Early Life Stress and Trauma and Enhanced Limbic Activation to Emotionally Valenced Faces in Depressed and Healthy Children

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Objective: Previous studies have examined the relationships between structural brain characteristics and early life stress in adults. However, there is limited evidence for functional brain variation associated with early life stress in children. We hypothesized that early life stress and trauma would be associated with increased functional brain activation response to negative emotional faces in children with and without a history of depression. **Method:** Psychiatric diagnosis and life events in children (starting at age 3–5 years) were assessed in a longitudinal study. A follow-up magnetic resonance imaging (MRI) study acquired data (N = 115 at ages 7–12, 51% girls) on functional brain response to fearful, sad, and happy faces relative to neutral faces. We used a region-of-interest mask within cortico-limbic areas and conducted regression analyses and repeated-measures analysis of covariance. **Results:** Greater activation responses to fearful, sad, and happy faces in the amygdala and its neighboring regions were found in children with greater life stress. Moreover, an association between life stress and left hippocampal and globus pallidus activity depended on children's diagnostic status. Finally, all children with greater life trauma showed greater bilateral amygdala and cingulate activity specific to sad faces but not the other emotional faces, although right amygdala activity was moderated by psychiatric status. **Conclusions:** These findings suggest that limbic hyperactivity may be a biomarker of early life stress and trauma in children and may have implications in the risk trajectory for depression and other stress-related disorders. However, this pattern varied based on emotion type and history of psychopathology. J. Am. Acad. Child Adolesc. Psychiatry, 2014;53(7):800–813. **Key Words:** early life stress, early life trauma, fMRI, emotion, child

Experiences of chronic stress and trauma have deleterious effects on neurobiological, affective, and behavioral functions.[1] For example, animal studies have found that chronic exposure to stress changes molecular and cellular activities, such as dendritic remodeling,[2] shifts in the dendritic spine population,[3] reduced axon density,[4] decreased astroglial cells,[5] and altered neuropeptide mRNA expression[6] in the cortico-limbic-striatal system, including the prefrontal cortex (PFC), amygdala, hippocampus, caudate putamen, and nucleus accumbens. Likewise, human adults who report chronic stress exhibit reduced volume in the amygdala, hippocampus, medial and dorsolateral PFC, anterior cingulate cortex (ACC), and subgenual ACC (sgACC), striatum, and insula,[7-10] as well as increased functional response to emotional stimuli in the amygdala, hippocampus, ventromedial PFC, and ACC.[10-12]

Structural and functional brain differences similar to those found in currently stressed adults may also be present in previously stressed individuals.[13] Animal studies have shown that early life stress (e.g., abuse by mother) leads to functional amygdala changes in adolescence, including increased activation of protein kinase[14] and increased cFos-labeled neural activation.[15] In humans, adults who retrospectively report child maltreatment show altered volume or functional activity in the hippocampus, amygdala, PFC, ACC, and other limbic regions.[8-10,12]

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Some additional studies have focused on children who experienced a specific type of stressor (e.g., low maternal support) and have found that these children showed altered volume in the hippocampus,[16,17] orbitofrontal cortex,[18] and amygdala.[19]

In contrast to these structural imaging studies, evidence for functional brain changes in children with cumulative stress/trauma is limited. Some functional magnetic resonance imaging (fMRI) studies report that, compared to healthy children, children with a history of institutional care showed increased bilateral amygdala activity in response to fearful faces.[20] Although these previous studies provided evidence of a relationship between early life stress/trauma and functional amygdala activity in children, it focused on a unique type of early life stress/trauma (i.e., institutional rearing) in a sample of children both with and without psychopathology. Hence, it still remains unclear whether amygdala hyperactivity occurs in relation to stressful/traumatic life events other than early institutionalization, and whether the presence or absence of psychopathology in children influences the relationship between early stress and functional amygdala changes.

It is important to investigate the influence of psychopathology, particularly major depressive disorder (MDD), on the relationship between early life stress or trauma and functional brain activity in children, because stress is thought to contribute to the development of MDD,[21,22] and high levels of stressful or traumatic life events in childhood increase the risk for preschool-onset MDD (PO-MDD).[23] Thus, the goal of the current study was to examine the relationships between early life stress/trauma and functional brain response to faces portraying negative emotions in a sample of school-aged children with and without a history of psychiatric disorders.

To achieve this goal, we tested 2 hypotheses. First, we hypothesized that early life stress/trauma would be associated with an increased functional activation response to negative emotion stimuli in the amygdala, hippocampus, basal ganglia, medial and dorsolateral PFC, and/or ACC. These regions have been shown to be sensitive to stress in previous animal and human studies,[10,13,22,24-28] and functional hyperactivity response to negative emotion in some of these brain regions has been associated with a history of child maltreatment.[10,12,20] To clarify whether these functional brain changes were specific to negatively valenced emotions, the present study examined functional brain response to both negative and positive stimuli in relation to early life stress and trauma. The present study used fearful and sad faces as negative stimuli and happy faces as positive stimuli because these stimuli have been commonly used in neuroimaging research on the effects of maltreatment,[20,29] MDD,[30,31] and mood-congruent brain reactivity,[32-34] compared to the other facial stimuli.

Second, we also hypothesized that the effects of life stress/trauma on functional brain activity would be exacerbated in the context of a positive early history of MDD. This hypothesis was based in part on the findings that PO-MDD is associated with neurobiological alterations in stress-responsive brain regions, including reduced hippocampal volume,[35] decreased functional connectivity between sgACC and cognitive control regions,[36] and greater functional activation response to sad faces in the amygdala and hippocampus.[30,31]

METHOD

Study Participants

Between 2003 and 2005, preschoolers between the ages of 3.0 and 5.11 years were recruited from the St. Louis metropolitan area, using the Preschool Feelings Checklist,[37,38] and preschoolers with symptoms of MDD were oversampled. With written consent from parents and assent from the children, a sample of 306 children without head trauma, neurological disease, severe developmental delays, or premature birth were enrolled in the Validation of Preschool Depression Study, a longitudinal study approved by the Institutional Review Board at the Washington University School of Medicine.

A total of 168 children completed follow-up annual waves over a 5- to 8-year period, after which an MRI study at school age was conducted. Forty-one additional healthy children were recruited for the MRI study to increase the size of the healthy control group (age matched to the children with psychiatric disorders). A total of 209 children between the ages of 7 and 12 years participated in a training sequence using a mock scanner, as described previously.[35] After applying criteria for image quality (detailed below), 148 children were screened, and 115 medication-free children who did not show structural brain abnormalities (59 girls and 56 boys; mean age, 9.88 $\pm$ 1.33 years) were included in the present study. A total of 33 subjects were excluded because of these, 27 had psychotropic medication before scanning, 3 had brain abnormalities, 1 had both, and 2 had missing diagnostic data.

Diagnostic Assessment

Trained interviewers conducted in-person annual interview sessions using an age-appropriate diagnostic

interview: the Preschool Age Psychiatric Assessment (PAPA) for preschool-age children[39,40] and the Child and Adolescent Psychiatric Assessment (CAPA) for school-age children.[41,42] Methods to avoid drift and to maintain reliability and quality control, including review of 20% audiotaped interviews with a master clinician, were used.[43] The PAPA and CAPA consist of a series of developmentally appropriate questions covering the *DSM-IV* criteria for Axis I disorders of childhood. Parent-reports were used for children less than 8.0 years of age, and child- and parent-reports were combined for children 8.0 years or more of age. Standard *DSM-IV* algorithms were applied to derive all diagnoses, with the exception that the 2-week duration of symptoms requirement for MDD was set aside for subjects who were younger than 6.0 years based on data suggesting that it is not an appropriate threshold for this developmental period.[38,44,45]

Based on diagnoses using the PAPA and CAPA, children were classified into 1 of the following 3 groups: the MDD group (n = 42) if they met *DSM-IV* criteria for MDD at any annual wave before the MRI scan; the other psychiatric control (OPC) group (n = 22) if they met *DSM-IV* criteria for any Axis I disorder (ADHD, ODD, CD, and anxiety disorders) without MDD comorbidity at any wave before the scan; and the healthy control group (n = 51) if they did not meet *DSM-IV* criteria for any Axis I disorder across all waves prior to scan. In addition, PAPA and CAPA items in the MDD module were used to derive a 'core' *DSM-IV* MDD symptom score at each wave.[46] Then, the number of core MDD symptoms at the time of scan was summed into a core MDD severity score.

Life Events

The PAPA and CAPA also assessed how frequently children experienced stressful and traumatic life events within the last year, as reported by their caregiver annually at each study wave. A subgroup of healthy children who were newly added to the MRI study retrospectively reported how frequently they had ever experienced any stressful and traumatic events in their lives. The PAPA and CAPA have established test–retest reliability for parental reports of life events[47] and define early life trauma as any type of emotionally harmful life events up to school age (i.e., in the past 7–12 years), including, for example, physical and sexual abuse, automobile accidents, natural disaster, or death of sibling; we defined early life stress as any type of less intense but still distressing life event up to school age, including, for example, death of a pet, change in daycare/school, and birth of a new sibling.

Functional Task and Stimuli

The fMRI task was a facial emotion–processing task using the MacArthur Network Face Stimuli Set, a validated stimulus set that contains 43 different actors from different ethnic/cultural backgrounds.[48] Children were shown faces that varied in affective content (fearful, sad, angry, happy, and neutral) from 10 sets of adults and were asked to decide whether the face was male or female. The purpose of this gender judgment was to ensure that all subjects were awake and viewed the stimuli, and accuracy was very high. We chose to use a task that did not require explicit attention to the emotional content because of evidence that heightened amygdala responses associated with MDD may be more apparent with tasks that do not explicitly require a focus on the emotional content.[49,50] In addition, we created intermediate affective expressions by morphing the neutral expression for each individual with that individual's emotional expression (MorphAge software). We included these stimuli because behavioral and brain activation biases in depression may be more apparent when viewing emotional expressions that are less intense. Thus, each "actor" in the stimulus set provided a total of 9 facial expressions (neutral, 50% fearful, sad, angry, and happy, 100% fearful, sad, angry, and happy). Children had not previously seen any of these faces, and each stimulus was presented once (no repeats) for 2,500 milliseconds, followed by an intertrial interval (ITI) ranging between 500 and 6,500 milliseconds. The task was programmed in PsyScope, and behavioral responses in the scanner were acquired via a fiberoptic button box interfaced with the PsyScope button box. Each run consisted of 45 stimuli, 5 from each of the 9 conditions. Selection of the specific face to be presented on each trial was determined by PsyScope using a random without replacement algorithm, within the constraint of the number of faces of each type to be presented in a run. The image projected on a screen behind the subject's head was viewed by a mirror positioned approximately 8 cm above the subject's face. For the current analyses, activation values for the fear (50% and 100% fear > neutral), the sad (50% and 100% sad > neutral), and the happy (50% and 100% happy > neutral) conditions were used.

Imaging Data Acquisition

Imaging data acquisition, including structural, functional, and diffusion tensor imaging, was performed on a 3.0-Tesla TIM TRIO Siemens whole-body system. The whole MRI session took approximately 1 hour and 15 minutes. During the scan, children completed a film-processing task (~5 minutes), 2 face task runs (~12 minutes), 2 resting state runs (~12 minutes), and 2 diffusion tensor imaging runs (~15 minutes). Only functional imaging data acquired during the facial emotion–processing task were used for the present study. Two 3-dimensional T1-weighted magnetization prepared rapid gradient echo (MPRAGE) scans (~6 minutes each; TR = 2,400 milliseconds, TE = 3.16 milliseconds, flip angle = 8°, voxel size 1 mm^3) were acquired in the sagittal plane. Blood oxygen level–dependent (BOLD) images during the face task were acquired with a T2*-weighted asymmetric spin-echo

echo-planar sequence (~5 minutes; TR = 2500 milliseconds, TE = 27 milliseconds, flip angle = 90°, voxel size = 4 mm^3) with a 12-channel head coil; for each functional run, 99 sets of 36 contiguous axial images with isotropic voxels (4 mm^3) were acquired parallel to the anterior–posterior commissure plane.

Functional Data Preprocessing

The fMRI data were preprocessed using the following steps: compensation for slice-dependent time shifts; removal of the first 4 images of each run to allow the BOLD signal to reach steady state; elimination of odd/even slice intensity differences due to interpolated acquisition; realignment of data acquired in each subject within and across runs to compensate for rigid body motion[51]; intensity normalization to a whole brain mode of 1,000; registration of the 3-dimensional structural volume (T1) to the atlas representative template in the Talairach coordinate system[52] using a 12-parameter affine transform and resampling to 1-mm^3 representation[51,53]; coregistration of the 3-dimensional fMRI volume to the T2, and the T2 to the participant's structural image; transformation of the fMRI to atlas space using a single affine 12-parameter transform that included resampling to a 3-mm^3 representation; and spatial smoothing using a 6-mm full-width-at-half-maximum Gaussian filter. Prior research has validated the use of this approach with children in our age range.[54,55]

Further processing of fMRI data was performed using in-house software (FIDL analysis package, http://www.nil.wustl.edu/labs/fidl/index.html) that was used in previously published studies.[30,31,35,56-61] Estimates of BOLD response to each face type in each subject were obtained using fixed-effects general linear models incorporating regressors for linear trend and baseline shifts. A hemodynamic response shape was assumed (Boynton function) and used to derive magnitude estimates relative to fixation baseline. These single-subject estimates were then entered into group-level analyses that treated subjects as random effects.

Image Quality Criteria

We applied stringent criteria for image data quality. First, the signal-to-noise ratio was calculated on the face task runs, and subjects with a signal-to-noise ratio greater than 200 were initially screened (n = 174 of 209). This is a loss rate of approximately 17%, which is typical for developmental neuroimaging studies. Second, a "motion scrubbing" procedure, previously validated corrections for head motion used for functional connectivity analysis,[62] was applied to the present task-related fMRI analysis by assessing framewise displacement based on the movement parameters.[63] In this procedure, framewise displacement detects the differential head motion from the previous frame summing across linear (x, y, z) and rotational displacements (yaw, pitch, roll, where degrees of rotation are converted to millimeters of movement by calculating displacement on the surface of a sphere with a radius of 50 mm) for any given frame (i.e., timepoint). A temporal mask was created to remove any frame with a sum displacement greater than 0.9 mm. This threshold was selected to be stringent and to remove any spikes in head motion while still maintaining the majority of the data. We retained 148 subjects who had more than 100 frames of data that survived scrubbing. Details on the validity and efficacy of this procedure have been reported previously.[64]

Data Analysis

Demographic and clinical differences (age, gender, handedness, family income at scan, average core MDD severity score across the assessments, and comorbidity) among the MDD, healthy, and OPC groups were tested using one-way analyses of variance (ANOVAs) or χ^2 tests. If the ANOVAs revealed significant group differences, post hoc tests with a Bonferroni correction were used. The total number of each of stressful and traumatic life events up to the scan was also compared between the groups. Each variable had 1 to 3 outliers with a standard score of 3 or greater, thus Winsorizing was performed such that these extreme values were set to the closest nonextreme value (with a standard score <3). If any demographic variable was related to diagnostic group or life events, we included that variable as covariate in subsequent analyses.

To examine the relationship between life events and functional brain activity, we used a priori region-of-interest (ROI) mask. As described above, the selected ROIs were those demonstrated to be relevant in affective processing associated with MDD: namely, the amygdala, hippocampus, basal ganglia, medial and dorsolateral PFC, and ACC. Anatomical templates for our mask were derived from prior work[65-67] (Figure S1, available online). The PFC mask was defined on an atlas-representative image using the boundaries described by Rajkowska and Goldman-Rakic.[68,69] The cingulate mask used centroids of activation identified in prior studies[49,70,71] around which we drew 25-mm diameter spherical ROIs edited to respect gray matter boundaries on an atlas-representative image.

We computed 6 sets of voxelwise regression analyses within the mask described above. For the dependent variables, we subtracted the magnitude of BOLD response to neutral faces from the magnitude of BOLD response to fearful faces, sad faces, and happy faces for each participant. The predictor variables were MDD status, OPC status, either cumulative stressful or traumatic life events, and their interactions. These regression analyses were conducted with correction for multiple comparisons using simulations to generate a p value and cluster size criterion that provide a false-positive rate of $p < .05$ for the whole ROI mask.[72,73] This threshold/cluster-size requirement provides protection against type I error and was chosen based on Monte-Carlo simulations via

AlphaSim[74] and was set at a threshold of $z = 2.6$ at $p < .0094$ and 20 voxels. If any effect was found to be significant, multivariate outliers were evaluated, assessing the probability of Mahalanobis distance. If any multivariate outliers were detected (i.e., Mahalanobis D^2 with $p \leq .001$), we removed them and tested the effect again. All results reported below were those that survived when multivariate outliers were removed. For exploratory purposes, we also ran whole-brain analyses of life stress and trauma relationships to fearful, sad, and happy faces (presented in Tables S2 and S3, available online).

Moreover, for some regions, we found significant relationships between life events and brain activity in response to 1 facial emotion type, but not for another emotion type. To determine whether such relationships were significantly stronger for 1 emotion type versus another, we used repeated-measures analyses of covariance (ANCOVAs) for each identified region. These follow-up ANCOVAs added emotional face type and all possible interactions with emotional face type as within-subject variables to each original regression model. When the interaction with emotional face type was significant, we computed partial correlations between an identified predictor and BOLD response (covarying for the other predictors) for each emotional face type to confirm the pattern of relationships.

RESULTS

Demographic and Clinical Characteristics

As shown in Table 1, there were no significant differences in age, gender, handedness, or family income among the MDD, healthy, and OPC groups. However, the groups differed in stressful ($F_{2,112} = 9.15$, $p < .01$) and traumatic life events ($F_{2,112} = 14.16$, $p < .01$). Post hoc contrasts indicated that the MDD group experienced more stressful and traumatic life events than the healthy control group ($p < .01$). Moreover, the OPC group showed more traumatic life events than the healthy control group ($p < .05$). Within the healthy control group, those whose life events were assessed retrospectively reported less stressful ($F_{1,49} = 16.02$, $p < .01$) and traumatic life events ($F_{1,49} = 37.62$, $p < .01$) than those who were enrolled since the baseline assessment.

We also assessed whether age, gender, or family income was associated with stressful or traumatic life events, respectively. Age was not related to stressful life events, but it was related to traumatic life events ($r_{113} = 0.23$, $p < .05$). There were no gender differences in stressful or traumatic life events. Finally, family income was related to stressful life events ($r_{113} = -0.35$, $p < .01$) but not traumatic life events. Therefore, we subsequently controlled for family income in the analysis of stressful life events and age in the analysis of traumatic life events.

Table 1 also indicates that comorbidity rates within the MDD group were 57% for any externalizing disorders and 62% for non-MDD internalizing disorders; 40% of the MDD group

TABLE 1 Demographic and Clinical Characteristics of the Study Sample (N = 115)

Variable	MDD (n = 42)	Healthy (n = 51)	Other Psychiatric Disorders (n = 22)	F or χ^2
Age (y)[a]	9.81 (1.23)	9.80 (1.36)	10.18 (1.47)	0.70
Gender (girls/boys)	22/20	24/27	13/9	0.92
Handedness (left/right/both)	2/40/0	7/43/1	2/20/0	3.51
Family income at scan				
≤$20,000	13	7	3	8.69
$20,001–$40,000	8	11	3	
$40,001–$60,000	6	11	2	
≥$60,000	15	22	14	
Cumulative life events[a]				
Stress	11.71 (6.32)	6.45 (5.34)	9.41 (6.46)	9.15**
Trauma	8.21 (7.80)	2.47 (2.00)	6.36 (4.52)	14.16**
Average core MDD severity across assessments[a]				
Comorbidity	3.13 (1.14)	1.10 (0.92)	1.77 (0.84)	48.42**
Externalizing	24 (17)[b]	0	8 (5)[b]	38.44**
Non-MDD internalizing	26 (17)[b]	0	17 (5)[b]	56.19**

Note: MDD = major depressive disorder.

[a]*Data are presented as mean (standard deviation).*

[b]*A value within parentheses indicates the number of subjects who showed both externalizing and non-MDD internalizing comorbidities.*

**p < .01.

TABLE 2 Region-of-Interest Analysis of Stressful Life Events (SLE; N = 115)

	Regression Coefficient				Talairach Coordinate				Interaction With Emotion
Brain Region	**B**	**SE B**	**β**	**t**	**X**	**Y**	**Z**	**Cluster Size**	**F**
Outcome Variable: Fearful > Neutral									
Predictor Variable: Main Effect of SLE									
R PEC (BA28)/amygdala	0.033	0.009	0.464	3.61**	19	−14	−10	25	3.14*
R lateral GP	0.011	0.003	0.518	4.17**	16	−7	5	27	1.00
No other significant main effects or interactions									
Outcome Variable: Sad > Neutral									
Predictor Variable: Main Effect of SLE									
L amygdala	0.016	0.008	0.293	2.15*	−19	−12	−9	32	0.36
Predictor Variable: Main Effect of MDD									
No main effect									
Predictor Variable: Main Effect of OPC									
L pgACC (BA32)	−0.404	0.108	−0.624	3.76**	−6	42	0	20	2.12
Predictor Variable: Interaction of SLE × MDD									
L hippocampus	0.016	0.007	0.469	2.38*	−25	−14	−9	20	1.04
Predictor Variable: Interaction of SLE × OPC									
L medial GP	0.041	0.016	0.541	2.61*	−18	−11	−7	31	1.19
Outcome Variable: Happy > Neutral									
Predictor Variable: Main Effect of SLE									
L medial GP	0.025	0.007	0.463	3.46**	−17	−11	−8	31	1.31
R amygdala	0.020	0.010	0.318	2.06*	19	−6	−12	22	2.74
No other significant main effects or interactions									

Note: Multivariate outliers were excluded. The column "Interaction With Emotion" represents the F ratio for the interaction between emotional face type and the variable indicated in each row. B = nonstandardized coefficient; β = standardized coefficient; BA = Brodmann area; GP = globus pallidus; L = left hemisphere; MDD = major depressive disorder; OPC = other psychiatric control; PEC = posterior entorhinal cortex; pgACC = perigenual anterior cingulate cortex; R = right hemisphere; SE B = standard error of B.

*p < .05; **p < .01.

FIGURE 1 (A) Brain activity response to negative faces (green areas activated by fearful faces; blue areas activated by sad faces) and happy faces (red areas) increased as a function of cumulative stressful life events. Note: scatterplots illustrate interactions between (B) cumulative stressful life events and major depressive disorder (MDD) status and (C) cumulative stressful life events and other psychiatric control (OPC) status. BOLD = blood oxygen level-dependent; R = right side.

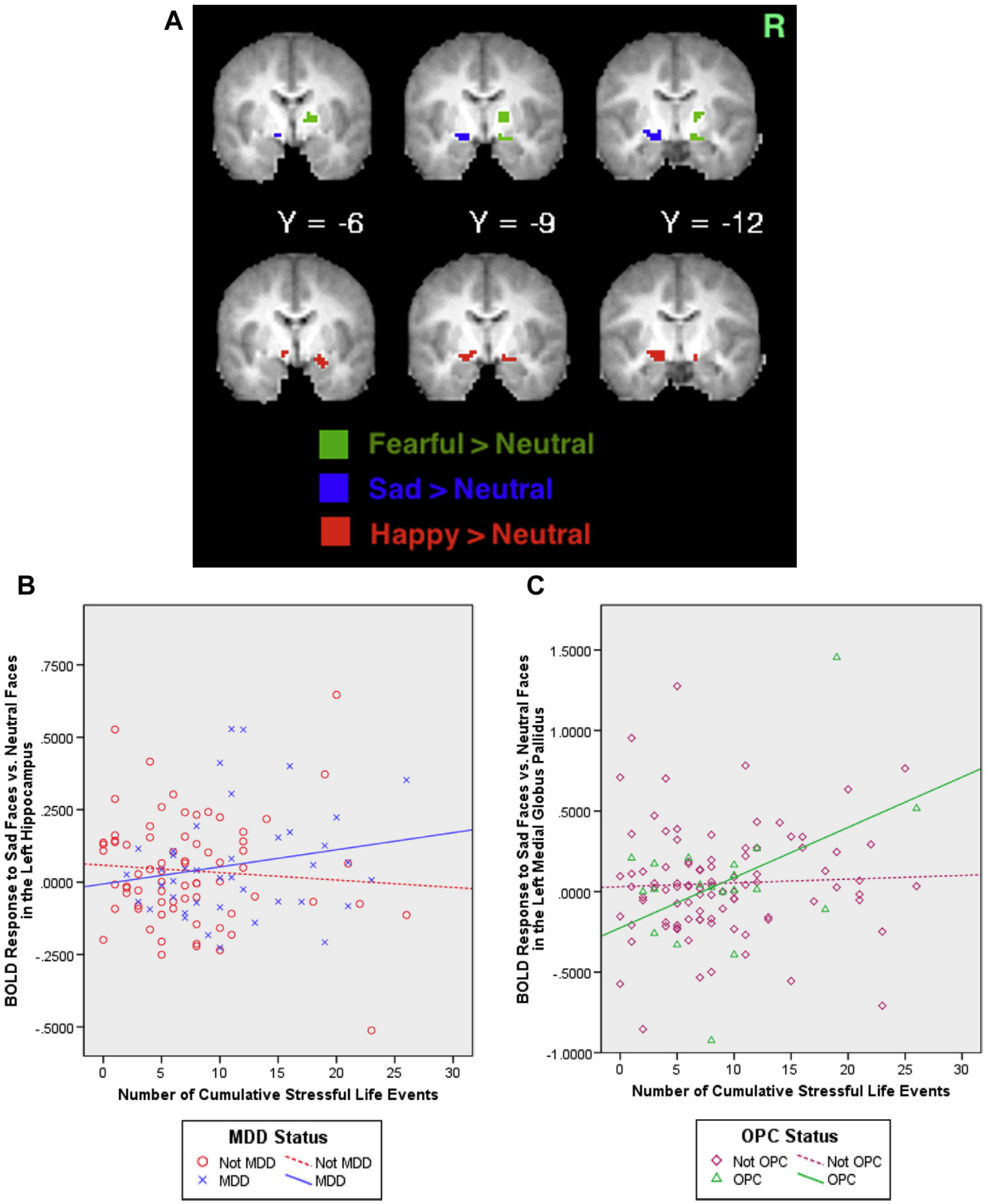


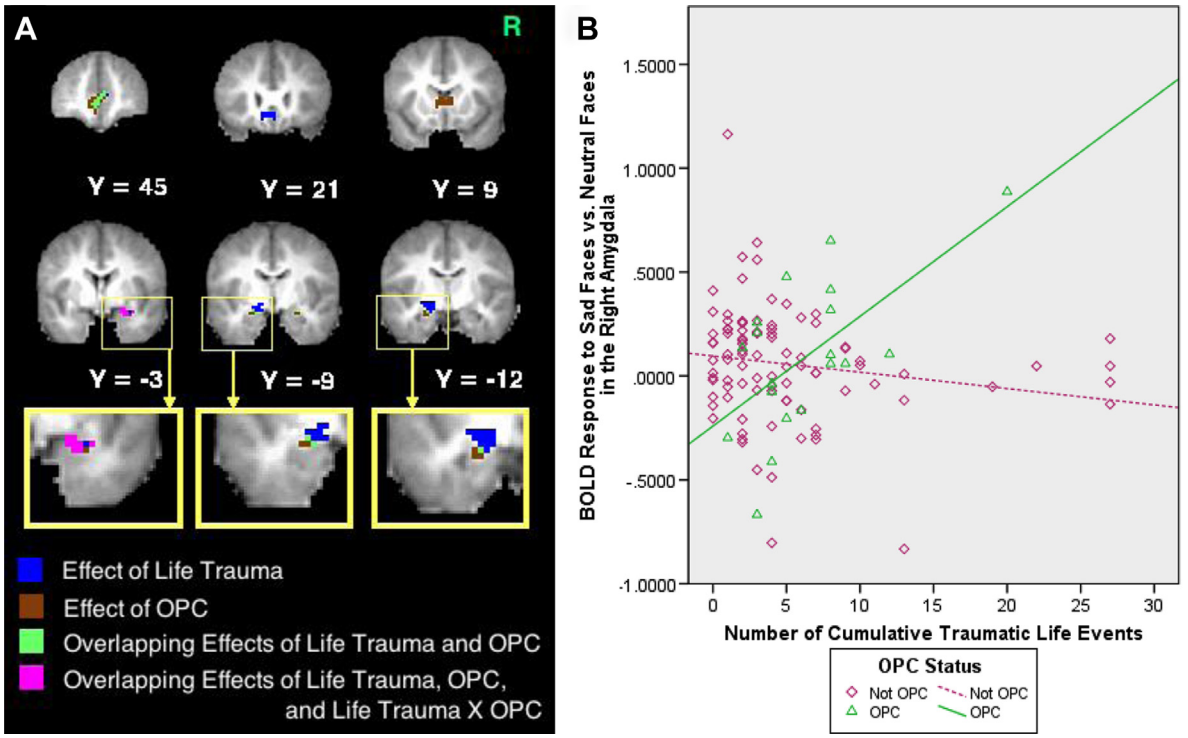
TABLE 3 Region-of-Interest Analysis of Traumatic Life Events (TLE; N = 115)

	Regression Coefficient				Talairach Coordinate				Interaction With Emotion
Brain Region	**B**	**SE B**	**β**	**t**	**X**	**Y**	**Z**	**Cluster Size**	**F**
Outcome Variable: Fearful > Neutral									
No significant main effects or interactions									
Outcome Variable: Sad > Neutral									
Predictor Variable: Main Effect of TLE									
L PEC (BA28)/amygdala	0.034	0.012	0.377	2.79**	−17	−11	−9	40	0.33
R amygdala	0.042	0.009	0.619	4.93**	24	−1	−15	32	10.79**
Bi sgACC (BA25)	0.041	0.009	0.522	4.34**	−1	19	−7	31	10.25**
Bi pgACC (BA32)	0.029	0.007	0.596	4.48**	−1	41	1	49	7.98**
Predictor Variable: Main Effect of MDD									
No main effect									
Predictor Variable: Main Effect of OPC									
L PEC (BA28)/amygdala	−0.292	0.083	−0.586	3.53**	−22	−14	−18	24	4.90**
R amygdala	−0.534	0.126	−0.669	4.14**	24	−2	−15	34	7.59**
Bi pgACC (BA32)	−0.442	0.114	−0.637	3.86**	−3	43	2	73	4.89**
Bi caudate head	−0.286	0.079	−0.610	3.63**	1	10	4	52	4.04*
Predictor Variable: Interaction of TLE × MDD									
No interaction effect									
Predictor Variable: Interaction of TLE × OPC									
R amygdala	0.086	0.025	1.070	3.50**	24	−2	−15	26	2.66
Outcome Variable: Happy > Neutral									
Predictor Variable: Main Effect of OPC									
R PEC (BA28)/Amygdala	−0.300	0.115	−0.443	2.60*	23	−13	−19	24	1.59
Bi dorsal ACC (BA32)	−0.346	0.099	−0.582	3.49**	0	16	34	37	2.99
No significant main effects or interactions									

Note: Multivariate outliers were excluded. The column "Interaction With Emotion" represents the F ratio for the interaction between emotional face type and the variable indicated in each row. ACC = anterior cingulate cortex; B = nonstandardized coefficient; β = standardized coefficient; BA = Brodmann area; Bi = bilateral; L = left hemisphere; MDD = major depressive disorder; OPC = other psychiatric control; PEC = posterior entorhinal cortex; pg = perigenual; R = right hemisphere; SE B = standard error of B; sg = subgenual.

*p < .05; **p < .01.

FIGURE 2 Brain activity response to sad faces predicted by each effect. (A) Voxels predicted by each effect and (B) scatterplot illustrating an interaction between cumulative traumatic life events and other psychiatric control (OPC) status. Note: R = right side.



showed both externalizing and internalizing comorbid disorders. Table S1 (available online) illustrates a comparison of each Axis I disorder between the MDD and OPC groups. Within the OPC group, there were relatively high proportions of anxiety disorders. However, there were no significant differences in the proportion of each specific Axis I disorder, except MDD (by definition), between the MDD and OPC groups.

Stressful Life Events

As shown in Table 2, stressful life events predicted the following: increased BOLD response to fearful faces in the right amygdala/posterior entorhinal cortex and lateral globus pallidus; increased BOLD response to sad faces in the left amygdala; and increased BOLD response to happy faces in the left medial globus pallidus and right amygdala (Figure 1A). Furthermore, stressful life events significantly interacted with MDD status to predict BOLD response to sad faces in the left hippocampus, and OPC status to predict BOLD response to sad faces in the left medial globus pallidus. As shown in Figure 1B, the MDD group tended to show a positive relationship between stressful life events and left hippocampal activity, whereas the non-MDD groups tended to show a negative relationship. For sad faces, there was also a main effect of OPC status; children with other psychiatric disorders showed less activation in the left perigenual ACC (pgACC) than the other children, despite their stressful experience. As shown in Figure 1C, the OPC group demonstrated a positive relationship between stressful life events and left medial globus pallidus activity compared to the non-OPC groups.

Even after accounting for family income as a covariate, stressful life events continued to predict left amygdala activity response to sad faces ($\beta = 0.25$, $t_{105} = 1.75$, $p = .083$) and right amygdala activity response to happy faces ($\beta = 0.27, t_{106} = 1.72, p = .089$) at a marginal level. The other effects and interactions remained significant at $p < .05$. Finally, as described above, some regions showed relationships between stressful life events and responses to an emotional face type. Follow-up ANCOVAs showed that the right amygdala identified in the regression for fearful faces showed a significant interaction with emotion type (Table 2). The relationship between stressful life events and right amygdala activity was significant only when children viewed fearful faces ($p < .01$) and happy faces ($p < .01$), but not sad faces.

Traumatic Life Events

As shown in Table 3, none of the variables predicted BOLD response to fearful faces. However, when processing sad faces (Figure 2A), traumatic life events were associated with greater functional activation in the left amygdala/posterior entorhinal cortex, the right amygdala, and the bilateral sgACC and pgACC. Moreover, there was a main effect of OPC status, such that despite their traumatic experience, the OPC group showed less activity in the bilateral amygdala, pgACC, and caudate head, compared to the non-OPC groups. Finally, there was a significant interaction between traumatic life events and OPC status predicting right amygdala a response to sad faces; Figure 2B shows that the positive relationship between traumatic life events and right amygdala response to sad faces was present only in the children with other psychiatric disorders. Thus, traumatic life events influenced left amygdala response to sad faces among all children, but the effects of traumatic life events on right amygdala response to sad faces depended on OPC status (Figure 2A). All of the above effects remained significant at $p < .05$ when controlling for age.

When processing happy faces, despite their traumatic experience, the OPC group showed less brain activity in the left dorsal ACC and right amygdala/posterior entorhinal cortex. Again, these main effects remained significant at $p < .05$ when controlling for age.

As with stressful life events, specificity between traumatic life events and responses by emotion type was also found in some regions. Follow-up ANCOVAs identified that traumatic life events significantly interacted with emotional face type in predicting right amygdala activity, bilateral sgACC activity, and bilateral pgACC activity, and that OPC status significantly interacted with emotional face type in predicting left amygdala, right amygdala, bilateral pgACC, and bilateral caudate head activity (Table 3). Subsequent partial correlations confirmed that the relationships between trauma and activity in the right amygdala, bilateral sgACC, and bilateral pgACC were present for sad ($p < .01$) and happy faces ($p < .05$), but not for fearful faces. Moreover, the relationships to OPC status indicated that children with other psychiatric disorders showed reduced activation in the left amygdala and bilateral pgACC on sad faces ($p < .01$), as well as the right amygdala and caudate on sad ($p < .01$) and happy ($p < .05$) faces.

DISCUSSION

The aim of the present study was to examine our hypotheses that a greater number of stressful and traumatic life events would predict greater cortico-limbic activation in children, particularly in response to fearful or sad faces, depending on the child's history of MDD. Three major findings were obtained.

First, our results revealed that both stressful and traumatic life events show similar relationships to amygdala reactivity. That is, an increase in the number of life events, including both stress and trauma, was associated with increased functional activation response to emotional faces in the amygdala, particularly the centromedial subregion and even extending dorsally. These results demonstrate that increased amygdala reactivity can occur not only in individuals with a history of child deprivation and maltreatment,[10,20] but also in individuals who have experienced a broader array of life stressors and traumas. However, the pattern of effects across face types was somewhat different, depending on whether children experienced stressful or traumatic life events. Children exposed to stressful life events showed increased functional reactivity to emotional face processing across a number of facial emotion types (Figure 1A). Although the effect of stressful life events on right amygdala activity was exceptionally specific to fearful and happy faces, no other valence-specific effects were found (Table 2). Thus, exposure to stressful life events increases reactivity to emotional faces relatively generally. In contrast, children exposed to traumatic life events demonstrated increased amygdala and ACC activity response only to sad faces (Table 3), suggesting a more specific effect of this experience. It was somewhat surprising that amygdala reactivity to fearful faces was not related to traumatic life events. This could be consistent with desensitization or "burn-out" to fearful stimuli in those experiencing early trauma, although directed study of this issue is needed. Interestingly, there is mixed evidence regarding the effects of stressors on amygdala reactivity, as relationships are sometimes found across emotional valence[75] but also sometimes found only with sad stimuli.[76] Our findings suggest that the pattern of effects across emotion types may vary as a function of stressor severity, and more research is needed to examine this issue.

Another interesting finding about stress/trauma effects was that early life trauma was associated with increased functional activity in the

bilateral sgACC (close to ventral medial PFC) and pgACC, and this relationship was present only while viewing sad faces; in contrast, emotional ACC reactivity was not related to early life stress. The sgACC and pgACC are involved in the neurocircuitry of anxiety, sadness, and MDD.[77-79] For example, a high proportion (46%) of neuroimaging studies have found that functional activation in the ACC is associated with the induction of sad mood,[80] and structural differences in the ACC have been consistently reported in adults and adolescents with MDD.[81,82] Moreover, it has been reported that electrical stimulation of the sgACC helps recovery in patients with treatment-resistant MDD.[81,83,84] Our results suggest that the ACC function during sadness processing may be altered as a function of early life trauma, which may provide a neurobiological explanation for why early life trauma is a risk factor for increasing depression severity.[13,23,38,85]

The second major finding was that there was an interaction between early life stress and MDD status in predicting left hippocampal activity (Table 2). Specifically, children with a history of MDD tended to show greater functional activation in the hippocampus in response to sad faces as the amount of early life stress increased. A few studies have reported that adults and children with MDD show increased right (but not left) hippocampal activity when processing sad faces.[31,86] Interestingly, MDD is frequently associated with a bias toward sad faces,[87,88] and, in prior work, patients with MDD showed increased left hippocampal activity while viewing sad faces relative to happy faces.[89] In contrast, healthy individuals typically show a bias toward happy faces,[88] and, in prior work, healthy individuals showed increased left hippocampal activity while viewing happy faces relative to sad faces.[89] These studies (i.e., the differing face conditions during which MDD versus healthy controls showed increased left hippocampal activity) suggest the possibility, albeit speculative, that the left hippocampus may be involved in subjects' attentional bias. However, the present study did not measure an attentional bias, and additional work will be needed to test this hypothesis more directly. Furthermore, we did not find any other main effect or interaction relating specifically to MDD. For instance, there was no interaction between traumatic life events and MDD status in predicting amygdala or ACC reactivity. One speculative hypothesis is that interactions between MDD status and life events may become more apparent as these children pass through puberty and into adulthood, but this hypothesis needs to be tested through longitudinal follow-up.

The third major finding was that there were interactions between life events and other psychiatric status in predicting functional brain activity. Children with psychiatric disorders other than MDD (mostly anxiety disorders, as shown in Table S1, available online) showed increased left medial globus pallidus activity response to sad faces when they had experienced a greater number of stressful life events (Table 2). They also demonstrated increased right amygdala activity response to sad faces with an increased number of traumatic life events (Table 3). In contrast, children with a history of MDD and healthy children did not show a change in functional response in these regions as a function of life events. Hence, although traumatic life events had a main effect on left amygdala activity response to sad faces in children with or without any psychiatric disorder, the functional change in the right amygdala was more pronounced in children with a history of non-MDD psychiatric disorders. This may be consistent with prior findings that children with a history of institutional care who exhibit any externalizing or internalizing problem showed bilateral amygdala hyperactivity response to negative stimuli.[20] Furthermore, early life trauma and altered right amygdala activity response to sadness could be important in understanding the developmental trajectory of these disorders.

Some limitations in our study should be mentioned. First, although we found significant associations between stress or trauma and functional brain changes, inferences about causal relationships cannot be made. Second, approximately half of the healthy control group was recruited at the scan wave (28 of 51 children) and reported stress and trauma retrospectively. Because their retrospective reporting showed less stressful and traumatic life events than did the other healthy children (discussed above), the occurrence of life events might be underestimated in this group. Third, our MDD group showed high levels of comorbid anxiety or other psychiatric disorders (common in childhood MDD), making it difficult to test stress or trauma effects between the MDD and OPC groups. Nevertheless, as shown in Table S1 (available online), there was no group difference in the proportion of any Axis I disorder except MDD. Hence, our results suggest that differential effects of stress or

trauma on brain activity between the MDD and OPC groups are present. Fourth, although the present study followed a common procedure in the literature where neutral faces were used as baseline, functional brain response to neutral faces themselves could vary in relation to life events and/or diagnostic status.[90] If this is the case, then neutral faces may not be an ideal control condition. Future research would benefit from administering other types of control conditions (e.g., nonfacial images) in addition to neutral faces to examine any stress/MDD effects on functional brain activity response to neutral faces relative to nonfacial stimuli.

In summary, our data extend the previous literature and highlight the critical neurobiological effects of cumulative experience of stress and trauma during early childhood. Overall, not only children with MDD or other psychiatric disorders but also healthy children showed enhanced functional limbic activity in areas such as the amygdala and ACC based on past experiences of stress and trauma. Moreover, MDD status interacted with life stress in predicting left hippocampal activity, and other psychiatric diagnostic status interacted with stress and trauma in predicting left medial globus pallidus activation and right amygdala activation. These data suggest that there may be unique developmental trajectories of alterations in emotion processing in response to early life stress and trauma informing risk pathways for childhood psychiatric outcomes. &

CG Clinical Guidance

- Children with a history of high life stress, whether or not they had a psychiatric disorder, showed increased functional reactivity to both negative and positive emotional faces; such increased activity was found in the amygdala and globus pallidus.
- Children with a history of high life trauma, whether or not they had a psychiatric disorder, showed increased functional reactivity to only sad faces; such increased activity was found in the amygdala and subgenual and perigenual anterior cingulate cortex.
- Children with a history of MDD showed increased left hippocampal reactivity to sad faces if their life stress was high, whereas this relationship was not present in the other children.
- Children with a history of non-MDD psychiatric disorder showed increased left globus pallidus reactivity (when their life stress was high) or right amygdala reactivity (when their life trauma was high) to sad faces, but the other children did not show this relationship.

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REFERENCES

1. Juster RP, McEwen BS, Lupien SJ. Allostatic load biomarkers of chronic stress and impact on health and cognition. Neurosci Biobehav Rev. 2010;35:2-16.
2. Vyas A, Mitra R, Shankaranarayana Rao BS, Chattarji S. Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. J Neurosci. 2002;22:6810-6818.
3. Radley JJ, Rocher AB, Rodriguez A, *et al*. Repeated stress alters dendritic spine morphology in the rat medial prefrontal cortex. J Comp Neurol. 2008;507:1141-1150.
4. Kuramochi M, Nakamura S. Effects of postnatal isolation rearing and antidepressant treatment on the density of serotonergic and noradrenergic axons and depressive behavior in rats. Neuroscience. 2009;163:448-455.
5. Czeh B, Simon M, Schmelting B, Hiemke C, Fuchs E. Astroglial plasticity in the hippocampus is affected by chronic psychosocial stress and concomitant fluoxetine treatment. Neuropsychopharmacology. 2006;31:1616-1626.
6. Lucas LR, Celen Z, Tamashiro KL, *et al*. Repeated exposure to social stress has long-term effects on indirect markers of

dopaminergic activity in brain regions associated with motivated behavior. Neuroscience. 2004;124:449-457.
7. Ansell EB, Rando K, Tuit K, Guarnaccia J, Sinha R. Cumulative adversity and smaller gray matter volume in medial prefrontal, anterior cingulate, and insula regions. Biol Psychiatry. 2012; 72:57-64.
8. Andersen SL, Tomada A, Vincow ES, Valente E, Polcari A, Teicher MH. Preliminary evidence for sensitive periods in the effect of childhood sexual abuse on regional brain development. J Neuropsychiatry Clin Neurosci. 2008;20:292-301.
9. Edmiston EE, Wang F, Mazure CM, *et al*. Corticostriatal-limbic gray matter morphology in adolescents with self-reported exposure to childhood maltreatment. Arch Pediatr Adolesc Med. 2011; 165:1069-1077.
10. Dannlowski U, Stuhrmann A, Beutelmann V, *et al*. Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. Biol Psychiatry. 2012;71:286-293.
11. Admon R, Lubin G, Stern O, *et al*. Human vulnerability to stress depends on amygdala's predisposition and hippocampal plasticity. Proc Natl Acad Sci U S A. 2009;106:14120-14125.
12. Herringa RJ, Phillips ML, Fournier JC, Kronhaus DM, Germain A. Childhood and adult trauma both correlate with dorsal anterior cingulate activation to threat in combat veterans. Psychol Med. 2013;43:1533-1542.
13. Pechtel P, Pizzagalli DA. Effects of early life stress on cognitive and affective function: an integrated review of human literature. Psychopharmacology (Berl). 2011;214:55-70.
14. Huang TY, Lin CH. Role of amygdala MAPK activation on immobility behavior of forced swim rats. Behav Brain Res. 2006; 173:104-111.
15. Raineki C, Cortes MR, Belnoue L, Sullivan RM. Effects of early-life abuse differ across development: infant social behavior deficits are followed by adolescent depressive-like behaviors mediated by the amygdala. J Neurosci. 2012;32:7758-7765.
16. Luby JL, Barch DM, Belden A, *et al*. Maternal support in early childhood predicts larger hippocampal volumes at school age. Proc Natl Acad Sci U S A. 2012;109:2854-2859.
17. Hanson JL, Chandra A, Wolfe BL, Pollak SD. Association between income and the hippocampus. PLoS One. 2011;6(5):e18712.
18. Hanson JL, Chung MK, Avants BB, *et al*. Early stress is associated with alterations in the orbitofrontal cortex: a tensor-based morphometry investigation of brain structure and behavioral risk. J Neurosci. 2010;30:7466-7472.
19. Tottenham N, Hare TA, Quinn BT, *et al*. Prolonged institutional rearing is associated with atypically large amygdala volume and difficulties in emotion regulation. Dev Sci. 2010; 13:46-61.
20. Tottenham N, Hare TA, Millner A, Gilhooly T, Zevin J, Casey BJ. Elevated amygdala response to faces following early deprivation. Dev Sci. 2011;14:190-204.
21. Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. Biol Psychiatry. 2001;49:1023-1039.
22. McEwen BS, Gianaros PJ. Central role of the brain in stress and adaptation: links to socioeconomic status, health, and disease. Ann N Y Acad Sci. 2010;1186:190-222.
23. Luby JL, Belden AC, Spitznagel E. Risk factors for preschool depression: the mediating role of early stressful life events. J Child Psychol Psychiatry. 2006;47:1292-1298.
24. Herman JP, Ostrander MM, Mueller NK, Figueiredo H. Limbic system mechanisms of stress regulation: hypothalamo-pituitary-adrenocortical axis. Prog Neuropsychopharmacol Biol Psychiatry. 2005;29:1201-1213.
25. Tottenham N, Sheridan MA. A review of adversity, the amygdala and the hippocampus: a consideration of developmental timing. Front Hum Neurosci. 2010;3:68.
26. McEwen BS, Eiland L, Hunter RG, Miller MM. Stress and anxiety: structural plasticity and epigenetic regulation as a consequence of stress. Neuropharmacology. 2012;62:3-12.
27. Carrion VG, Garrett A, Menon V, Weems CF, Reiss AL. Posttraumatic stress symptoms and brain function during a response-inhibition task: an fMRI study in youth. Depress Anxiety. 2008;25: 514-526.
28. Carrion VG, Haas BW, Garrett A, Song S, Reiss AL. Reduced hippocampal activity in youth with posttraumatic stress symptoms: an fMRI study. J Pediatr Psychol. 2010; 35:559-569.
29. Goff B, Gee DG, Telzer EH, *et al*. Reduced nucleus accumbens reactivity and adolescent depression following early-life stress. Neuroscience. 2013;249:129-138.
30. Gaffrey MS, Luby JL, Belden AC, Hirshberg JS, Volsch J, Barch DM. Association between depression severity and amygdala reactivity during sad face viewing in depressed preschoolers: an fMRI study. J Affect Disord. 2011;129: 364-370.
31. Barch DM, Gaffrey MS, Botteron KN, Belden AC, Luby JL. Functional brain activation to emotionally valenced faces in school-aged children with a history of preschool-onset major depression. Biol Psychiatry. 2012;72:1035-1042.
32. Stuhrmann A, Dohm K, Kugel H, *et al*. Mood-congruent amygdala responses to subliminally presented facial expressions in major depression: associations with anhedonia. J Psychiatry Neurosci. 2013;38:249-258.
33. Suslow T, Konrad C, Kugel H, *et al*. Automatic mood-congruent amygdala responses to masked facial expressions in major depression. Biol Psychiat. 2010;67:155-160.
34. Victor TA, Furey ML, Fromm SJ, Ohman A, Drevets WC. Relationship between amygdala responses to masked faces and mood state and treatment in major depressive disorder. Arch Gen Psychiatry. 2010;67:1128-1138.
35. Suzuki H, Botteron KN, Luby JL, *et al*. Structural-functional correlations between hippocampal volume and cortico-limbic emotional responses in depressed children. Cogn Affect Behav Neurosci. 2013;13:135-151.
36. Gaffrey MS, Luby JL, Repovs G, *et al*. Subgenual cingulate connectivity in children with a history of preschool-depression. Neuroreport. 2010;21:1182-1188.
37. Luby J, Heffelfinger A, Mrakrotsky C, Hildebrand T. Preschool Feelings Checklist. 1999, St. Louis, MO: Washington University.
38. Luby JL, Si X, Belden AC, Tandon M, Spitznagel E. Preschool depression: homotypic continuity and course over 24 months. Arch Gen Psychiatry. 2009;66:897-905.
39. Egger H, Ascher B, Angold A. The Preschool Age Psychiatric Assessment: Version 1.4. Durham, NC: Center for Developmental Epidemiology, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center; 1999:2003.
40. Egger HL, Erkanli A, Keeler G, Potts E, Walter BK, Angold A. Test-retest reliability of the Preschool Age Psychiatric Assessment (PAPA). J Am Acad Child Adolesc Psychiatry. 2006;45: 538-549.
41. Angold A, Prendergast M, Cox A, Harrington R, Simonoff E, Rutter M. The Child and Adolescent Psychiatric Assessment (CAPA). Psychol Med. 1995;25:739-753.
42. Angold A, Costello EJ. A test-retest reliability study of child-reported psychiatric symptoms and diagnoses using the Child and Adolescent Psychiatric Assessment (CAPA-C). Psychol Med. 1995;25:755-762.
43. Luby JL, Belden AC, Pautsch J, Si X, Spitznagel E. The clinical significance of preschool depression: impairment in functioning and clinical markers of the disorder. J Affect Disorders. 2009;112: 111-119.
44. Luby JL, Heffelfinger AK, Mrakotsky C, Hessler MJ, Brown KM, Hildebrand T. Preschool major depressive disorder: preliminary validation for developmentally modified DSM-IV criteria. J Am Acad Child Adolesc Psychiatry. 2002;41:928-937.
45. Gaffrey MS, Belden AC, Luby JL. The 2-week duration criterion and severity and course of early childhood depression: implications for nosology. J Affect Disorders. 2011;133:537-545.
46. Luby JL, Mrakotsky C, Heffelfinger A, Brown K, Spitznagel E. Characteristics of depressed preschoolers with and without anhedonia: evidence for a melancholic depressive subtype in young children. Am J Psychiatry. 2004;161:1998-2004.
47. Costello EJ, Angold A, March J, Fairbank J. Life events and post-traumatic stress: the development of a new measure for children and adolescents. Psychol Med. 1998;28:1275-1288.
48. Tottenham N, Tanaka JW, Leon AC, *et al*. The NimStim set of facial expressions: judgments from untrained research participants. Psychiatry Res. 2009;168:242-249.
49. Fales CL, Barch DM, Rundle MM, *et al*. Altered emotional interference processing in affective and cognitive-control brain circuitry in major depression. Biol Psychiatry. 2008;63:377-384.

50. Monk CS, Klein RG, Telzer EH, *et al*. Amygdala and nucleus accumbens activation to emotional facial expressions in children and adolescents at risk for major depression. Am J Psychiatry. 2008;165:90-98.
51. Ojemann J, Akbudak E, Snyder A, McKinstry R, Raichle M, Conturo T. Anatomic localization and quantitative analysis of gradient refocused echo-planar fMRI susceptibility artifacts. Neuroimage. 1997;6:156-167.
52. Talairach J, Tournoux P. Co-planar Stereotaxic Atlas of the Human Brain. New York: Thieme; 1988.
53. Buckner RL, Head D, Parker J, *et al*. A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume. Neuroimage. 2004;23:724-738.
54. Burgund ED, Kang HC, Kelly JE, *et al*. The feasibility of a common stereotactic space for children and adults in fMRI studies of development. Neuroimage. 2002;17:184-200.
55. Kang HC, Burgund ED, Lugar HM, Petersen SE, Schlaggar BL. Comparison of functional activation foci in children and adults using a common stereotactic space. Neuroimage. 2003; 19:16-28.
56. Ollinger JM, Corbetta M, Shulman GL. Separating processes within a trial in event-related functional MRI—II. Analysis. Neuroimage. 2001;13:218-229.
57. Ollinger JM, Shulman GL, Corbetta M. Separating processes within a trial in event-related functional MRI—I. The method. Neuroimage. 2001;13:210-217.
58. Braver TS, Paxton JL, Locke HS, Barch DM. Flexible neural mechanisms of cognitive control within human prefrontal cortex. Proc Natl Acad Sci U S A. 2009;106:7351-7356.
59. Jimura K, Locke HS, Braver TS. Prefrontal cortex mediation of cognitive enhancement in rewarding motivational contexts. Proc Natl Acad Sci U S A. 2010;107:8871-8876.
60. Savine AC, Braver TS. Motivated cognitive control: reward incentives modulate preparatory neural activity during task-switching. J Neurosci. 2010;30:10294-10305.
61. Becerril KE, Repovs G, Barch DM. Error processing network dynamics in schizophrenia. Neuroimage. 2011;54:1495-1505.
62. Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage. 2012;59: 2142-2154.
63. Pagliaccio D, Luby JL, Gaffrey MS, *et al*. Functional brain activation to emotional and nonemotional faces in healthy children: evidence for developmentally undifferentiated amygdala function during the school-age period. Cogn Affect Behav Neurosci. 2013;13:771-789.
64. Siegel JS, Power JD, Dubis JW, *et al*. Statistical improvements in fMRI analyses produced by censoring high motion datapoints. Hum Brain Mapp. Under review.
65. Mamah D, Wang L, Csernansky JG, Rice JP, Smith M, Barch DM. Morphometry of the hippocampus and amygdala in bipolar disorder and schizophrenia. Bipolar Disord. 2010;12: 341-343.
66. Wang L, Mamah D, Harms MP, *et al*. Progressive deformation of deep brain nuclei and hippocampal-amygdala formation in schizophrenia. Biol Psychiatry. 2008;64:1060-1068.
67. Mamah D, Wang L, Barch D, de Erausquin GA, Gado M, Csernansky JG. Structural analysis of the basal ganglia in schizophrenia. Schizophr Res. 2007;89:59-71.
68. Rajkowska G, Goldman-Rakic PS. Cytoarchitectonic definition of prefrontal areas in the normal human cortex: II. Variability in locations of areas 9 and 46 and relationship to the talairach coordinate system. Cereb Cortex. 1995;5:323-337.
69. Rajkowska G, Goldman-Rakic PS. Cytoarchitectonid definition of prefrontal areas in normal human cortex: I. Remapping of areas 9 and 46 using quantitative criteria. Cereb Cortex. 1995;5:307-322.
70. Fales CL, Barch DM, Rundle MM, *et al*. Antidepressant treatment normalizes hypoactivity in dorsolateral prefrontal cortex during emotional interference processing in major depression. J Affect Disord. 2009;112:206-211.
71. Sheline YI, Barch DM, Price JL, *et al*. The default mode network and self-referential processes in depression. Proc Natl Acad Sci U S A. 2009;106:1942-1947.
72. McAvoy MP, Ollinger JM, Buckner RL. Cluster size thresholds for assessment of significant activation in fMRI. Neuroimage. 2001;13. S198-S198.
73. Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC. Improved assessment of significant activation in functional magnetic-resonance-imaging (fMRI)—use of a cluster-size threshold. Magnet Reson Med. 1995;33:636-647.
74. Ward BD. Simultaneous inference for FMRI data, 2000. Available at: http://afni.nimh.nih.gov/afni/doc/manual/AlphaSim. Accessed September 12, 2012.
75. van Harmelen AL, van Tol MJ, Demenescu LR, *et al*. Enhanced amygdala reactivity to emotional faces in adults reporting childhood emotional maltreatment. Soc Cogn Affect Neurosci. 2013;8: 362-369.
76. Dannlowski U, Kugel H, Huber F, *et al*. Childhood maltreatment is associated with an automatic negative emotion processing bias in the amygdala. Hum Brain Mapp. 2013;34: 2899-2909.
77. Pizzagalli DA. Frontocingulate dysfunction in depression: toward biomarkers of treatment response. Neuropsychopharmacology. 2011;36:183-206.
78. Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci. 2000;4:215-222.
79. Etkin A. Functional neuroanatomy of anxiety: a neural circuit perspective. Curr Top Behav Neurosci. 2010;2:251-277.
80. Phan KL, Wager TD, Taylor SF, Liberzon I. Functional neuroimaging studies of human emotions. CNS Spectr. 2004;9: 258-266.
81. Hamani C, Mayberg H, Stone S, Laxton A, Haber S, Lozano AM. The subcallosal cingulate gyrus in the context of major depression. Biol Psychiatry. 2011;69:301-308.
82. Botteron KN, Raichle ME, Drevets WC, Heath AC, Todd RD. Volumetric reduction in left subgenual prefrontal cortex in early onset depression. Biol Psychiatry. 2002;51:342-344.
83. Lozano AM, Giacobbe P, Hamani C, *et al*. A multicenter pilot study of subcallosal cingulate area deep brain stimulation for treatment-resistant depression. J Neurosurg. 2012;116:315-322.
84. Mayberg HS, Lozano AM, Voon V, *et al*. Deep brain stimulation for treatment-resistant depression. Neuron. 2005;45:651-660.
85. Hopkins J, Lavigne JV, Gouze KR, Lebailly SA, Bryant FB. Multidomain models of risk factors for depression and anxiety symptoms in preschoolers: evidence for common and specific factors. J Abnorm Child Psychol. 2013;41(5):705-722.
86. Fu CH, Williams SC, Cleare AJ, *et al*. Neural responses to sad facial expressions in major depression following cognitive behavioral therapy. Biol Psychiatry. 2008;64:505-512.
87. Gotlib IH, Krasnoperova E, Yue DN, Joormann J. Attentional biases for negative interpersonal stimuli in clinical depression. J Abnorm Psychol. 2004;113:121-135.
88. Joormann J, Gotlib IH. Selective attention to emotional faces following recovery from depression. J Abnorm Psychol. 2007; 116:80-85.
89. Victor TA, Furey ML, Fromm SJ, Bellgowan PS, Ohman A, Drevets WC. The extended functional neuroanatomy of emotional processing biases for masked faces in major depressive disorder. PLoS One. 2012;7:e46439.
90. Mourao-Miranda J, Oliveira L, Ladouceur CD, *et al*. Pattern recognition and functional neuroimaging help to discriminate healthy adolescents at risk for mood disorders from low risk adolescents. PLoS One. 2012;7: e29482.

FIGURE S1 Region-of-interest (ROI) mask used in the present study (shown in blue).

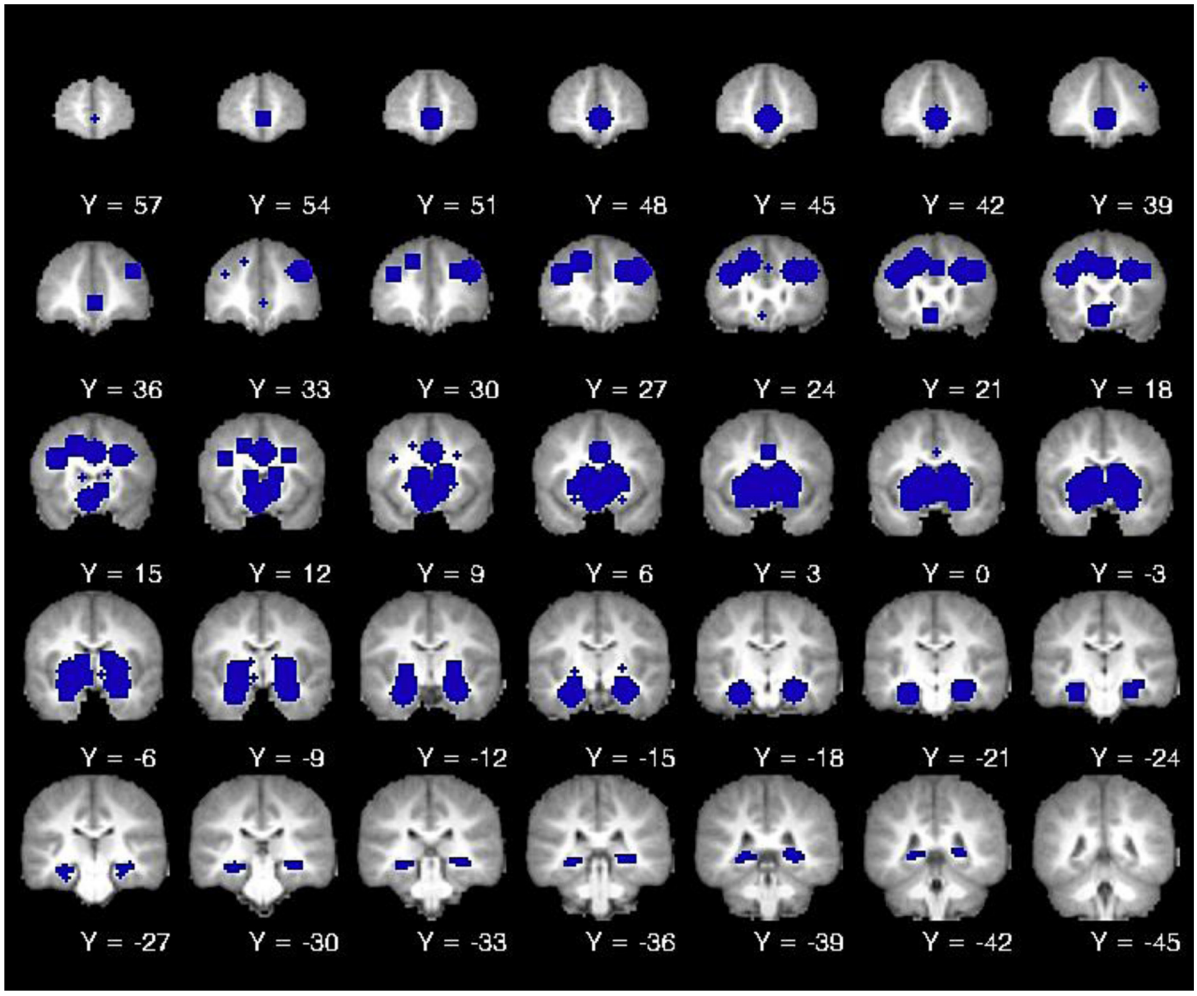

TABLE S1 Composition of Axis I Disorders in the Major Depressive Disorder (MDD) Group and the Other Psychiatric Control Group (n = 64)

Axis I Disorder, n (%)	MDD (n = 42)	Other Psychiatric Disorders (n = 22)	χ^2
ADHD	17 (40.5)	5 (22.7)	2.02
ODD	20 (47.6)	7 (31.8)	1.48
CD	12 (28.6)	4 (18.2)	0.83
PTSD	8 (19.0)	2 (9.1)	1.09
Anxiety disorders except PTSD	26 (61.9)	14 (63.6)	0.02
GAD	16 (38.1)	8 (36.4)	0.02
Separation anxiety	17 (40.5)	7 (31.8)	0.46
Panic attack	1 (2.4)	0 (0.0)	0.52
Agoraphobia	0 (0.0)	1 (4.5)	1.98
Social phobia	7 (16.7)	5 (22.7)	0.35
OCD	2 (4.8)	3 (13.6)	1.66
MDD	42 (100.0)	0 (0.0)	64.00**

Note: Some subjects showed comorbidity. ADHD = attention-deficit/hyperactivity disorder; CD = conduct disorder; GAD = generalized anxiety disorder; OCD = obsessive-compulsive disorder; ODD = oppositional defiant disorder; PTSD = posttraumatic stress disorder.

**p < .01.

TABLE S2 Whole-Brain Analysis of Stressful Life Events (SLE; N = 115)

Brain Region	Regression Coefficient				Talairach Coordinate			Cluster Size
	B	SE B	β	t	X	Y	Z	
Outcome Variable: Fearful > Neutral								
Predictor Variable: Main Effect of SLE								
L DEC (BA34)	0.050	0.010	0.618	5.18**	−16	−5	−22	20
L superior TG (BA38)	0.052	0.009	0.639	5.64**	−35	16	−28	61
L middle TG (BA21)	0.049	0.010	0.602	4.99**	−47	6	−29	30
L cuneus (BA18)	0.009	0.002	0.490	3.90**	−15	−79	29	23
L pons	0.022	0.004	0.610	5.11**	−5	−20	−22	18
R thalamus	0.015	0.003	0.539	4.31**	15	−8	5	17
R superior TG (BA38)	−0.085	0.018	−0.536	4.65**	37	14	−31	30
R middle TG (BA39)	0.011	0.003	0.510	4.08**	37	−67	29	24
R middle TG (BA22)	0.014	0.004	0.502	4.04**	54	−33	5	35
R middle TG	0.010	0.002	0.490	3.87**	43	−43	4	44
R inferior TG (BA20)	0.039	0.007	0.644	5.59**	47	−7	−22	112
R cuneus (BA19)	0.015	0.003	0.565	4.60**	11	−88	24	74
R red nucleus	0.030	0.005	0.670	5.73**	3	−18	−10	63
R cerebellum (tonsil)	0.045	0.009	0.592	4.84**	44	−57	−46	39
Predictor Variable: Main Effect of MDD								
No main effect								
Predictor Variable: Main Effect of OPC								
R superior TG (BA38)	1.388	0.315	0.693	4.41**	37	10	−32	59
R inferior TG (BA20)	−0.291	0.068	−0.671	4.31**	46	−9	−16	25
R inferior TG (BA20)	−1.724	0.336	−0.781	5.14**	62	−24	−24	20
R precuneus (BA7)	−0.533	0.137	−0.626	3.89**	6	−78	39	23
Predictor Variable: Interaction of SLE × MDD								
No interaction effect								
Predictor Variable: Interaction of SLE × OPC								
L superior TG (BA38)	0.093	0.019	0.899	4.99**	−37	17	−25	33
L middle TG (BA21)	0.111	0.026	0.806	4.30**	−48	6	−32	18
R DEC (BA34)	−0.198	0.035	−1.034	5.67**	13	4	−16	18
R superior TG (BA38)	−0.160	0.033	−0.873	4.84**	37	12	−31	48
R middle TG (BA22)	0.033	0.008	834	4.33**	57	−33	5	49
R inferior TG (BA20)	0.179	0.034	0.978	5.35**	60	−25	−24	36
R inferior TG (BA20)	0.037	0.007	0.968	5.35**	47	−9	−18	78
R postcentral gyrus (BA7)	0.054	0.014	0.685	3.79**	26	−48	66	18
R inferior PL (BA40)	0.019	0.005	0.764	4.05**	22	−37	53	43
R middle OG (BA19)	0.042	0.010	0.789	4.17**	8	−81	32	80
Pons	0.060	0.013	0.864	4.58**	0	−17	−25	17

TABLE S2 Continued

Brain Region	Regression Coefficient				Talairach Coordinate			Cluster Size
	B	SE B	β	t	X	Y	Z	
Outcome Variable: Sad > Neutral								
Predictor Variable: Main Effect of SLE								
L lateral GP	0.035	0.007	0.566	4.64**	−19	−16	−8	53
L superior TG (BA38)	0.069	0.014	0.587	4.96**	−35	17	−28	48
R superior TG (BA38)	−0.074	0.013	−0.618	5.50**	33	6	−33	118
R middle TG (BA21)	0.014	0.006	0.702	6.61**	47	−5	−18	392
R middle TG (BA22)	0.015	0.003	0.567	4.61**	55	−34	5	57
R inferior PL (BA40)	0.014	0.002	0.732	6.44**	52	−51	23	94
Predictor Variable: Main Effect of MDD								
L precuneus (BA7)	0.460	0.120	0.697	3.82**	−21	−73	49	21
R superior TG (BA39)	−0.230	0.052	−0.771	4.41**	46	−59	19	38
Predictor Variable: Main Effect of OPC								
L perigenual ACC (BA32)	−0.417	0.095	−0.713	4.37**	−10	42	1	30
R superior TG (BA38)	1.242	0.299	0.621	4.16**	34	6	−32	52
R superior TG (BA22)	−0.278	0.065	−0.695	4.32**	50	−38	7	28
R middle TG (BA21)	−0.656	0.118	−0.757	5.56**	52	−9	−16	150
R cerebellum (uvula)	−1.724	0.436	−0.651	3.96**	30	−89	−22	17
Predictor Variable: Interaction of SLE × MDD								
No interaction effect								
Predictor Variable: Interaction of SLE × OPC								
L medial GP	0.071	0.017	0.802	4.24**	−18	−14	−7	33
L superior TG (BA38)	0.129	0.026	0.902	4.90**	−38	15	−28	71
L mammillary body	−0.118	0.025	−0.885	4.81**	0	−10	−8	19
R superior TG (BA38)	−0.156	0.028	−0.982	5.63**	33	7	−34	130
R middle TG (BA22)	0.027	0.007	0.736	3.87**	52	−35	5	18
R inferior TG (BA20)	0.084	0.012	1.131	6.86**	49	−6	−18	452
Outcome Variable: Happy > Neutral								
Predictor Variable: Main Effect of SLE								
L PRC (BA35)	0.035	0.007	0.587	4.94**	−21	−24	−22	17
L ventral ACC (BA24)	0.014	0.004	0.502	3.97**	−3	−19	39	22
L substantia nigra	0.033	0.005	0.760	6.87**	−8	−19	−8	168
L superior TG (BA38)	0.081	0.013	0.695	6.24**	−36	14	−27	198
L middle TG (BA21)	−0.065	0.014	−0.530	4.52**	−40	−1	−32	40
L postcentral gyrus (BA43)	0.027	0.005	0.598	4.91**	−59	−8	14	26
L precuneus (BA19)	0.026	0.006	0.540	4.39**	−38	−75	39	35
L celleberum (declive)	0.011	0.002	0.539	4.31**	−7	−55	−13	37
R ventral ACC (BA24)	0.010	0.002	0.534	4.41**	11	2	28	21

TABLE S2 Continued

Brain Region	Regression Coefficient				Talairach Coordinate			Cluster Size
	B	SE B	β	t	X	Y	Z	
Predictor Variable: Main Effect of SLE								
R dorsal PCC (BA31)	0.014	0.004	0.448	3.52**	2	−50	32	24
R ventral lateral thalamus	0.015	0.003	0.581	4.77**	14	−9	5	17
R OFC (BA11)	0.171	0.029	0.648	5.79**	5	11	−22	17
R superior TG (BA22)	0.012	0.003	0.565	4.63**	48	−35	1	116
R superior TG (BA39)	0.031	0.005	0.677	5.82**	58	−59	19	61
R middle TG (BA21)	0.032	0.005	0.692	6.29**	48	−11	−15	555
R middle TG (BA21)	0.090	0.017	0.602	5.41**	48	11	−33	22
R inferior PL (BA40)	0.012	0.003	0.571	4.62**	49	−46	25	67
R middle OG (BA19)	0.029	0.006	0.555	4.47**	52	−74	5	21
Predictor Variable: Main Effect of MDD								
No main effect								
Predictor Variable: Main Effect of OPC								
L superior TG (BA38)	−1.616	0.431	−0.586	3.75**	−33	11	−33	34
L middle TG (BA21)	−1.189	0.257	−0.697	4.62**	−51	7	−31	20
L lateral geniculum body	−0.507	0.127	−0.616	3.99**	−21	−22	−4	18
L red nucleus	−0.664	0.131	−0.731	5.06**	0	−16	−9	42
R subgenual ACC (BA25)	2.739	0.478	0.887	5.73**	14	15	−17	24
R middle TG (BA21)	−0.674	0.132	−0.725	5.11**	49	−10	−16	214
Predictor Variable: Interaction of SLE × MDD								
No interaction effect								
Predictor Variable: Interaction of SLE × OPC								
L superior TG (BA38)	0.162	0.029	0.954	5.51**	−36	14	−28	148
L middle TG (BA21)	−0.109	0.025	−0.785	4.30**	−41	−1	−29	45
L red nucleus	0.072	0.013	0.970	5.66**	−1	−17	−10	66
R subgenual ACC (BA25)	−0.234	0.039	−1.070	6.04**	14	11	−16	23
R OFC (BA11)	0.362	0.062	1.008	5.85**	4	10	−22	19
R inferior FG (BA47)	0.101	0.020	0.912	4.93**	50	22	−7	17
R superior TG (BA22)	0.026	0.006	0.839	4.48**	48	−35	1	60
R middle TG (BA21)	0.193	0.035	0.955	5.50**	49	10	−32	21
R inferior TG (BA20)	0.072	0.011	1.077	6.37**	49	−12	−16	557
R lingual gyrus (BA17)	0.026	0.007	0.756	3.86**	10	−86	2	22
R medial geniculum body	0.039	0.008	0.941	5.05**	18	−25	−1	21

Note: Blood oxygen level-dependent responses to emotional faces. Threshold of z = 3.0 at p < .0026 and 17 voxels. Multivariate outliers were not assessed. ACC = anterior cingulate cortex; B = nonstandardized coefficient; β = standardized coefficient; BA = Brodmann area; Bi = bilateral; DEC = dorsal entorhinal cortex; FG = frontal gyrus; GP = globus pallidus; L = left hemisphere; MDD = major depressive disorder; OFC = orbitofrontal cortex; OG = occipital gyrus; OPC = other psychiatric control; PCC = posterior cingulate cortex; PL = parietal lobule; PRC = perirhinal cortex; R = right hemisphere; SE B = standard error of B; TG = temporal gyrus.

*p < .05; **p < .01.

TABLE S3 Whole-Brain Analysis of Traumatic Life Events (TLE; N = 115)

Brain Region	Regression Coefficient				Talairach Coordinate			Cluster Size
	B	SE B	β	t	X	Y	Z	
Outcome Variable: Fearful > Neutral								
Predictor Variable: Main Effect of TLE								
L medial FG (BA6)	0.024	0.006	0.587	4.22**	0	−21	52	24
L superior TG (BA22)	0.071	0.012	0.765	6.04**	−58	2	−5	27
L superior TG (BA42)	0.048	0.009	0.744	5.65**	−65	−26	8	31
L superior TG (BA38)	0.072	0.012	0.795	6.05**	−39	10	−31	167
L middle TG (BA19)	0.010	0.003	0.521	3.63**	−31	−63	14	17
L precentral gyrus (BA4)	0.026	0.006	0.612	4.39**	−37	−20	54	107
L cuneus (BA18)	0.010	0.002	0.597	4.21**	−15	−82	16	18
L inferior PL (BA40)	0.011	0.003	0.572	4.09**	−31	−36	33	24
L middle OG (BA19)	0.012	0.003	0.642	4.53**	−41	−72	7	24
L cerebellum (anterior)	0.019	0.004	0.694	5.00**	−15	−39	−32	133
L cerebellum (culmen)	0.015	0.004	0.545	3.76**	−9	−54	−13	29
L cerebellum (tonsil)	0.032	0.008	0.612	4.31**	−28	−55	−52	22
L cerebellum (ISL)	−0.093	0.021	−0.646	4.52**	−33	−78	−48	37
R DLPFC (BA46)	−0.037	0.007	−0.711	5.16**	42	41	25	17
R superior TG (BA38)	−0.105	0.027	−0.566	3.94**	37	15	−31	23
R superior TG (BA41)	0.013	0.003	0.572	3.97**	43	−28	4	17
R superior TG (BA13)	0.012	0.003	0.579	4.01**	43	−46	13	28
R superior TG (BA22)	0.031	0.006	0.723	5.32**	56	−8	9	53
R middle TG (BA39)	0.012	0.003	0.653	4.62**	37	−69	16	97
R middle TG (BA22)	0.024	0.005	0.625	4.46**	59	−31	5	37
R inferior TG (BA20)	0.066	0.013	0.719	5.25**	45	−5	−27	92
R postcentral gyrus (BA3)	0.026	0.004	0.823	6.69**	29	−31	59	488
R inferior PL	0.016	0.003	0.662	4.87**	46	−37	27	117
R cuneus (BA19)	0.027	0.005	0.688	5.24**	10	−82	33	222
R lingual gyrus (BA18)	0.014	0.004	0.547	3.84**	14	−80	1	20
R cerebellum (culmen)	0.021	0.004	0.679	4.89**	14	−59	−4	63
R cerebellum (culmen)	0.015	0.004	0.542	3.75**	8	−52	−13	18
R cerebellum (tonsil)	0.059	0.011	0.724	5.26**	44	−56	−46	33
R pons	0.056	0.010	0.774	5.75**	2	−17	−19	164
Predictor Variable: Main Effect of MDD								
L Precuneus (BA7)	0.471	0.127	0.517	3.71**	−7	−77	47	23
Predictor Variable: Main Effect of OPC								
L inferior FG (BA45)	0.898	0.205	0.704	4.39**	−54	24	5	21
L middle TG (BA21)	−0.929	0.197	−0.701	4.71**	−45	6	−29	54

TABLE S3 Continued

Brain Region	Regression Coefficient				Talairach Coordinate			Cluster Size
	B	SE B	β	t	X	Y	Z	
L middle TG (BA21)	−0.997	0.190	−0.758	5.25**	−57	4	−6	30
L precentral gyrus (BA4)	−0.303	0.087	−0.550	3.50**	−32	−26	56	18
R subgenual ACC (BA25)	20.386	0.428	0.842	5.57**	11	6	−17	21
Predictor Variable: Main Effect of OPC								
R middle TG (BA38)	1.693	0.451	0.617	3.76**	36	6	−36	25
R postcentral gyrus (BA7)	−0.583	0.143	−0.566	4.07**	22	−53	66	23
R postcentral gyrus (BA5)	−0.283	0.067	−0.600	4.23**	26	−38	59	48
R precentral gyrus (BA4)	−0.327	0.091	−0.572	3.59**	34	−22	55	24
R cuneus (BA19)	−0.453	0.106	−0.614	4.28**	10	−83	36	64
R pons	−0.679	0.176	−0.621	3.85**	7	−19	−22	28
Predictor Variable: Interaction of TLE × MDD								
L Superior PL (BA7)	−0.088	0.019	−1.200	4.55**	−27	−61	58	22
Predictor Variable: Interaction of TLE × OPC								
L superior TG (BA42)	0.161	0.031	1.367	5.13**	−66	−25	9	20
L middle TG (BA21)	0.193	.036	1.414	5.30**	−57	4	−6	29
L precentral gyrus (BA4)	0.057	0.016	1.047	3.65**	−30	−25	55	28
L lingual gyrus (BA18)	0.041	0.009	1.338	4.54**	−13	−80	−1	42
L lingual gyrus (BA19)	0.038	0.010	1.197	3.99**	−27	−64	0	19
R middle TG (BA22)	0.082	0.018	1.358	4.71**	62	−30	4	56
R postcentral gyrus (BA7)	0.133	0.031	1.056	4.31**	23	−50	68	31
R postcentral gyrus	0.032	0.009	1.095	3.66**	27	−26	34	20
R postcentral gyrus (BA5)	0.090	0.023	1.024	3.95**	35	−39	62	21
R inferior PL (BA40)	0.036	0.009	1.080	3.90**	21	−37	55	23
R inferior PL (BA40)	0.057	0.013	1.216	4.33**	49	−31	26	60
R lingual gyrus (BA19)	0.050	0.010	1.409	4.92**	21	−62	2	91
R pons	0.479	0.090	1.430	5.35**	8	−5	−21	19
Outcome Variable: Sad > Neutral								
Predictor Variable: Main Effect of TLE								
L ventral ACC (BA24)	0.021	0.005	0.593	4.09**	−1	−7	34	21
L ventral ACC (BA24)	0.035	0.006	0.767	5.61**	−1	28	−3	71
L lateral GP	0.046	0.010	0.667	4.74**	−20	−15	−8	48
L fusiform gyrus (BA20)	0.137	0.026	0.745	5.36**	−58	−39	−24	20
L superior TG (BA38)	0.070	0.013	0.736	5.43**	−40	12	−28	137
L superior TG (BA42)	0.033	0.006	0.758	5.58**	−61	−31	7	59
L middle TG (BA39)	0.012	0.003	0.612	4.31**	−31	−64	25	26
L angular gyrus (BA39)	0.033	0.007	0.656	4.60**	−53	−64	31	28
L precentral gyrus (BA4)	0.022	0.005	0.688	4.88**	−36	−21	53	88

TABLE S3 Continued

Brain Region	Regression Coefficient				Talairach Coordinate			Cluster Size
	B	SE B	β	t	X	Y	Z	
L paracentral lobule (BA6)	0.017	0.004	0.654	4.58**	−3	−27	49	90
L superior PL (BA7)	0.047	0.010	0.649	4.63**	−27	−50	65	20
L cerebellum (culmen)	0.019	0.004	0.720	5.22**	−11	−56	−7	91
L cerebellum (declive)	0.099	0.021	0.669	4.70**	−48	−68	−22	23
R superior TG (BA22)	0.041	0.005	1.020	8.76**	49	−19	−2	769
Predictor Variable: Main Effect of TLE								
R middle TG (BA39)	0.014	0.003	0.703	4.99**	39	−71	15	160
R inferior TG (BA20)	−0.077	0.016	−0.663	4.70**	31	1	−32	65
R precentral gyrus (BA6)	0.023	0.005	0.691	4.91**	35	−6	55	115
R postcentral gyrus (BA5)	0.118	0.027	0.620	4.43**	1	−48	70	23
R postcentral gyrus (BA5)	0.032	0.005	0.878	6.82**	22	−43	64	285
R precuneus (BA31)	0.015	0.004	0.569	3.93**	8	−52	34	43
R cuneus (BA19)	0.032	0.006	0.776	5.72**	5	−86	26	514
R cerebellum (culmen)	0.022	0.005	0.652	4.56**	13	−63	−5	30
R cerebellum (declive)	0.087	0.018	0.665	4.87**	25	−89	−20	34
R cerebellum (tonsil)	0.052	0.011	0.667	4.75**	47	−53	−43	29
Predictor Variable: Main Effect of MDD								
No Main Effect								
Predictor Variable: Main Effect of OPC								
L perigenual ACC (BA32)	−0.470	0.090	−0.815	5.23**	0	41	4	93
L anterior PFC (BA10)	−0.244	0.063	−0.636	3.90**	−13	43	13	29
L inferior FG (BA47)	−0.649	0.131	−0.776	4.96**	−42	13	−11	27
L superior TG (BA38)	−1.046	0.252	−0.639	4.15**	−41	13	−31	46
L superior TG (BA42)	−0.665	0.148	−0.685	4.50**	−65	−28	8	17
L middle TG (BA39)	−0.201	0.049	−0.657	4.12**	−31	−65	26	22
L middle TG (BA21)	−0.716	0.123	−0.880	5.83**	−57	−3	−13	81
L cuneus (BA18)	−0.194	0.047	−0.639	4.11**	−13	−85	18	23
R amygdala	−0.848	0.155	−0.792	5.47**	29	0	−17	53
R caudate head	−0.464	0.092	−0.794	5.02**	1	14	4	64
R superior TG (BA22)	−0.287	0.059	−0.746	4.85**	53	−29	6	71
R middle TG (BA21)	−0.400	0.088	−0.657	4.57**	56	−8	−13	28
R postcentral gyrus (BA7)	−1.180	0.241	−0.751	4.90**	17	−46	69	151
R cuneus (BA17)	−0.304	0.079	−0.626	3.86**	9	−91	4	20
R cuneus (BA19)	−0.578	0.116	−0.754	5.00**	12	−84	35	185
R middle OG (BA19)	−0.206	0.051	−0.639	4.02**	36	−74	14	25
R cerebellum (declive)	−1.588	0.311	−0.787	5.11**	26	−89	−19	47

TABLE S3 Continued

Brain Region	Regression Coefficient				Talairach Coordinate			Cluster Size
	B	SE B	β	t	X	Y	Z	
Predictor Variable: Interaction of TLE × MDD								
R PHG (BA30)	0.039	0.010	1.115	4.07**	28	−52	4	17
Predictor Variable: Interaction of TLE × OPC								
L caudate head	0.077	0.016	1.375	4.81**	−1	17	2	20
L superior TG (BA38)	0.173	0.039	1.224	4.46**	−39	17	−28	21
L middle TG (BA39)	0.038	0.009	1.215	4.17**	−30	−64	25	20
L middle TG (BA21)	0.074	0.018	1.230	4.21**	−41	−3	−7	19
R PHG (BA30)	0.046	0.011	1.268	4.29**	27	−50	3	20
Predictor Variable: Interaction of TLE × OPC								
R insula (BA13)	0.049	0.012	1.209	4.22**	45	−33	24	18
R superior TG (BA38)	0.138	0.026	1.339	5.34**	32	1	−17	42
R superior TG (BA22)	0.058	0.012	1.317	4.69**	56	−25	6	60
R inferior TG (BA20)	0.364	0.081	1.223	4.50**	52	−11	−30	29
R postcentral gyrus (BA7)	0.142	0.031	1.184	4.54**	21	−52	69	19
R cuneus (BA19)	0.115	0.028	1.112	4.08**	12	−85	37	48
Outcome Variable: Happy > Neutral								
Predictor Variable: Main Effect of TLE								
L medial FG (BA9)	0.027	0.006	0.613	4.26**	−3	50	20	28
L superior FG (BA6)	0.033	0.007	0.654	4.60**	−2	19	60	24
L superior TG (BA38)	0.095	0.017	0.754	5.55**	−37	12	−29	192
L superior TG (BA22)	0.075	0.011	0.857	6.79**	−59	1	−4	32
L superior TG (BA42)	0.038	0.007	0.773	5.69**	−63	−28	8	37
L angular gyrus (BA39)	0.037	0.008	0.638	4.46**	−54	−63	31	32
L precentral gyrus (BA43)	0.029	0.007	0.608	4.23**	−58	−9	13	19
L superior PL (BA7)	0.038	0.009	0.586	4.29**	−27	−50	65	18
L middle OG (BA18)	0.022	0.005	0.635	4.43**	−26	−95	4	18
L red nucleus	0.051	0.011	0.684	4.86**	−2	−18	−13	56
L lateral geniculum body	0.033	0.008	0.574	3.99**	−21	−21	−4	19
L cerebellum (tuber)	0.099	0.018	0.742	5.37**	−48	−69	−24	36
L cerebellum	0.040	0.009	0.608	4.32**	−2	−82	−24	24
R middle FG (BA6)	0.037	0.007	0.754	5.53**	31	−2	61	42
R superior TG (BA41)	0.020	0.003	0.803	5.98**	53	−26	6	216
R inferior TG (BA20)	0.111	0.021	0.724	5.35**	37	−19	−33	20
R inferior TG (BA20)	0.058	0.009	0.816	6.19**	48	−11	−20	279
R precentral gyrus (BA6)	0.025	0.005	0.692	4.94**	47	−6	49	40
R postcentral gyrus (BA3)	0.071	0.014	0.668	4.97**	15	−40	71	70
R postcentral gyrus (BA5)	0.031	0.006	0.751	5.60**	31	−44	63	84

TABLE S3 Continued

Brain Region	Regression Coefficient				Talairach Coordinate			Cluster Size
	B	SE B	β	t	X	Y	Z	
R inferior PL (BA40)	0.018	0.003	0.831	6.20**	48	−44	25	126
R cuneus (BA19)	0.040	0.008	0.688	4.98**	11	−86	37	81
R lingual gyrus (BA17)	0.032	0.007	0.665	4.75**	10	−92	0	63
R middle OG (BA19)	0.012	0.003	0.600	4.18**	38	−66	14	46
R cerebellum (declive)	0.072	0.016	0.635	4.47**	31	−85	−19	17
R cerebellum (tonsil)	0.044	0.010	0.619	4.30**	43	−55	−46	18
Predictor Variable: Main Effect of MDD								
No main effect								
Predictor Variable: Main Effect of OPC								
L Middle TG (BA21)	−1.154	0.267	−0.661	4.32**	−40	9	−31	68
Predictor Variable: Main Effect of OPC								
L middle TG (BA21)	−0.942	0.150	−0.907	6.26**	−59	−1	−6	51
R inferior FG (BA47)	−0.163	0.038	−0.590	4.34**	16	19	−20	18
R fusiform gyrus (BA20)	0.048	0.012	0.590	4.17**	45	−4	−23	54
R postcentral gyrus (BA3)	−1.319	0.270	−0.754	4.89**	15	−40	72	93
R postcentral gyrus (BA7)	−0.616	0.110	−0.832	5.59**	25	−48	65	73
R cuneus (BA19)	−0.557	0.134	−0.642	4.15**	10	−86	37	44
R lingual gyrus (BA17)	−0.553	0.126	−0.693	4.40**	9	−95	−2	42
Predictor Variable: Interaction of TLE × MDD								
No interaction effect								
Predictor Variable: Interaction of TLE × OPC								
R fusiform gyrus (BA20)	0.122	0.032	1.081	3.75**	45	−9	−22	33
R middle TG	0.060	0.013	1.265	4.48**	53	−32	2	34
R lingual gyrus (BA17)	0.060	0.015	1.136	3.88**	12	−93	1	22

Note: Blood oxygen level-dependent responses to emotional faces. Threshold of z = 3.0 at p < .0026 and 17 voxels. Multivariate outliers were not assessed. ACC = anterior cingulate cortex; B = nonstandardized coefficient; β = standardized coefficient; BA = Brodmann area; DLPFC = dorsolateral prefrontal cortex; FG = frontal gyrus; GP = globus pallidus; ISL = inferior semilunar lobule; L = left hemisphere; MDD = major depressive disorder; OG = occipital gyrus; OPC = other psychiatric control; PFC = prefrontal cortex; PL = parietal lobule; R = right hemisphere; SE B = standard error of B; TG = temporal gyrus.
*p < .05; **p < .01.