the right dlPFC partially mediated the relationship between CEM and adulthood anxiety. Taken together, these findings are consistent with the hypothesis that CEM predisposes individuals to the development of anxiety via a breakdown of cortical regulation of limbic responses to emotional stimuli that convey negative valence and/or potential threat. Moreover, these findings demonstrate the utility of adult brain measures in facilitating inference on etiological neural mechanisms that relate known risk factors to mental health outcomes. Such

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inferences, although *post-hoc* and retrospective, will likely be important contributors to the design of future longitudinal studies that can confirm or disconfirm hypothesized models.

The overall mediating neural activation pattern is consistent with an *emotional dysregulation* mechanism of CEM effects, such that exposure to stressful childhood emotional experiences like verbal abuse and emotional neglect disrupt normal socioemotional functioning by fostering enhanced emotional reactivity to threatening interpersonal stimuli (i.e. threat-priming), and over time this results in a dysregulation of stress and fear responses and the emergence of anxiety symptoms (Nolte *et al.* 2011). These findings dovetail nicely with recent longitudinal reports implicating frontal-amygdalar resting connectivity as another developmental mechanism linking early life stress to anxiety and internalizing symptoms later in life (Burghy *et al.* 2012; Herringa *et al.* 2013). Here, we observed the amygdala and right dlPFC to be two key nodes of one potential mechanism linking CEM with anxiety, both implicated in response to processing of negative valence facial emotions that convey potential threat (fear and anger), but not emotions lacking a threatening context (i.e. happy). These findings are broadly in accord with existing emotional regulatory theories that posit an important role for the dlPFC in regulating emotional reactivity in the amygdala (Delgado *et al.* 2008; Ray & Zald, 2012), particularly during use of top-down emotional regulatory strategies such as cognitive reappraisal (Ochsner & Gross, 2005). These interactions likely occur primarily via indirect connections between the dlPFC and amygdala by way of the ACC or orbitofrontal cortex, though the dlPFC and amygdala do share sparse direct connections but more plentiful indirect connections via thalamic pathways (Ray & Zald, 2012; Eden *et al.* 2015). In the context of emotional reactivity, the dlPFC co-activates with the amygdala in attending to stimuli of negative emotional valence as well as under conditions necessitating top-down attentional control (Comte *et al.* 2014). Moreover, prior findings in both adolescents and adults suggest early life stress impacts dlPFC and amygdala structure and function in the context of both emotional reactivity and regulation (Dannlowski *et al.* 2012, 2013; Marusak *et al.* 2015). These previously reported findings suggest: (*a*) dlPFC-amygdala interactions are important in regulating and attending to negative affect; (*b*) the dlPFC exerts a regulatory role over amygdala activity, most prominently under conditions that bring cognitive resources to bear; and (*c*) this relationship is disrupted from exposure to extreme stress early in life. Notably, increased dlPFC engagement to emotional conflict regulation was observed in adolescents exposed to childhood trauma (Marusak *et al.* 2015), consistent with the proposal that CEM will initially provoke increased compensatory prefrontal engagement for regulation of emotional state, which across development will lead to a breakdown of dlPFC regulatory processes in a subset of individuals that go on to manifest psychopathology. The current findings support the aforementioned hypotheses, demonstrating that greater amygdala and reduced dlPFC engagement to fear and anger cues in adulthood partially account for the positive relationship between CEM and anxiety symptoms across a large sample with a wide range of anxiety and mood psychopathology. These findings are also broadly consistent with highly-relevant prior work, which found indiscriminate amygdalar hyperactivation to emotional and neutral facial expressions as a function of CEM, with effect sizes being the largest for fear and anger (van Harmelen *et al.* 2013).

Further implicating the right dlPFC in CEM conferment of risk for anxiety, GM volumes in this region were also found to partially mediate the relationship between CEM and anxiety. Both anxiety and childhood maltreatment have been found to be associated with reduced GM volumes in the lateral prefrontal cortices (Yoo *et al.* 2005; Woodward *et al.* 2009; Eckart *et al.* 2010; Gatt *et al.* 2010). This convergence of functional and structural effects across studies in the same brain region leads us to speculate that the right dlPFC is a structure vulnerable to becoming 'scarred' by early maltreatment experiences, and this may promote dysregulatory effects on emotional processing that lead to anxiety. 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 casual relationships between dlPFC functional and structural effects. We also expected hippocampal GM volume to mediate the CEM-anxiety relationship, but we did not observe any significant effects. Meta-analyses have indicated variable effects of stress and trauma on hippocampal volume stratified by developmental stage (Karl *et al.* 2006; Woon & Hedges, 2008), and such effects may be most prominent in neuropsychiatric disorders manifesting a dysregulation of the hypothalamtic-pituitary-adrenal axis (Sapolsky, 2000). Thus, reductions in hippocampal volume may not be an enduring neural characteristic influencing the CEM-anxiety relationship, or this influence may occur via other types of maltreatment or be present more prominently within a specific subset of individuals.

We also observed a notable emotion specificity of mediation effects in the dorsal ACC and ventral ACC

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during anger processing. The finding of greater ventral ACC activation and decreasing dorsal ACC activation to anger cues partially mediating the CEM-anxiety relationship is broadly consistent with the pattern of dlPFC-amygdala findings across both anger and fear, indicating a mismatch between: (*a*) increasing activity of a ventral, 'automatic' emotion-processing stream (composed primarily of the amgydala and ventral ACC/mPFC) that is emotionally reactive and drives implicit regulatory activity; and (*b*) decreasing activity of a dorsal, 'deliberate' processing stream (composed primarily of dorsal ACC/mPFC and dlPFC) implicated in explicit, effortful top-down control of emotion and cognitive functions (Ochsner & Gross, 2005; Phillips *et al.* 2008; Etkin & Schatzberg, 2011). This finding is also consistent with a prior study that observed greater ventral ACC engagement to angry faces was associated with greater levels of childhood maltreatment in post-traumatic stress disorder (Fonzo *et al.* 2013). Though anger and fear are both negative valence emotions that signal potential threat, evidence indicates there are subtle behavioral and neural differences in the processing of these two facial expressions. A large meta-analysis of emotional face processing reported significant ACC activation for anger but not fear (Fusar-Poli *et al.* 2009), consistent with the anger-specific ACC effects observed here. Moreover, an angry face directed at oneself conveys a localizable, self-relevant, and imminent threat from the expresser, consistent with the role of the ACC/mPFC in self-relevance processing (Amodio & Frith, 2006), but a fear face conveys information regarding a potential threat elsewhere in the environment. Some evidence indicates these expressions, though both indicating threat, also induce subtle differences in approach/avoidance behaviors in the receiver (Marsh *et al.* 2005). From this perspective, we speculate CEM may interact with innate neural patterns of type-specific emotion processing to form dissociable mechanistic pathways contributing to the manifestation of anxiety symptoms later in life. It is notable that ventral ACC engagement in emotional contexts (particularly those presenting fear cues or generating fear states) may serve an adaptive response under certain conditions (Etkin *et al.* 2010) or in clinical manifestations of post-traumatic stress (Liberzon & Garfinkel, 2009; Milad *et al.* 2009). However, the current results and prior findings for ventral ACC hyperactivity in other anxiety manifestations (Amir *et al.* 2005; Pillay *et al.* 2007; Goldin *et al.* 2009; Labuschagne *et al.* 2012) and individuals exposed to childhood maltreatment (Williams *et al.* 2009) suggest that greater ventral ACC engagement to emotional cues may signal very conceptually different processes depending on the emotional context, behavior, or clinical population.

Finally, we would like to briefly comment on the effects observed in response to happy faces. We did not observe any hypothesized mediation effects in the amygdala, which seems inconsistent with a prior study that observed increased amygdala activation to happy (and neutral) faces in individuals exposed to CEM (van Harmelen *et al.* 2013). However, another study in a non-clinical sample also failed to observe significant relationships between history of childhood maltreatment and amygdala reactivity to subliminal presentation of happy faces (Dannlowski *et al.* 2013). Differences in task design and sample composition may account for these conflicting findings, or CEM effects on amygdala response to facial expressions of happiness may be weaker and only variably reach statistical significance. As we used mediation models to detect mechanistic pathways that account for the relationship between CEM and anxiety, another possibility is that CEM effects on amygdala responses to happy faces may not serve to provoke anxiety in afflicted individuals. Indeed, the pattern of findings observed here, specifically decreasing ventral striatal/pallidal activation to happy faces partially mediating the CEM-anxiety relationship, suggests that CEM-related blunting of emotional responses in reward-sensitive basal ganglia structures (Smith *et al.* 2009) may render vulnerability to anxiety. Given that the ventral striatum and ventral pallidum are heavily implicated in approach behavior, positive affect, reward, and motivation (O'Doherty, 2004; Smith *et al.* 2009), this effect could reflect a CEM-rendered vulnerability to blunted representation of positive affect. We were unable to disentangle anxiety and depression-specific effects here, given the extensive overlap in BSI subscale variance observed in this sample. However, consistent with prior work linking reward circuitry abnormalities to early life stress (Dillon *et al.* 2009; Mehta *et al.* 2010) and major depression (Pizzagalli *et al.* 2009; Pizzagalli, 2014), these findings hint at an alternative mechanistic pathway linking CEM to future psychopathology via blunted emotional responsivity to positive-valence (or rewarding) emotional stimuli.

There are several limitations to the current study. Importantly, the design of this study was cross-sectional and retrospective and the results were correlational in nature. As such, we were unable to acquire measurements of CEM, neural characteristics, and anxiety in successive order to establish temporal precedence. Thus, we are unable to draw definitive conclusions on the causal effects of CEM on brain function/structure or how any such effects may influence susceptibility to development of anxiety. Although the analytic approach of the current study was informed by theory and prior evidence, longitudinal studies are necessary to establish that CEM exerts

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effects on brain structure and function which promote susceptibility to the emergence of later anxiety symptoms. There are also other interpretations of the current findings aside from the proposed maltreatment threat-priming mechanism promoting manifestation of anxiety, including the possibility that these neural effects relate to other processes, influences, or vulnerabilities that co-occur with maltreatment and anxiety symptoms. Thus, the primary utility of the current findings lies in hypothesis-generation and informing design of future studies. Second, the sample utilized was composed of healthy participants as well as those with a variety of clinical and non-clinical anxiety manifestations. Given power constraints, we are unable to determine whether mediation effects are specific to a particular syndromal manifestation or whether diagnostic status impacted the strength of mediation effects. However, the current analysis is most consistent with the dimensional approach to psychopathology laid out in the NIMH RDoC (Insel *et al.* 2010; Insel, 2014) in its focus on developmental factors that may contribute to alteration in the domain of negative (and positive) valence brain systems. Third, many of the clinical anxiety participants met criteria for comorbid depressive disorders, and this may reduce specificity of the results to the relationship between CEM and anxiety. However, inclusion of these subjects is also consistent with the high comorbidity among anxiety/depressive disorders in the population (Kessler *et al.* 2005) as well as the substantial overlap of neurocircuitry abnormalities in both types of disorders (Etkin & Wager, 2007; Hamilton *et al.* 2012). Fourth, the majority of the sample was composed of adult Caucasian females with low levels of CEM and anxiety symptoms, though these measures did range from none to severe. Thus, these results may not generalize well to male populations or other ethnic groups, and the negative skew towards low levels of symptoms and maltreatment experiences may not have provided optimal power to detect effects. Fifth, the emotion-processing task used here presents two faces with matching emotional expressions in the presence of a third, non-congruent emotional expression on each trial. Thus, the results of this study are not directly comparable to those presenting single faces or non-facial threat stimuli. Sixth, mediation model fit measures were generally poor when constraining the direct effect to zero for both the proposed mediation model (the brain mediating the CEM-anxiety relationship) and the alternative mediation model (anxiety mediating the relationship between CEM and the brain). However, the indirect effects for the proposed model were significant while those for the alternative model were not, indicating a partial (but not full) mediation effect of the brain on the CEM-anxiety relationship. Thus, the current findings must be considered preliminary in light of these factors, and future studies should attempt to incorporate additional variables to develop sophisticated multivariate models that can fully account for the relationship between CEM and anxiety (e.g. multiple indirect effects, moderated mediation, etc.). Finally, we did not collect information on current life stress or adult trauma across this sample of participants, which may have been useful in establishing the specificity of neural effects to childhood experiences.

In closing, this study provides strong preliminary evidence supporting a neurodevelopmental mechanism linking CEM to anxiety in adulthood. This evidence suggests CEM exaggerates bottom-up emotional reactivity and attenuates top-down regulatory control when encountering negative-valence and/or threat-conveying emotional cues, which is consistent with existing evidence for emotional dysregulation as a psychological characteristic in survivors of childhood maltreatment (Wright *et al.* 2009; Pechtel & Pizzagalli, 2010; Tottenham *et al.* 2010). It is notable the mediation effects observed here, though statistically significant, were subtle in magnitude and accounted for only 1–3% of the total variance in anxiety symptoms. This fact is encouraging on two fronts – first, subtle influences of developmental factors on *in-vivo* dynamics of the adult brain are detectable much later in life and can be used to postulate mechanisms related to later mental health outcomes; and second, there is still a great deal of individual variability in neural characteristics left to be explored that may reflect other parallel or intersecting developmental pathways to anxiety in adulthood. We hope the effects demonstrated here may provide further impetus for the consideration of developmental characteristics in systems neuroscience etiological models of anxiety and lead to the undertaking of more rigorous longitudinal studies. These studies will be crucial in supporting or refuting results from retrospective investigations, and will sharpen insights into other developmental considerations such as neurodevelopmental trajectories, sensitive periods, and transactional relationships between individual characteristics conferring risk and resilience (Casey *et al.* 2014). Such efforts will hopefully lead to the identification of several distinct developmental pathways to anxiety disorders with unique and shared neural mechanisms, potentially informing development or modification of interventions to target 'ecophenotypic' variants of psychopathology (Teicher & Samson, 2013).

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291715002603.

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Declaration of Interest

None.

References

Amir N, Klumpp H, Elias J, Bedwell JS, Yanasak N, Miller LS (2005). Increased activation of the anterior cingulate cortex during processing of disgust faces in individuals with social phobia. *Biological Psychiatry* **57**, 975–981.

Amir N, Taylor CT, Bomyea JA, Badour CL (2009). Temporal allocation of attention toward threat in individuals with posttraumatic stress symptoms. *Journal of Anxiety Disorders* **23**, 1080–1085.

Amodio DM, Frith CD (2006). Meeting of minds: the medial frontal cortex and social cognition. *Nature Reviews Neuroscience* **7**, 268–277.

Asami T, Yamasue H, Hayano F, Nakamura M, Uehara K, Otsuka T, Roppongi T, Nihashi N, Inoue T, Hirayasu Y (2009). Sexually dimorphic gray matter volume reduction in patients with panic disorder. *Psychiatry Research* **173**, 128–134.

Ashburner J, Friston KJ (2000). Voxel-based morphometry – the methods. *NeuroImage* **11**, 805–821.

Bernstein DP, Stein JA, Newcomb MD, Walker E, Pogge D, Ahluvalia T, Stokes J, Handelsman L, Medrano M, Desmond D, Zule W (2003). Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse & Neglect* **27**, 169–190.

Bertolino A, Arciero G, Rubino V, Latorre V, De Candia M, Mazzola V, Blasi G, Caforio G, Hariri A, Kolachana B, Nardini M, Weinberger DR, Scarabino T (2005). Variation of human amygdala response during threatening stimuli as a function of 5′HTTLPR genotype and personality style. *Biological Psychiatry* **57**, 1517–1525.

Blake DD, Weathers FW, Nagy LM, Kaloupek DG (1995). The development of a Clinician-Administered PTSD Scale. *Journal of Traumatic Stress* **8**, 75–90.

Bonne O, Vythilingam M, Inagaki M, Wood S, Neumeister A, Nugent AC, Snow J, Luckenbaugh DA, Bain EE, Drevets WC, Charney DS (2008). Reduced posterior hippocampal volume in posttraumatic stress disorder. *Journal of Clinical Psychiatry* **69**, 1087–1091.

Burghy CA, Stodola DE, Ruttle PL, Molloy EK, Armstrong JM, Oler JA, Fox ME, Hayes AS, Kalin NH, Essex MJ, Davidson RJ, Birn RM (2012). Developmental pathways to amygdala-prefrontal function and internalizing symptoms in adolescence. *Nature Neuroscience* **15**, 1736–1741.

Carrion VG, Weems CF, Reiss AL (2007). Stress predicts brain changes in children: a pilot longitudinal study on youth stress, posttraumatic stress disorder, and the hippocampus. *Pediatrics* **119**, 509–516.

Casey BJ, Oliveri ME, Insel T (2014). A neurodevelopmental perspective on the research domain criteria (RDoC) framework. *Biological Psychiatry* **76**, 350–353.

Comte M, Schon D, Coull JT, Reynaud E, Khalfa S, Belzeaux R, Ibrahim EC, Guedj E, Blin O, Weinberger DR, Fakra E (2014). Dissociating bottom-up and top-down mechanisms in the cortico-limbic system during emotion processing. *Cerebral Cortex* (*New York*). Published online 27 August 2015. doi:10.1093/cercor/bhu185.

Cox RW (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research, an International Journal* **29**, 162–173.

Cuthbert BN (2014). The RDoC framework: facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. *World Psychiatry* **13**, 28–35.

Dannlowski U, Kugel H, Huber F, Stuhrmann A, Redlich R, Grotegerd D, Dohm K, Sehlmeyer C, Konrad C, Baune BT, Arolt V, Heindel W, Zwitserlood P, Suslow T (2013). Childhood maltreatment is associated with an automatic negative emotion processing bias in the amygdala. *Human Brain Mapping* **34**, 2899–2909.

Dannlowski U, Stuhrmann A, Beutelmann V, Zwanzger P, Lenzen T, Grotegerd D, Domschke K, Hohoff C, Ohrmann P, Bauer J, Lindner C, Postert C, Konrad C, Arolt V, Heindel W, Suslow T, Kugel H (2012). Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. *Biological Psychiatry* **71**, 286–293.

Delgado MR, Nearing KI, Ledoux JE, Phelps EA (2008). Neural circuitry underlying the regulation of conditioned fear and its relation to extinction. *Neuron* **59**, 829–838.

Derogatis LR, Fitzpatrick M (2004). The SCL-90-R, the Brief Symptom Inventory (BSI), and the BSI-18. In *The Use of Psychological Testing for Treatment Panning and Outcomes Assessment: Volume 3: Instruments for Adults*, 3rd edn. (ed. M. E. Maruish), pp. 1–41. Lawrence Erlbaum Associates Publishers: Mahwah, NJ, US.

Dillon DG, Holmes AJ, Birk JL, Brooks N, Lyons-Ruth K, Pizzagalli DA (2009). Childhood adversity is associated with left basal ganglia dysfunction during reward anticipation in adulthood. *Biological Psychiatry* **66**, 206–213.

Eckart C, Stoppel C, Kaufmann J, Tempelmann C, Hinrichs H, Elbert T, Heinze HJ, Kolassa IT (2010). Structural alterations in lateral prefrontal, parietal and posterior midline regions of men with chronic posttraumatic stress disorder. *Journal of Psychiatry & Neuroscience* **35**, 100010.

Eden AS, Schreiber J, Anwander A, Keuper K, Laeger I, Zwanzger P, Zwitserlood P, Kugel H, Dobel C (2015). Emotion regulation and trait anxiety are predicted by the microstructure of fibers between amygdala and prefrontal cortex. *Journal of Neuroscience* **35**, 6020–6027.

Egeland B (2009). Taking stock: childhood emotional maltreatment and developmental psychopathology. *Child Abuse & Neglect* **33**, 22–26.

Etkin A, Prater KE, Hoeft F, Menon V, Schatzberg AF (2010). Failure of anterior cingulate activation and connectivity with the amygdala during implicit regulation of emotional processing in generalized anxiety disorder. *American Journal of Psychiatry* **165**, 545–554.

Etkin A, Schatzberg AF (2011). Common abnormalities and disorder-specific compensation during implicit regulation of emotional processing in generalized anxiety and major depressive disorders. *American Journal of Psychiatry* **168**, 968–978.

Etkin A, Wager TD (2007). Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *American Journal of Psychiatry* **164**, 1476–1488.

First MB, Spitzer RL, Gibbon M, Williams JBW (1998). *Structured Clinical Interview for DSM-IV Axis I Disorders*. Biometrics Research, New York State Psychiatric Institute: New York.

Fonzo GA, Flagan TM, Sullivan S, Allard CB, Grimes EM, Simmons AN, Paulus MP, Stein MB (2013). Neural functional and structural correlates of childhood maltreatment in women with intimate-partner violence-related posttraumatic stress disorder. *Psychiatry Research: Neuroimaging* **211**, 93–103.

Fonzo GA, Ramsawh HJ, Flagan TM, Sullivan SG, Letamendi A, Simmons AN, Paulus MP, Stein MB (2015). Common and disorder-specific neural responses to emotional faces in generalised anxiety, social anxiety and panic disorders. *British Journal of Psychiatry* **206**, 206–215.

Fonzo GA, Simmons AN, Thorp SR, Norman SB, Paulus MP, Stein MB (2010). Exaggerated and disconnected insular-amygdalar blood oxygenation level-dependent response to threat-related emotional faces in women with intimate-partner violence posttraumatic stress disorder. *Biological Psychiatry* **68**, 433–441.

Fusar-Poli P, Placentino A, Carletti F, Landi P, Allen P, Surguladze S, Benedetti F, Abbamonte M, Gasparotti R, Barale F, Perez J, McGuire P, Politi P (2009). Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. *Journal of Psychiatry & Neuroscience* **34**, 418–432.

Gatt JM, Williams LM, Schofield PR, Dobson-Stone C, Paul RH, Grieve SM, Clark CR, Gordon E, Nemeroff CB (2010). Impact of the HTR3A gene with early life trauma on emotional brain networks and depressed mood. *Depression and Anxiety* **27**, 752–759.

Gibb BE, Schofield CA, Coles ME (2009). Reported history of childhood abuse and young adults' information-processing biases for facial displays of emotion. *Child Maltreatment* **14**, 148–156.

Goldin PR, Manber T, Hakimi S, Canli T, Gross JJ (2009). Neural bases of social anxiety disorder: emotional reactivity and cognitive regulation during social and physical threat. *Archives of General Psychiatry* **66**, 170–180.

Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS (2001). A voxel-based morphometric study of ageing in 465 normal adult human brains. *NeuroImage* **14**, 21–36.

Hamilton JP, Etkin A, Furman DJ, Lemus MG, Johnson RF, Gotlib IH (2012). Functional neuroimaging of major depressive disorder: a meta-analysis and new integration of base line activation and neural response data. *The American Journal of Psychiatry* **169**, 693–703.

Hariri AR, Drabant EM, Munoz KE, Kolachana BS, Mattay VS, Egan MF, Weinberger DR (2005). A susceptibility gene for affective disorders and the response of the human amygdala. *Archives of General Psychiatry* **62**, 146–152.

Hayes AF (2013). *Introduction to Mediation, Moderation, and Conditional Process Analysis*. Guilford Press: New York.

Herringa RJ, Birn RM, Ruttle PL, Burghy CA, Stodola DE, Davidson RJ, Essex MJ (2013). Childhood maltreatment is associated with altered fear circuitry and increased internalizing symptoms by late adolescence. *Proceedings of the National Academy of Sciences USA* **110**, 19119–19124.

Hettema JM, Kettenmann B, Ahluwalia V, McCarthy C, Kates WR, Schmitt JE, Silberg JL, Neale MC, Kendler KS, Fatouros P (2012). Pilot multimodal twin imaging study of generalized anxiety disorder. *Depression and Anxiety* **29**, 202–209.

IBM SPSS Inc. (2010). IBM SPSS Statistics for Windows, version 19.0. Released 2010. Armonk, NY: IBM Corp.

Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, Sanislow C, Wang P (2010). Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *American Journal of Psychiatry* **167**, 748–751.

Insel TR (2014). The NIMH Research Domain Criteria (RDoC) Project: precision medicine for psychiatry. *American Journal of Psychiatry* **171**, 395–397.

Karl A, Schaefer M, Malta LS, Dorfel D, Rohleder N, Werner A (2006). A meta-analysis of structural brain abnormalities in PTSD. *Neuroscience and Biobehavioral Reviews* **30**, 1004–1031.

Kelley K (2007*a*). Methods for the behavioral, educational, and social sciences: an R package. *Behavior Research Methods* **39**, 979–984.

Kelley K (2007*b*). Confidence intervals for standardized effect sizes: theory, application, and implementation. *Journal of Statistical Software* **20**, 1–24.

Kelley K, Lai K (2012). MBESS version 3.3.3 (https://cran.r-project.org/package=MBESS).

Kelly PA, Viding E, Wallace GL, Schaer M, De Brito SA, Robustelli B, McCrory EJ (2013). Cortical thickness, surface area, and gyrification abnormalities in children exposed to maltreatment: neural markers of vulnerability? *Biological Psychiatry* **74**, 845–852.

Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry* **62**, 617–627.

Klumpp H, Amir N (2009). Examination of vigilance and disengagement of threat in social anxiety with a probe detection task. *Anxiety, Stress & Coping* **22**, 283–296.

Kremen WS, O'Brien RC, Panizzon MS, Prom-Wormley E, Eaves LJ, Eisen SA, Eyler LT, Hauger RL, Fennema-Notestine C, Fischl B, Grant MD, Hellhammer DH, Jak

AJ, Jacobson KC, Jernigan TL, Lupien SJ, Lyons MJ, Mendoza SP, Neale MC, Seidman LJ, Thermenos HW, Tsuang MT, Dale AM, Franz CE (2010). Salivary cortisol and prefrontal cortical thickness in middle-aged men: a twin study. *NeuroImage* **53**, 1093–1102.

Kuo JR, Goldin PR, Werner K, Heimberg RG, Gross JJ (2011). Childhood trauma and current psychological functioning in adults with social anxiety disorder. *Journal of Anxiety Disorders* **25**, 467–473.

Labuschagne I, Phan KL, Wood A, Angstadt M, Chua P, Heinrichs M, Stout JC, Nathan PJ (2012). Medial frontal hyperactivity to sad faces in generalized social anxiety disorder and modulation by oxytocin. *International Journal of Neuropsychopharmacology* **15**, 883–896.

Liberzon I, Garfinkel SN (2009). Functional neuroimaging in post-traumatic stress disorder. In *Post-Traumatic Stress Disorder: Basic Science and Clinical Practice* (ed. P. J. Shiromani, T. M. Keane and J. E. LeDoux), pp. 297–317. Humana Press: Totowa, NJ, US.

MacKinnon DP, Fairchild AJ, Fritz MS (2007). Mediation analysis. *Annual Review of Psychology* **58**, 593–614.

Marsh AA, Ambady N, Kleck RE (2005). The effects of fear and anger facial expressions on approach- and avoidance-related behaviors. *Emotion* (*Washington, D.C*) **5**, 119–124.

Marusak HA, Martin KR, Etkin A, Thomason ME (2015). Childhood trauma exposure disrupts the automatic regulation of emotional processing. *Neuropsychopharmacology* **40**, 1250–1258.

Masten CL, Guyer AE, Hodgdon HB, McClure EB, Charney DS, Ernst M, Kaufman J, Pine DS, Monk CS (2008). Recognition of facial emotions among maltreated children with high rates of post-traumatic stress disorder. *Child Abuse & Neglect* **32**, 139–153.

Mehta MA, Gore-Langton E, Golembo N, Colvert E, Williams SC, Sonuga-Barke E (2010). Hyporesponsive reward anticipation in the basal ganglia following severe institutional deprivation early in life. *Journal of Cognitive Neuroscience* **22**, 2316–2325.

Mendlowicz MV, Stein MB (2000). Quality of life in individuals with anxiety disorders. *American Journal of Psychiatry* **157**, 669–682.

Milad MR, Pitman RK, Ellis CB, Gold AL, Shin LM, Lasko NB, Zeidan MA, Handwerger K, Orr SP, Rauch SL (2009). Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. *Biological Psychiatry* **66**, 1075–1082.

Muthén LK, Muthén BO (1998–2012). *Mplus User's Guide*, 7th edn. Muthén & Muthén: Los Angeles.

Nolte T, Guiney J, Fonagy P, Mayes LC, Luyten P (2011). Interpersonal stress regulation and the development of anxiety disorders: an attachment-based developmental framework. *Frontiers in Behavioral Neuroscience* **5**, 55.

Ochsner KN, Gross JJ (2005). The cognitive control of emotion. *Trends in Cognitive Sciences* **9**, 242–249.

O'Doherty JP (2004). Reward representations and reward-related learning in the human brain: insights from neuroimaging. *Current Opinion in Neurobiology* **14**, 769–776.

Paulus MP (2008). The role of neuroimaging for the diagnosis and treatment of anxiety disorders. *Depression and Anxiety* **25**, 348–356.

Paulus MP, Feinstein JS, Castillo G, Simmons AN, Stein MB (2005). Dose-Dependent Decrease of Activation in Bilateral Amygdala and Insula by Lorazepam During Emotion Processing. *Archives of General Psychiatry* **62**, 282–288.

Pechtel P, Pizzagalli DA (2010). Effects of early life stress on cognitive and affective function: an integrated review of human literature. *Psychopharmacology* **14**, 55–70.

Phillips ML, Ladouceur CD, Drevets WC (2008). A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. *Molecular Psychiatry* **13**, 829, 833–857.

Pillay SS, Rogowska J, Gruber SA, Simpson N, Yurgelun-Todd DA (2007). Recognition of happy facial affect in panic disorder: an fMRI study. *Journal of Anxiety Disorders* **21**, 381–393.

Pizzagalli DA (2014). Depression, stress, and anhedonia: toward a synthesis and integrated model. *Annual Review of Clinical Psychology* **10**, 393–423.

Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R, Dougherty DD, Iosifescu DV, Rauch SL, Fava M (2009). Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. *American Journal of Psychiatry* **166**, 702–710.

R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria (http://www.R-project.org/).

Ray RD, Zald DH (2012). Anatomical insights into the interaction of emotion and cognition in the prefrontal cortex. *Neuroscience and Biobehavioral Reviews* **36**, 479–501.

Sabatinelli D, Fortune EE, Li Q, Siddiqui A, Krafft C, Oliver WT, Beck S, Jeffries J (2011). Emotional perception: meta-analyses of face and natural scene processing. *NeuroImage* **54**, 2524–2533.

Sapolsky RM (2000). Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Archives of General Psychiatry* **57**, 925–935.

Shaw P, Kabani NJ, Lerch JP, Eckstrand K, Lenroot R, Gogtay N, Greenstein D, Clasen L, Evans A, Rapoport JL, Giedd JN, Wise SP (2008). Neurodevelopmental trajectories of the human cerebral cortex. *Journal of Neuroscience* **28**, 3586–3594.

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry* **59** (Suppl. 20), 22–33; quiz 34–57.

Simon NM, Herlands NN, Marks EH, Mancini C, Letamendi A, Li Z, Pollack MH, Van Ameringen M, Stein MB (2009). Childhood maltreatment linked to greater symptom severity and poorer quality of life and function in social anxiety disorder. *Depression and Anxiety* **26**, 1027–1032.

Simpson HB (2012). The rdoc project: a new paradigm for investigating the pathophysiology of anxiety. *Depression and Anxiety* **29**, 251–252.

Smith KS, Tindell AJ, Aldridge JW, Berridge KC (2009). Ventral pallidum roles in reward and motivation. *Behavioural Brain Research* **196**, 155–167.

Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady JM, Matthews PM (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage* **23** (Suppl. 1), S208–S219.

Sobanski T, Wagner G, Peikert G, Gruhn U, Schluttig K, Sauer H, Schlosser R (2010). Temporal and right frontal lobe alterations in panic disorder: a quantitative volumetric and voxel-based morphometric MRI study. *Psychological Medicine* **40**, 1879–1886.

Spinhoven P, Elzinga BM, Hovens JGFM, Roelofs K, Zitman FG, van Oppen P, Penninx BWJH (2010). The specificity of childhood adversities and negative life events across the life span to anxiety and depressive disorders. *Journal of Affective Disorders* **126**, 103–112.

Stein MB, Simmons AN, Feinstein JS, Paulus MP (2007). Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. *American Journal of Psychiatry* **164**, 318–327.

Talairach J, Tournoux P (1998). *Co-planar Stereotaxic Atlas of the Human Brain: 3-Dimensional Proportional System: an Approach to Cerebral Imaging*. Thieme Medical Publishers: New York.

Teicher MH, Samson JA (2013). Childhood maltreatment and psychopathology: a case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. *The American Journal of Psychiatry* **170**, 1114–1133.

Thomaes K, Dorrepaal E, Draijer N, de Ruiter MB, van Balkom AJ, Smit JH, Veltman DJ (2010). Reduced anterior cingulate and orbitofrontal volumes in child abuse-related complex PTSD. *Journal of Clinical Psychiatry* **71**, 1636–1644.

Tottenham N, Hare TA, Quinn BT, McCarry TW, Nurse M, Gilhooly T, Millner A, Galvan A, Davidson MC, Eigsti I, Thomas KM, Freed PJ, Booma ES, Gunnar MR, Altemus M, Aronson J, Casey BJ (2010). Prolonged institutional rearing is associated with atypically large amygdala volume and difficulties in emotion regulation. *Developmental Science* **13**, 46–61.

Uchida RR, Del-Ben CM, Busatto GF, Duran FL, Guimaraes FS, Crippa JA, Araujo D, Santos AC, Graeff FG (2008). Regional gray matter abnormalities in panic disorder: a voxel-based morphometry study. *Psychiatry Research* **163**, 21–29.

van Harmelen AL, van Tol MJ, Dalgleish T, van der Wee NJ, Veltman DJ, Aleman A, Spinhoven P, Penninx BW, Elzinga BM (2014). Hypoactive medial prefrontal cortex functioning in adults reporting childhood emotional maltreatment. *Social Cognitive and Affective Neuroscience* **9**, 2026–2033.

van Harmelen AL, van Tol MJ, Demenescu LR, van der Wee NJ, Veltman DJ, Aleman A, van Buchem MA, Spinhoven P, Penninx BW, Elzinga BM (2013). Enhanced amygdala reactivity to emotional faces in adults reporting childhood emotional maltreatment. *Social Cognitive and Affective Neuroscience* **8**, 362–369.

van Harmelen AL, van Tol MJ, van der Wee NJ, Veltman DJ, Aleman A, Spinhoven P, van Buchem MA, Zitman FG, Penninx BW, Elzinga BM (2010). Reduced medial prefrontal cortex volume in adults reporting childhood emotional maltreatment. *Biological Psychiatry* **68**, 832–838.

Waters AM, Bradley BP, Mogg K (2014). Biased attention to threat in paediatric anxiety disorders (generalized anxiety disorder, social phobia, specific phobia, separation anxiety disorder) as a function of 'distress' *versus* 'fear' diagnostic categorization. *Psychological Medicine* **44**, 607–616.

Williams LM, Gatt JM, Schofield PR, Olivieri G, Peduto A, Gordon E (2009). 'Negativity bias' in risk for depression and anxiety: brain-body fear circuitry correlates, 5-HTT-LPR and early life stress. *NeuroImage* **47**, 804–814.

Woodward SH, Schaer M, Kaloupek DG, Cediel L, Eliez S (2009). Smaller global and regional cortical volume in combat-related posttraumatic stress disorder. *Archives of General Psychiatry* **66**, 1373–1382.

Woon FL, Hedges DW (2008). Hippocampal and amygdala volumes in children and adults with childhood maltreatment-related posttraumatic stress disorder: a meta-analysis. *Hippocampus* **18**, 729–736.

Wright MO, Crawford E, Del Castillo D (2009). Childhood emotional maltreatment and later psychological distress among college students: the mediating role of maladaptive schemas. *Child Abuse & Neglect* **33**, 59–68.

Yoo HK, Kim MJ, Kim SJ, Sung YH, Sim ME, Lee YS, Song SY, Kee BS, Lyoo IK (2005). Putaminal gray matter volume decrease in panic disorder: an optimized voxel-based morphometry study. *European Journal of Neuroscience* **22**, 2089–2094.

Zlotnick C, Johnson J, Kohn R, Vicente B, Rioseco P, Saldivia S (2008). Childhood trauma, trauma in adulthood, and psychiatric diagnoses: results from a community sample. *Comprehensive Psychiatry* **49**, 163–169.