Limbic Scars: Long-Term Consequences of Childhood Maltreatment Revealed by Functional and Structural Magnetic Resonance Imaging

Udo Dannlowski, Anja Stuhrmann, Victoria Beutelmann, Peter Zwanzger, Thomas Lenzen, Dominik Grotegerd, Katharina Domschke, Christa Hohoff, Patricia Ohrmann, Jochen Bauer, Christian Lindner, Christian Postert, Carsten Konrad, Volker Arolt, Walter Heindel, Thomas Suslow, and Harald Kugel

Background: Childhood maltreatment represents a strong risk factor for the development of depression and posttraumatic stress disorder (PTSD) in later life. In the present study, we investigated the neurobiological underpinnings of this association. Since both depression and PTSD have been associated with increased amygdala responsiveness to negative stimuli as well as reduced hippocampal gray matter volume, we speculated that childhood maltreatment results in similar functional and structural alterations in previously maltreated but healthy adults.

Methods: One hundred forty-eight healthy subjects were enrolled via public notices and newspaper announcements and were carefully screened for psychiatric disorders. Amygdala responsiveness was measured by means of functional magnetic resonance imaging and an emotional face-matching paradigm particularly designed to activate the amygdala in response to threat-related faces. Voxel-based morphometry was used to study morphological alterations. Childhood maltreatment was assessed by the 25-item Childhood Trauma Questionnaire (CTQ).

Results: We observed a strong association of CTQ scores with amygdala responsiveness to threat-related facial expressions. The morphometric analysis yielded reduced gray matter volumes in the hippocampus, insula, orbitofrontal cortex, anterior cingulate gyrus, and caudate in subjects with high CTQ scores. Both of these associations were not influenced by trait anxiety, depression level, age, intelligence, education, or more recent stressful life events.

Conclusions: Childhood maltreatment is associated with remarkable functional and structural changes even decades later in adulthood. These changes strongly resemble findings described in depression and PTSD. Therefore, the present results might suggest that limbic hyperresponsiveness and reduced hippocampal volumes could be mediators between the experiences of adversities during childhood and the development of emotional disorders.

Key Words: Amygdala, childhood maltreatment, fMRI, hippocampus, stress, voxel-based morphometry

Childhood maltreatment is highly prevalent in Western countries with estimations of about 30% to 40% of the adult population having experienced at least some form of maltreatment during childhood (1). Maltreatment includes a spectrum of sexual, physical, and emotional forms of abuse, as well as emotional or physical neglect. Epidemiologic studies have shown that childhood maltreatment is a strong risk factor for developing major depression in later life (2), one of the most debilitating diseases worldwide, with up to 30% of all maltreated children fulfilling DSM-IV criteria for major depression in their late 20s (3). Furthermore, childhood maltreatment increases the susceptibility for developing posttraumatic stress disorder (PTSD) after experiencing further traumata in later life (2). To understand the underpinnings of the relationship between maltreatment and such emotional disorders, a considerable body of research investigated the neurobiological consequences of childhood maltreatment, which could thereby help to identify potential risk markers for depression and PTSD. In endocrinological studies, it was repeatedly shown that childhood maltreatment causes lasting changes in the hypothalamic-pituitary-adrenal axis responsiveness to stress and could thereby increase the risk for developing depression (4,5). Studies using neuroimaging techniques revealed notable structural changes in maltreated children as morphologic correlates for impaired brain development, including smaller brain volume and corpus callosum atrophy (6). More recent studies have focused on the association of childhood maltreatment and hippocampal volumes. The hippocampus is highly susceptible for stress and involved in the regulation of the hypothalamic-pituitary-adrenal axis. Furthermore, several studies have shown that depression and PTSD are associated with smaller hippocampal volumes (7,8), which seem to be apparent also in subjects at risk for depression or PTSD (9–11). Accordingly, it was demonstrated that patients suffering from depression show even smaller hippocampal volumes if they experienced emotional neglect (12) and physical or sexual abuse as a child (13).

A second imaging finding that has been frequently described in both depression (14–18) and PTSD (19–21) is amygdala hyperresponsiveness to emotionally negative stimuli. The amygdala is a central structure in limbic emotion processing circuits (22), critically involved in the rapid processing particularly of threat-related stimuli (23), and amygdala hyperactivity has been implicated in the

From the Departments of Psychiatry (UD, AS, VB, PZ, TL, DG, KD, CH, PO, JB, CL, CP, VA, TS), Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy (CP), and Clinical Radiology (WH, HK), University of Münster, Münster; Department of Psychiatry(CK), University of Marburg, Marburg; and Department of Psychosomatic Medicine and Psychotherapy (TS), University of Leipzig, Leipzig, Germany.

Address correspondence to Udo Dannlowski, M.D., Ph.D., University of Münster, Department of Psychiatry, Albert-Schweitzer-Str. 11, Münster 48149, Germany; E-mail: dannlow@uni-muenster.de.

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pathogenesis of major depression, probably by causing negatively biased emotion processing (24,25). One recent study reported a positive correlation of childhood maltreatment and right amygdala responsiveness to sad facial expression in a subsample of depressed patients ($n = 20$), driven by the physical abuse scale (26; but see [27,28] for conflicting findings). Therefore, the authors suggested that the association of childhood maltreatment and depression could be mediated by amygdala hyperresponsiveness.

However, the majority of imaging studies describing maltreatment-related functional and structural changes investigated patients already affected by major depression or PTSD. Thus, it is difficult to infer whether limbic alterations following childhood maltreatment are only evident in subjects who eventually develop emotional disorders in later life or if these changes are detectable consequences of maltreatment in subjects without any history of psychiatric disorders and accordingly constitute promising vulnerability markers. To the best of our knowledge, only one recent study provided evidence of an association between early-life adversity and smaller hippocampal volumes in healthy adolescents (29). Furthermore, the study data suggest that small hippocampal volumes, indeed, could mediate the association of early-life adversity and the onset of depression (29).

In the present study, we sought to further clarify the role of childhood maltreatment on functional (amygdala responsiveness to aversive stimuli) and structural (hippocampus gray matter volume) imaging markers associated with depression and PTSD in a large sample of healthy adults carefully screened for psychiatric conditions. We employed a robust amygdala activation paradigm and high-resolution structural images for morphometric analyses. We hypothesized that healthy adults having experienced maltreatment as children would show amygdala hyperresponsiveness to negative facial expressions and reduced hippocampal volumes.

Methods and Materials

Subjects

One hundred forty-eight right-handed healthy subjects participated in the present study. Subjects responded to local newspaper ads and public notices with no direct reference to childhood maltreatment as a key variable in the study. All subjects were thoroughly investigated by experienced psychologists and were free from any lifetime history of psychiatric disorders according to DSM-IV criteria (30), as diagnosed with the Structured Clinical Interview for DSM-IV interview (31). Exclusion criteria were scores ≥ 10 on the Beck Depression Inventory (32), any neurological abnormalities, history of seizures, head trauma or unconsciousness, intake of any psychotropic medication, and the usual magnetic resonance imaging contraindications. Two subjects had to be excluded for anatomical abnormalities (abnormally enlarged ventricles) discovered in the structural magnetic resonance imaging images, checked by visual inspection, and identified as extreme outliers in the check data quality function of the VBM8-Toolbox (version 419; http://dbm.neuro.uni-jena.de/vbm). The Childhood Trauma Questionnaire (CTQ) was administered to assess maltreatment during childhood. The CTQ is a 25-item retrospective self-report questionnaire designed to assess five types of negative childhood experiences (33). The reliability was high in the present sample (Cronbach's $\alpha = .93$). Furthermore, the Perceived Stress Scale (PSS) and the List of Threatening Experiences Questionnaire (LTE-Q) were administered. The PSS is a measure of the degree to which situations in the subject's life are appraised as stressful and how unpredictable, uncontrollable, and overloaded respondents find their lives during the past month (34). The LTE-Q assesses 12 different stressful life events that could have occurred during the last 12 months (35). Trait anxiety was measured with the State-Trait Anxiety Inventory (trait version). Neuroticism and harm avoidance were measured with the NEO Five Factor Inventory (36) and the Tridimensional Personality Questionnaire (37). Verbal intelligence was estimated by the Mehrfachwahl-Wortschatz-Intelligenztest (multiple choice vocabulary intelligence test) (38). Table 1 lists sociodemographic, questionnaire, and behavioral data of study participants. The study was approved by the Ethics Committee of the University of Münster. After complete description of the study to the participants, written informed consent was obtained. Participants received a financial compensation of 30 €.

Table 1. Sociodemographic, Questionnaire, and Behavioral Data of Study Participants

Age	33.8 ± 10.4 (20–57)
Education Years	15.6 ± 2.1 (10–21)
Sex (M/F)	75/70
Verbal Intelligence[a]	117.0 ± 12.3 (93–145)
BDI	1.6 ± 1.9 (0–9)
STAI-T	31.4 ± 6.6 (20–53)
CTQ Score	33.4 ± 10.0 (25–74)
CTQ Emotional Neglect	8.8 ± 4.1 (5–25)
CTQ Emotional Abuse	7.2 ± 3.4 (5–23)
CTQ Physical Abuse	5.7 ± 2.1 (5–20)
CTQ Physical Neglect	6.4 ± 1.9 (5–13)
CTQ Sexual Abuse	5.2 ± 1.0 (5–14)
PSS	18.6 ± 6.6 (5–35)
LTE-Q	1.1 ± 1.3 (0–7)
% Correct Faces	99.3 ± 2.0 (91.7–100)
% Correct Shapes	98.6 ± 2.3 (86.7–100)
Mean RT Faces (milliseconds)	1032.4 ± 170.4 (668.3–1579.0)
Mean RT Shapes (milliseconds)	861.8 ± 148.0 (559.0–1449.6)

$n = 145$ representing the final sample included in the morphometry analysis; mean ± SE (range).

BDI, Beck Depression Inventory; CTQ, Childhood Trauma Questionnaire; F, female; LTE-Q, List of Threatening Experiences Questionnaire; M, male; PSS, Perceived Stress Scale; RT, reaction time; STAI-T, State-Trait Anxiety Inventory-Trait version.

[a]Assessed with the Mehrfachwahl-Wortschatz-Intelligenztest (38).

Face-Matching Paradigm

For the functional magnetic resonance imaging (fMRI) study, a robust paradigm for eliciting amygdala responses to fearful and angry faces was used. The paradigm has already been employed in numerous previous imaging studies to investigate amygdala responsiveness (e.g., [39–41]). The task consisted of four blocks of a face-processing task alternating with five blocks of a sensorimotor control task. During the face-processing task, participants viewed a trio of faces (all three expressing either anger or fear) from the Ekman and Friesen (42) stimulus set. Subjects were instructed to selected one of two faces (bottom) that was identical to a target face (top). Each face-processing block consisted of six images, balanced for gender and emotion (angry or fearful). During the sensorimotor control blocks, participants viewed a trio of geometric shapes (circles and ellipses) and selected one of two shapes (bottom) that were identical to a target shape (top). Each sensorimotor control block consisted of six different shape trios. All blocks were preceded by an instruction (match faces or match shapes in German) that lasted 2 seconds. In the face-processing blocks, each of the six face trios was presented for 4 seconds with a variable interstimulus interval of 2 seconds to 6 seconds (mean, 4 seconds), for a total block length of 48 seconds. In the sensorimotor control blocks, each of the six shape trios was presented for 4 seconds with a fixed

interstimulus interval of 2 seconds, for a total block length of 36 seconds. Total task time was 390 seconds. Participant performance (accuracy and reaction time) was recorded.

fMRI Methods

Images were projected to the rear end of the scanner (Sharp XG-PC10XE with additional high-frequency shielding; Osaka, Japan). T2* functional data were acquired at a 3T scanner (Gyroscan Intera 3T, Philips Medical Systems, Best, The Netherlands), using a single-shot echo planar sequence with parameters selected to minimize distortion in the region of central interest, while retaining adequate signal-to-noise ratio and T2* sensitivity. Volumes consisting of 34 slices were acquired (matrix 64 × 64, resolution 3.6 × 3.6 × 3.6 mm; repetition time = 2.1 seconds, echo time = 30 milliseconds, flip angle = 90°). The slices were tilted 25° from the anterior commissure/posterior commissure line to minimize dropout artifacts in the orbitofrontal and mediotemporal regions.

Functional imaging data were realigned and unwarped, spatially normalized to standard Montreal Neurological Institute space and smoothed (Gaussian kernel, 6 mm full-width at half maximum) using Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm). Twenty-two subjects did not receive functional scans for technical reasons. For the fMRI analysis, 10 further subjects had to be excluded due to excessive head movement (exclusion criterion > 2 mm and/or 2°), leaving $n = 114$ complete datasets for fMRI analyses. However, including these subjects would not weaken (but slightly strengthen) the reported fMRI results.

Onsets and durations of the two experimental conditions (faces and shapes) were modeled with a canonical hemodynamic response function in the context of the general linear model and the model was corrected for serial correlations. For each participant, one contrast image was generated in each individual fixed-effects first-level analysis comparing activation in response to fear-relevant faces with the shapes baseline. The resulting contrast images were then entered into second-level random-effects group analyses, regressing CTQ scores on brain activation.

fMRI Data Analysis

We tested our main hypothesis of amygdala responsiveness modulation by childhood maltreatment via regressing CTQ scores on amygdala responsiveness to aversive facial expressions. A statistical threshold of $p < .05$, family wise error (FWE) corrected for the bilateral amygdala was used. The amygdala was defined according to Tzourio-Mazoyer *et al.* (43) and the amygdala mask was created by means of the WFU PickAtlas (44). In a second step, the mean contrast values of the significant cluster from this analysis were extracted for each participant and further analyzed with PASW Statistics 18 (IBM, Armonk, New York). We conducted a multiple regression model predicting amygdala responsiveness by CTQ scores, age, gender, total education time (years), verbal intelligence, trait anxiety, and depression level, as well as PSS scores and LTE-Q scores. Furthermore, each of the five CTQ subscales was separately correlated with amygdala responsiveness to explore which maltreatment type was the strongest predictor. Additionally, we conducted a nonparametric correlation of CTQ and amygdala responsiveness.

Voxel-Based Morphometry

T1-weighted high-resolution anatomical images were acquired with a three-dimensional (3D) fast gradient echo sequence (turbo field echo), repetition time = 7.4 milliseconds, echo time = 3.4 milliseconds, flip angle = 9°, two signal averages, inversion prepulse every 814.5 milliseconds, acquired over a field of view of 256 (feet-head [FH]) × 204 (anterior-posterior [AP]) × 160 (right-left [RL]) mm, phase encoding in AP and RL direction, reconstructed to cubic voxels of .5 mm × .5 mm × .5 mm. The VBM8 Toolbox was used for preprocessing the structural images with default parameters. Images were bias-corrected, tissue classified, and normalized to Montreal Neurological Institute space using linear (12-parameter affine) and nonlinear transformations, within a unified model (45) including high-dimensional DARTEL normalization. Gray matter (GM) and white matter (WM) segments were modulated only by the nonlinear components to preserve actual GM and WM values locally (modulated GM and WM volumes).

Homogeneity of gray matter images was checked using the covariance structure of each image with all other images, as implemented in the check data quality function. As described above, two extreme outliers showing anatomical abnormalities were identified and excluded. One further subject had to be excluded because of an incomplete T1 scan. The remaining $n = 145$ images were clear of such problems. The modulated gray matter images were smoothed with a Gaussian kernel of 8 mm FWHW. Group statistics were calculated with second-level models using SPM8. We used the same analysis strategy as in the fMRI analysis, starting with a voxel-wise regression restricted to the bilateral hippocampus as defined by Tzourio-Mazoyer *et al.* (43) with a rigorous FWE-correction for multiple comparisons. Again, values of the significant cluster from this analysis were extracted for all subjects and further processed as described above using the same regression model and nonparametric statistics.

Given several previous reports of childhood trauma affecting the structure of other brain regions, including the prefrontal cortex (12,46) and visual areas (47), a supplementary whole-brain analysis correlating CTQ scores with the gray matter images was also performed at $p < .001$ (uncorrected), with a cluster threshold of k = 50 voxels (see Table 2 for results). The anatomical labeling for the whole-brain data was performed by means of the AAL-Toolbox (43), and the Brodmann areas (BA) were identified with the Talairach Daemon atlas (http://www.talairach.org).

Results

Behavioral Results

Table 1 lists mean reaction times and mean percent correct responses for the two experimental conditions (faces and shapes). There was no significant association of CTQ scores and any behavioral measure.

fMRI Results

The regression analysis conducted with SPM8 yielded a strong positive association of CTQ scores and right amygdala responsiveness to fearful/angry faces (x = 26, y = −2, z = −12; $t = 5.43$, df = 112, $p_{\text{uncorrected}} < .0001$; $p_{\text{FWE-corrected}} = .001$; $r = .46$, cluster size k = 64) (Figure 1). These results also survived a FWE correction for the entire brain ($p_{\text{FWE-corrected}} = .008$).

In the subsequent multiple regression analysis predicting the mean activation of the significant cluster by CTQ score, Beck Depression Inventory, State-Trait Anxiety Inventory trait, PSS, LTE-Q, age, gender, verbal intelligence, and total education time, the strong effect of CTQ remained practically unchanged ($\beta = .49$, $t = 5.31$, df = 104, $p < .0001$). Except for a significant (negative) association of total education time and amygdala responsiveness ($\beta = -.22$, $t = -2.36$, df = 104, $p = .02$), no other predictor had any significant effect (all $ps > .20$). Thus, the association of childhood maltreatment and limbic hyperresponsiveness was not confounded by recent stressful life events, current levels of subclinical

Table 2. Results of a Whole-Brain Regression Analysis of CTQ Scores on Gray Matter Volumes Conducted at $p < .001$, Uncorrected, k = 50 Voxels

Anatomical Region	BA	Side	Cluster Size	x	y	z	*Z*-Score	*p* Value (Uncorrected)
Insula, Hippocampus, STG, Putamen	13,38,21,47,22	R	1095	38	−16	−11	4.54	<.00001
SFG, MidFG	9	R	202	20	33	34	4.38	<.00001
SMG, Rolandic Operculum, Postcentral Gyrus	1–4,6,40, 43	R	787	56	−25	31	4.30	<.00001
Precentral Gyrus, IFG, MidFG	9,6,8	R	216	50	9	37	4.20	.00001
STG, SMG, MTG, Rolandic Operculum, Heschl's Gyrus	21,22,13,40–42	L	1769	−46	−30	19	4.20	.00001
Cuneus, Precuneus, SOG, SPG	7,18,19,31	L	634	−8	−70	31	4.05	.00003
Precuneus, SPG	5,7	R	133	10	−48	58	3.88	.00005
SOG, MOG	19,7	L	59	−26	−85	34	3.81	.00007
Insula, IFG (Orbital Part), SFG (Orbital Part)	47	R	54	22	20	−14	3.63	.00014
IFG (Orbital Part), Insula	47,38	L	57	−44	15	−9	3.63	.00014
SFG (Medial Part), ACC	10,31,9	R/L	214	4	63	13	3.44	.00029
Caudate, Putamen, Olfactory Gyrus	—	R	114	12	18	−8	3.42	.00031

ACC, anterior cingulate cortex; BA, Brodmann area; CTQ, Childhood Trauma Questionnaire; IFG, inferior frontal gyrus; L, left; MidFG, middle frontal gyrus; MOG, middle occipital gyrus; MTG, middle temporal gyrus; R, right; SFG, superior frontal gyrus; SMG, supramarginal gyrus; SOG, superior occipital gyrus; SPG, superior parietal gyrus; STG, superior temporal gyrus.

depression and anxiety symptoms, verbal intelligence, or sociodemographic factors. Also a nonparametric correlation of CTQ scores and amygdala responsiveness (Spearman's rho) was highly significant $r_s = .29$, $p = .002$. There was no significant association of amygdala responsiveness with neuroticism or harm avoidance ($ps > .13$).

From all five subscales, emotional abuse ($r = .47$, $p < .0001$) and emotional neglect ($r = .37$, $p < .0001$) were the strongest predictors for amygdala responsiveness, followed by physical abuse ($r = .34$, $p = .0002$), physical neglect ($r = .29$, $p = .002$), and sexual abuse ($r = .27$, $p = .004$).

There was no anatomical area in the entire brain showing a negative association with CTQ scores, even at a lenient threshold ($p < .005$, uncorrected).

Voxel-Based Morphometry Results

The region of interest analysis of the bilateral hippocampus revealed a significant negative association of hippocampal gray matter volume and CTQ scores only in the right hippocampus (x = 38, y = −15, z = −12; $t = 4.69$, df = 143, $p_{\text{uncorrected}} < .0001$; $p_{\text{FWE-corrected}} = .001$; $r = -.37$, cluster size k = 102) (Figure 2). Again, using FWE correction for the entire brain, this peak still reached significance ($p_{\text{FWE-corrected}} = .048$).

In the multiple regression analysis, the association of CTQ and hippocampal volume remained highly significant ($\beta = -.33$, $t = -3.89$, df = 135, $p = .0002$). A marginally significant negative association of LTE-Q scores and hippocampal gray matter volumes emerged ($\beta = -.14$, $t = -1.78$, df = 135, $p = .078$), but no other predictor had any significant effect (all $ps > .20$). Again, nonparametric correlation of CTQ scores and hippocampal volume yielded comparable results, $r_s = -.29$, $p = .006$. There was no significant association of hippocampus morphometry with neuroticism or harm avoidance ($ps > .5$).

All CTQ subscales showed very similar associations with hippocampal volume. Physical neglect was the strongest predictor ($r = -.32$, $p < .0001$), followed by emotional abuse ($r = -.32$, $p < .0001$), sexual abuse ($r = -.31$, $p = .0001$), physical abuse ($r = -.30$, $p = .0003$), and emotional neglect ($r = -.24$, $p = .003$).

The whole-brain results are listed in Table 2. Notably, areas in the

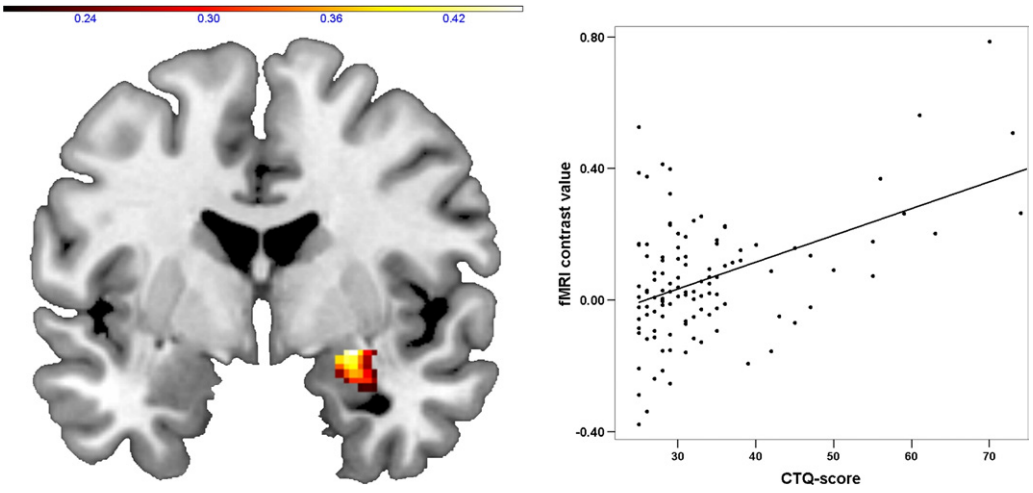

Figure 1. Childhood maltreatment (Childhood Trauma Questionnaire [CTQ] scores) is positively associated with right amygdala responsiveness to negative facial expressions. Left: Coronal view (y = −2) depicting amygdala responsiveness modulated by CTQ scores. For display reasons, the statistical threshold was set to $p < 01$, uncorrected. Color bar, correlation coefficient *r*. Right: Scatter plot depicting the positive correlation ($r = .456$, $p < .0001$) of the mean cluster activation values (left panel) and CTQ scores. fMRI, functional magnetic resonance imaging.

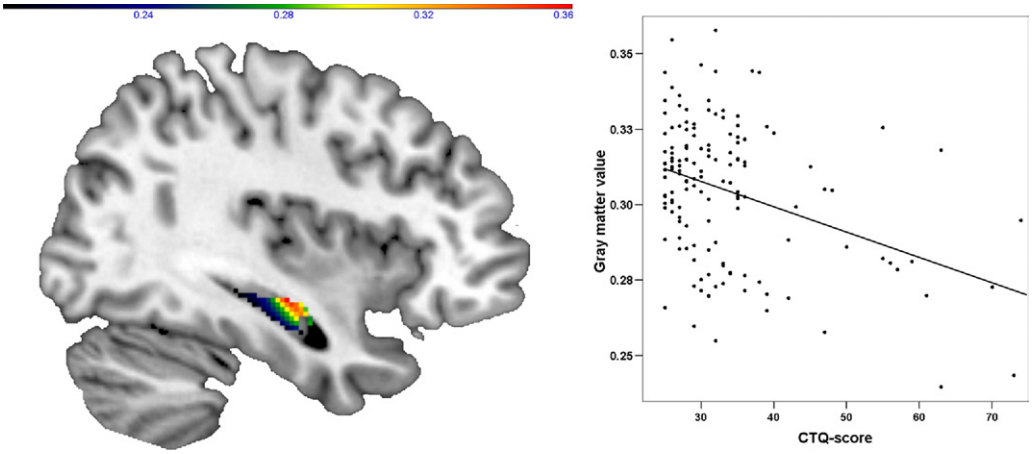

Figure 2. Childhood maltreatment (Childhood Trauma Questionnaire [CTQ] scores) is negatively associated with right hippocampal gray matter volume. Left: Sagittal view (x = 38) depicting gray matter volumes correlating with CTQ scores. For display reasons, the statistical threshold was set to $p < .01$, uncorrected. Color bar, negative correlation coefficient $-r$. Right: Scatter plot depicting the negative correlation ($r = -.365$, $p < .0001$) of the cluster values (left panel) and CTQ scores.

prefrontal cortex emerged showing gray matter volume reductions in dorsomedial and also ventromedial parts, including the anterior cingulate gyrus. There were no brain areas revealing positive associations with CTQ scores at the exploratory threshold.

Discussion

The present data suggest a robust effect of childhood maltreatment on two separate neuroimaging markers previously associated with depression and PTSD—amygdala responsiveness to negative facial expressions and reduced hippocampal volumes. These associations were demonstrated in a large sample of healthy subjects without any history of psychiatric disorders and they were not confounded by age, verbal intelligence, education, current depression and trait anxiety levels, level of perceived stress during the past month, or stressful life events during the year before participation.

Common to all neurobiological theories of emotion is the notion that the amygdala plays a key role in a neural circuit processing emotional valence and generating rapid affective responses (22,48,49). In human imaging studies, high amygdala responsiveness to negative stimuli has been shown to be associated with trait anxiety (50,51), depression level (52), and cognitive biases favoring the processing of negative stimuli (24,53). Several studies reported amygdala hyperresponsiveness to negative stimuli in acutely depressed patients (14–18,54–58). However, due to the lack of longitudinal studies, it is not clear whether amygdala hyperresponsiveness represents a feature of current major depression or a risk factor for depression onset. On the one hand, pharmaco-fMRI studies in healthy subjects, as well as in depressed patients, suggest that antidepressant medication reduces amygdala responsiveness to aversive stimuli (15,59–61), even within less than a day after application of a single dose (62,63). On the other hand, amygdala hyperresponsiveness to negative stimuli has been described in healthy subjects at risk for depression (64,65) and also in remitted patients (16). Since childhood maltreatment is a strong risk factor for depression, the present data further suggest that also unaffected risk populations show stronger amygdala responsiveness to negative stimuli, which might nourish speculations that the increased risk could be mediated by limbic hyperresponsiveness. Our findings are in line with a previous study investigating the relationship of childhood maltreatment and amygdala responsiveness to negative facial expressions (26) but contradict results reported by Taylor *et al.* (28). Differences regarding the fMRI task and different assessment tools for adverse childhood experiences could explain these discrepant findings.

Also, smaller hippocampus volumes are a frequent imaging finding in major depression (7). Since this has already been demonstrated in subjects at risk for depression (9,10,29), it was argued that reduced hippocampal volumes could be rather a risk factor for than a feature of depression (10). There is evidence that smaller hippocampus volume could act as a mediator for the relation between childhood maltreatment and depression (29). The same holds for PTSD, since smaller hippocampus volumes were associated with increased risk for developing PTSD after combat exposure (11). The hippocampus is a highly susceptible structure for the detrimental effects of stress, considering the high expression of glucocorticoid receptors. Since childhood trauma is associated with sensitization of the neuroendocrine stress response (4), it seems plausible to conclude that the hippocampus, as one of the most plastic structures in the brain, would show structural abnormalities resulting from repeated maltreatment experiences during childhood. Our morphometric results provide support for this hypothesis, and furthermore, this is the first evidence that these maltreatment-associated hippocampal volume reductions persist into adulthood, even in healthy subjects.

Regarding etiological specificity, it might be the case that childhood maltreatment generally increases the susceptibility for stress in later life with amygdala hyperresponsiveness and hippocampal atrophy representing two different aspects of this vulnerability. Therefore, it could be just a matter of which kind of stress occurs during later life, e.g., acute and traumatizing events could result in the onset of PTSD and/or more subtle but chronic stress could rather result in the development of depression. Ultimately, using such neuroimaging markers could be clinically useful to estimate individual risks for developing depression or PTSD.

Our morphometric finding regarding medial prefrontal cortex volume reductions in maltreated subjects stands in line with a previous study reporting a similar association (46). The medial prefrontal cortex is critically involved in emotion regulation processes and has dense connections with the amygdala. Volume reduction in this area as a sign for inhibition of growth or structural damage could be associated with lasting deficits in emotion processing and emotion regulation and therefore increase the risk for depression.

Further, gray matter volume decreases associated with maltreatment were found in the bilateral insula, anterior cingulate gyrus, orbitofrontal cortex, and caudate—again mirroring results previously obtained in major depression compared with healthy control subjects (66–69).

Our data might shed a new light on several previous imaging studies in major depression and PTSD. Since childhood maltreatment is strongly associated with these disorders, it seems very likely that most neuroimaging studies comparing patients and control subjects regarding functional or structural abnormalities were confounded by this variable. Thus, it might well be that some of the neurobiological findings previously reported in depression and PTSD could actually be attributed to differences regarding maltreatment experiences as a child. Future studies should address this issue by including measures of childhood maltreatment in samples of patients and control subjects.

Both neuroimaging measures showed their association with childhood maltreatment lateralized to the right. Laterality has already been described previously, e.g., associations of hippocampus morphometry and maltreatment measures have been reported predominantly left-sided in subjects suffering from depression or PTSD (70–73) but rather right-sided in borderline personality disorders (74–77). However, such laterality results should be treated with care, since it might well be the case that findings on one side exceed the significance threshold, while results on the other side just stay below and the actual laterality difference would not be significant. In our case, at a more lenient threshold of $p < .005$ (uncorrected), both amygdala responsiveness and hippocampus morphometry showed significant associations with CTQ scores also on the left side, which were not apparent at our rigorously corrected threshold.

For amygdala responsiveness, the strongest associations were found with the emotional abuse and emotional neglect subscales. While these results parallel a study of Teicher *et al.* (78) showing that emotional abuse has similar effects on psychiatric symptoms compared with sexual abuse and even larger effects compared with physical abuse, these results should be treated with care since all subscales showed significant effects in the same direction and had comparable effect sizes. Furthermore, the physical and sexual abuse subscales were those with the smallest variance and our sample was still not large enough to detect significant differences between different forms of maltreatment. Additionally, it may be the case that there are differential responses related to different types of abuse (e.g., effects of verbal abuse on superior temporal gyrus [79] and arcuate fasciculus [80] versus sexual abuse on occipital regions [47]). It may also be the case that there are sensitive periods when specific brain regions are most vulnerable (13,14), and one type of abuse may seem more important than another, as it may be more likely to occur at a specific age (e.g., neglect and physical abuse may tend to occur at younger ages than sexual abuse), which cannot be investigated with the present study design (81,82).

Some limitations must be acknowledged. The assessment of traumatic experiences during childhood was performed retrospectively by means of a self-report measure, which could be problematic. Subjects with high amygdala responsiveness and/or low hippocampus volumes could have a negative recall bias and a better memory for negative events during childhood. While we do not think that this constitutes a major problem in the present study since we could partial out the effects of more recent life stress as well as depression and anxiety levels, only prospective studies could definitely rule out this possibility. Furthermore, future studies should also address genetic effects (e.g., serotonin-transporter-linked polymorphic region or brain-derived neurotrophic factor Valine66Methionine) on the association of childhood maltreatment and neuroimaging measures, which seem to play a moderating role in terms of gene-environment interactions (83–85).

In sum, this is the first evidence that childhood maltreatment is associated with amygdala hyperresponsiveness to negative stimuli as well as lower hippocampal volumes in healthy adults without any history of psychiatric disorders. These neurobiological traits could therefore be a marker of an increased vulnerability for emotional disorders.

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