Reduced Medial Prefrontal Cortex Volume in Adults Reporting Childhood Emotional Maltreatment

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Background: Childhood emotional maltreatment (CEM) has been associated with a profound and enduring negative impact on behavioral and emotional functioning. Animal models have shown that adverse rearing conditions, such as maternal separation, can induce a cascade of long-term structural alterations in the brain, particularly in the hippocampus, amygdala, and prefrontal cortex. However, in humans, the neurobiological correlates of CEM are unknown.

Methods: Using high-resolution T1-weighted 3T magnetic resonance imaging, anatomical scans and a whole-brain optimized voxel-based morphometry approach, we examined whether healthy control subjects and unmedicated patients with depression and/or anxiety disorders reporting CEM before age 16 ($n = 84$; age: mean $= 38.7$) displayed structural brain changes compared with control subjects and patients who reported no childhood abuse ($n = 97$; age: mean $= 36.6$).

Results: We found that self-reported CEM is associated with a significant reduction in predominantly left dorsal medial prefrontal cortex volume, even in the absence of physical or sexual abuse during childhood. In addition, reduced medial prefrontal cortex in individuals reporting CEM is present in males and females, independent of concomitant psychopathology.

Conclusions: In this study, we show that CEM is associated with profound reductions of medial prefrontal cortex volume, suggesting that sustained inhibition of growth or structural damage can occur after exposure to CEM. Given the important role of the medial prefrontal cortex in the regulation of emotional behavior, our finding might provide an important link in understanding the increased emotional sensitivity in individuals reporting CEM.

Every year, approximately 1 in 10 children growing up in Western societies experiences childhood emotional maltreatment (CEM) (1). Emotional maltreatment encompasses any act of commission (i.e., verbal abuse) or omission (i.e., emotional neglect) that is (potentially) harmful, or insensitive to the child's emotional development (1,2) and has been associated with a profound and enduring negative impact on behavioral, emotional, and social functioning (1,2). For instance, CEM is associated with maladaptive emotional functioning in adulthood (3), which in turn is a key vulnerability factor for the development of psychiatric disorders when faced with stressors in later life (4). In line with this, CEM is an important predictor for the development of depressive and anxiety disorders in adulthood (5,6). However, the neurobiological correlates underlying the emotional sensitivity in individuals reporting CEM remain unknown.

In animals, adverse rearing environments such as maternal separation, loss, or isolation rearing induce a cascade of long-term alterations on the level of cognitive functioning, hypothalamic-pituitary-adrenal axis functioning, (immediate) gene expression, and brain morphology (7). Structural alterations in the brain include reduced dendrite length, dendritic branching, spine density, and suppression of neurogenesis and have predominantly been observed in limbic structures (amygdala, hippocampus) and prefrontal cortex (PFC) (7–10). In line with this, human studies examining the neuroanatomical correlates of childhood maltreatment in adults found decreased gray matter (GM) volume in the hippocampus (11,12) and medial (m)PFC (13–17). However, these studies focused mainly on the impact of sexual (11–13) and/or physical abuse (15) or did not exclude co-occurence of different types of abuse (14,16,17).

One way through which chronic stress may lead to structural changes is through enhanced activation of neuroendocrine systems (10). During chronic stress, increased secretion of glucocorticoids (i.e., the stress hormone cortisol in humans) interferes with the transcriptional mechanisms that control the expression of brain-derived neurotrophic factor (BDNF), a growth factor that has been linked to neuronal proliferation and plasticity (10,18). In this way, chronic stress may inhibit cytogenesis and increase vulnerability to attrition within the hippocampus, amygdala, or PFC (9,10). In line with these findings, childhood maltreatment has been linked to enhanced cortisol reactivity to psychosocial stress in patients with depression and anxiety disorders (19–21) and to blunted cortisol reactivity in healthy subjects (22,23). Additionally, altered patterns of cortisol reactivity during stress have been found in individuals reporting CEM (24). Furthermore, white matter (WM) tract abnormalities were found in a small sample of young adults reporting CEM ($n = 16$) (25). However, it is unknown whether CEM is similarly associated with structural GM abnormalities in adulthood. Given the important role of the limbic brain regions (hippocampus and amygdala) and the

mPFC in the perception and regulation of emotional behavior and stress response (7–10,26), GM abnormalities in (one of) these regions might underlie the maladaptive emotional functioning associated with CEM.

Therefore, we sought to investigate the effect of CEM on adult brain morphology in unmedicated patients currently diagnosed with depression and/or anxiety disorder and healthy control subjects (HCs). We used high-resolution magnetic resonance imaging (MRI) and a whole-brain optimized voxel-based morphometry (VMB) analysis approach, specifying the amygdala, hippocampus, and mPFC (medial prefrontal gyrus and anterior cingulate gyrus) as regions of interest (ROIs). We examined whether adult patients and HCs reporting multiple incidents of CEM before age 16 (*n* = 84) displayed structural brain changes in compared with patients and HCs who did not report a history of childhood abuse (*n* = 97). In addition, to examine whether these structural brain changes are related to the development of psychopathology, we investigated whether these brain alterations were more apparent in individuals with a depression or anxiety disorder compared with individuals who never developed a depression or anxiety disorder.

Methods and Materials

The Netherlands Study of Depression and Anxiety MRI Study

Participants were drawn from the Netherlands Study of Depression and Anxiety (NESDA), (*n* = 2981), a large cohort study (27). A subset of the NESDA participants (both patients and HCs) was selected to undergo MRI scanning for the NESDA MRI study. Inclusion criteria for patients in the NESDA-MRI study were current major depressive disorder (MDD) and/or anxiety disorder (ANX; panic disorder [PD] and/or social anxiety disorder [SAD] and/or generalized anxiety disorder [GAD] in the past 6 months according to DSM-IV criteria). Diagnoses were established using the structured Composite International Diagnostic Interview (28,29), administered by a trained interviewer. Exclusion criteria were the presence of Axis I disorders other than MDD, PD, SAD, or GAD; any use of psychotropic medication other than a stable use of selective serotonin reuptake inhibitors or infrequent benzodiazepine use (three times two tablets weekly or within 48 hours before scanning). Additional exclusion criteria for both patients and HCs were the presence or history of major internal or neurological disorder; dependency or recent abuse (past year) of alcohol or drugs; hypertension (>180/130 mmHg); heavy smoker (>5 cigarettes/day); and general MRI contraindications. The HCs had no lifetime depressive or anxiety disorders and were not taking any psychotropic drugs. Thus, 301 native Dutch-speaking participants (235 patients and 66 HCs) were included and underwent MRI at one of the three participating centers (i.e., Leiden University Medical Center, Amsterdam Medical Center, and University Medical Center Groningen). The ethical review boards of each participating center approved this study. All participants provided written informed consent.

Clinical Assessments

In the NESDA study, childhood maltreatment was assessed with the Nemesis Trauma Interview (30). In this interview, respondents were asked whether they had experienced emotional neglect, psychological abuse, physical abuse, and/or sexual abuse before age 16; how often this had occurred (i.e., never, once, sometimes, regularly, often, or very often); and what their relationship with the perpetrator was. Emotional neglect was described as "people at home didn't listen to you, your problems were ignored, and you felt unable to find any attention or support from the people in your house." Psychological abuse was described as "you were cursed at,

unjustly punished, your brothers and sisters were favored— but no bodily harm was done." CEM was defined as multiple incidents (more than once) of emotional neglect and/or emotional abuse before age 16 years, because we assumed that only multiple incidents of emotional abuse and/or emotional neglect might be associated with neuroanatomical changes. Overall CEM frequency was defined as the most frequent occurrence as reported (e.g., if psychological abuse occurred often and emotional neglect sometimes, overall CEM score is often).

Negative life events were assessed using the List of Threatening Events Questionnaire (LTE-Q), (31). In addition, at the day of scanning, depression and anxiety severity was measured using the Montgomery Åsberg Depression Rating Scale (MADRS) (32) and the Beck Anxiety Inventory (BAI) (33).

Additional Exclusion Criteria

High-resolution anatomical images were obtained from 291 participants (imaging data from 10 participants were excluded because of poor image quality). Additionally, two healthy control subjects were excluded from the NESDA-MRI study because of MADRS scores that indicated possible depressive symptomatology on the day of scanning (MADRS > 8) (34). For this study, individuals using selective serotonin reuptake inhibitors were excluded (*n* = 79) given their potential effect on neuronal plasticity (35). Additionally, individuals reporting physical or sexual abuse but no CEM were also excluded (*n* = 5). Finally, individuals reporting only a single incident of CEM (*n* = 24) were excluded. Our final sample (*n* = 181) consisted of 84 participants reporting CEM and 97 participants who reported no abuse (the No Abuse group).

The CEM and No Abuse Groups

The CEM group consisted of participants who reported emotional neglect and/or psychological abuse during childhood that had occurred sometimes, regularly, often, or very often (*n* = 84: i.e., MDD, *n* = 20; ANX, *n* = 21; comorbid depression and anxiety disorder [CDA], *n* = 30), and HC, *n* = 13; 36 of these 84 participants also reported childhood physical and/or sexual abuse, Table 1). The No Abuse group consisted of individuals who did not report CEM, physical abuse, or sexual abuse (*n* = 97: i.e., MDD, *n* = 22; ANX, *n* = 22; CDA, *n* = 13; and HC, *n* = 40). In the CEM group, 96.4% (*n* = 81) of the participants reported having been emotionally neglected, whereas 57.1% (*n* = 48) reported having been psychologically abused, and 54% (*n* = 45) reported both emotional neglect and psychological abuse. In addition, 97.6% reported that the individual's biological parents were the perpetrators of CEM (*n* = 82).

Magnetic Resonance Imaging

Image Acquisition. Imaging data were acquired using Philips 3T MR systems (Philips, Best, The Netherlands) located at the participating centers, equipped with a SENSE-8 (Leiden University Medical Center and University Medical Center Groningen) and a SENSE-6 (Amsterdam Medical Center) channel head coil. For each subject, an anatomical image was obtained using a sagittal three-dimensional gradient-echo T1-weighted sequence (repetition time: 9 msec; echo time: 3.5 msec; matrix 256 × 256; voxel size: 1 × 1 × 1 mm; 170 slices). Each scanning session also included several functional MRI runs, both "resting state" and task related. These results, as well as those of VBM comparisons between diagnostic groups (irrespective of childhood maltreatment), will be reported elsewhere (36).

Image Processing. An optimized VBM approach following the Diffeomorphic Anatomical Registration through Exponentiated Lie algebra (DARTEL) (37) was performed using SPM5 (Statistical Parametric Mapping software; http://www.fil.ion.ucl.ac.uk/spm) imple-

Table 1. Clinical and Demographic Characteristics of Participants Reporting Childhood Emotional Maltreatment Versus No Abuse

	No Abuse ($n = 97$)	CEM ($n = 84$)	F	U	χ^2	p
Gender, % M/F	33/67	34.5/65.5			.05	.83
Age, Mean (SEM)	36.57 (1.09)	38.68 (1.09)	1.86			.17
Education, Mean (SEM)	13.27 (0.29)	12.81 (0.35)		3706.5		.29
Handedness, % Left/Right	11/89	5/95			2.56	.11
Current Diagnosis,						
MDD, *n*	22	20			.09	.76
ANX, *n*	22	21			.02	.88
CDA, *n*	13	30			6.72	.01
HC, *n*	40	13			13.75	.00
Lifetime Diagnosis						
% MDD	43.29	77.38			25.64	.00
% ANX	41.24	67.86			12.83	.00
MADRS, Mean (SEM)	7.10 (.94)	14.45 (1.89)		2272.5		.00
BAI, Mean (SEM)	8.79 (1.04)	12.85 (1.08)		2651.5		.00
Scan Location, % A/L/G	28.9/41.2/29.9	38.1/38.1/23.8			1.89	.39
Frequency of CEM, %S/R/O/V	0	10.8/37.4/21.7/30.1				
Concurrent Abuse						
n Physical	0	15				
n Sexual abuse	0	8				
n Physical and Sexual abuse	0	13				
Gray Matter, Mean (SEM)	740.40 (7.98)	721.78 (7.33)	2.89			.09
White Matter, Mean (SEM)	491.33 (6.94)	494.69 (6.53)	.12			.73

A, Amsterdam Medical Center; ANX, anxiety disorder; BAI, Beck Anxiety Inventory; CDA, comorbid major depressive disorder and anxiety disorder; CEM, childhood emotional maltreatment; G, University Medical Center Groningen; HC, healthy control subjects; L, Leiden University Medical Center; MADRS, Montgomery Åsberg Depression Rating Scale; MDD, major depressive disorder; O, often; R, regularly; S, sometimes; V, very often.

mented in Matlab 7.1.0 (MathWorks, Natick, Massachusetts). VBM-DARTEL preprocessing included the following steps: 1) manual reorientation of the images to the anterior commissure; 2) segmentation of the anatomical images using the standard segmentation option implemented in SPM5; 3) applying the DARTEL approach for registration, normalization, and modulation, leaving the images in DARTEL space (In this approach, a DARTEL template is created based on the deformation fields that are produced by the segmentation procedure. Next, all individual deformation fields are warped (and modulated) to match this template.), and 4) smoothing of the GM and WM images using an 8-mm, full-width-at-half-maximum Gaussian kernel to increase the signal-to-noise ratio. In the resulting GM images, each voxel represents an absolute amount of GM volume, equivalent to the GM volume per unit before normalization.

VMB Analysis. GM (or WM) segments in native space were used to calculate absolute total GM (WM) volumes. Next, smoothed GM (WM) density images were entered into a voxel-by-voxel analysis of variance for between-group comparisons, with age and total absolute GM (WM) as covariate to correct for total brain volume. Effect of center was added by means of two dummy variables as extra regressors in all analyses. To achieve maximal sensitivity and to optimize voxel residual smoothness estimation and exclude false positives in non-GM (WM) tissue, voxelwise comparisons were masked using a comparison-specific explicit optimal threshold GM

(WM) mask created using the Masking toolbox (http://www.cs.ucl.ac.uk/staff/g.ridgway/masking) (38).

For the a priori–set ROIs (mPFC, amygdala, and hippocampus), we set a threshold of $p < .001$, uncorrected, with a spatial extent threshold of 50 contiguous voxels for group interactions. To further protect against Type I error, small volume correction (SVC) was applied by centering a sphere of 16 mm around the peak voxel. The resulting volumes of interest had to meet $p < .05$, corrected for family wise error (FWE) rate at the voxel level, to be considered significant (i.e., $Z > 3.50$). For regions not specified a priori, a voxel level threshold of $p < .05$ whole brain, FWE corrected, was set. If significant group differences were observed in the VBM analysis, we exported the volume of the significant clusters (= K centered on the peak voxel) per subject to SPSS. Clinical and demographic group differences were analyzed using SPSS-17 (http://www.spss.com), and in all analyses, age, total GM (WM) volume, and dummy regressors for the scan centers were included as covariates.

Results

The Neuroanatomical Correlates of CEM

To investigate the neuroanatomical correlates of CEM, we first set up a VBM analysis to compare the GM density maps/images of individuals reporting CEM ($n = 84$) with GM density maps of the No
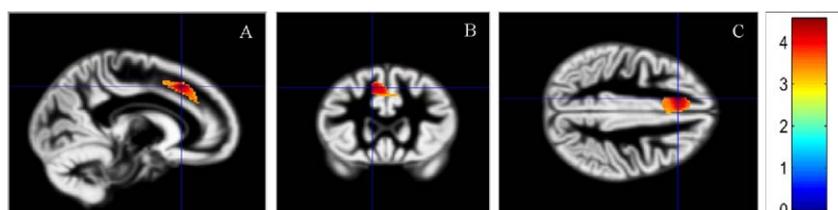

Figure 1. The medial prefrontal cortex region showing 7.2% volume reduction among individuals reporting only childhood emotional maltreatment displayed on sagittal **(A)**, transversal **(B)**, and coronal **(C)** planes.

Table 2. The Neuroanatomical Correlates of the CEM Versus No Abuse

		R/L	BA	Region	DARTEL Coordinate				
					k	x	y	z	z Value
CEM ($n = 97$) vs. No Abuse ($n = 84$)	CEM < No Abuse	L	8	Medial prefrontal gyrus	263	−11	23	40	3.80[a]
Only CEM ($n = 48$) vs. No Abuse ($n = 97$)	CEM < No Abuse	L+R	8	Medial prefrontal gyrus	767	−11	21	40	4.37[a]
						−5	9	42	
						6	18	36	
		R	9/32	Cingulate gyrus/medial prefrontal	87	9	44	16	3.53[a]
		R	10/32	Cingulate gyrus/medial prefrontal		11	47	9	

BA, Brodmann area; CEM, childhood emotional maltreatment; DARTEL, Diffeomorphic Anatomical Registration through Exponentiated Lie algebra; k, cluster size; L, left sided; R, right sided.

[a]$p < .05$, small volume correction 16-mm FWE corrected.

Abuse group ($n = 97$). These analyses revealed that CEM was associated with a 5.14% reduction in the left dorsal mPFC ($x = -11$, $y = 23$, $z = 40$), Brodmann area 8, cluster size/number of voxels (K) = 263, $Z = 3.80$, $p < .05$ (SVC; Table 2). No significant differences were observed in hippocampus or amygdala or in other brain regions. Only at a very low threshold was CEM associated with reduced right posterior hippocampal volume ($x = 29$; $y = -35$, $z = -6$), $Z = 2.06$, ns). Additionally, CEM was not associated with a significant increase in regional GM volumes. Finally, CEM was not associated with WM reductions in or surrounding our ROIs or with increased regional GM volume.

To explore possible interactions among CEM, current diagnosis, and gender, a 2 (CEM) × 4 (diagnosis: MDD, ANX, CDA, and HC) × 2 (gender) univariate analysis of covariance (ANCOVA) was performed, with local mPFC volume (milliliters) as a dependent factor. Again, individuals from the CEM group had smaller mPFC volumes than the No Abuse group ([CEM ($M \pm SEM$)]: 4.80 ± .06 mL vs. no abuse: 5.06 ± .06 mL) [$F(1,161) = 12.36$, $p < .01$, Cohen's $d = .53$]. Interestingly, there was no interaction between CEM and diagnosis [$F(3,161) = .45$, $p = .72$, $d = .01$], and post hoc analyses indicated that the mPFC reductions are present in all groups, even though the numbers were relatively small for such comparisons [one-sided: MDD, $F(1,34) = 8.65$, $p < .01$, $d = .93$; ANX, $F(1,35) = 2.55$, $p = .06$, $d = .50$; CDA, $F(1,35) = 2.63$, $p = .06$, $d = .55$; and HC, $F(1,45) = 1.85$, $p = .09$, $d = .44$]. In addition, there was no interaction between CEM and gender [$F(1,161) = 2.01$, $p = .99$, $d = .21$]. Taken together, these results indicate that reduced mPFC volume was present in all CEM groups (i.e., male and female subjects with MDD, ANX, CDA, and in the HC group). Moreover, similar results were obtained when depression and anxiety severity were added as covariates [$F(1,155) = 12.41$, $p < .01$, $d = .53$],[1] indicating that our results cannot be explained by the presence of more severe depressive and/or anxious symptomatology among individuals reporting CEM.

Neuroanatomical Correlates of Isolated Emotional Maltreatment in Childhood

To exclude the possibility that our results are driven by concurrent history of physical and/or sexual abuse in some of the participants, we conducted a whole-brain VBM analysis to compare the GM density maps of individuals reporting only CEM [$n = 48$, i.e. MDD, $n = 13$, ANX, $n = 12$, CDA, $n = 13$, and HC, $n = 10$, Table S1 in Supplement 1] with individuals reporting No Abuse ($n = 97$). In this analysis, the 36 individuals who also reported childhood physical

and/or sexual abuse were excluded. This analysis showed that individuals reporting only CEM had a volume reduction of 7.2% in left and right (although predominantly left) dorsal medial mPFC ([$x = -11$, $y = 21$, $z = 40$], Brodmann's area 8, K = 767, Z = 4.37, $p < .05$ [SVC]; Table 2), extending into the anterior mPFC and anterior cingulate gyrus (Figure 1, Table 2). Furthermore, no hippocampal, or amygdalar differences were observed, nor decreases in other brain regions. Again, only at a very low threshold was CEM associated with reduced right posterior hippocampal volume ([$x = 29$, $y = -35$, $z = -6$], Z = 2.45, ns). Finally, CEM was not associated with WM reductions in or surrounding our ROIs or with increased regional GM volume.

An ANCOVA confirmed the main effect of CEM [CEM: $M \pm SEM$: 4.78 ± .07 mL; No Abuse: 5.15 ± .06 mL; $F(1125 = 15.15$, $p < .001$, $d = .69$]. Moreover, the reduced mPFC volume was present in all CEM groups and in both male and female individuals [i.e., no interaction was found with diagnosis; $F(3,125) = .27$, $p = .85$, $d = .09$], and even within these small groups, post hoc analyses revealed a (marginally) significant (one-sided) impact of CEM only on mPFC volume [MDD, $F(1,27) = 7.72$, $p < .01$, $d = 1$; ANX, $F(1,26) = 2.93$, $p < .05$, $d = .63$; CDA, $F(1,18) = 3.20$, $p < .05$, $d = .73$; and HC, $F(1,42) = 1.96$, $p = .08$, $d = .51$], and CEM did not interact with gender [$F(1,125) = .08$, $p = .78$, $d = .05$]. Additionally, these results could not be explained by higher symptom severity among individuals reporting CEM because similar results were obtained when depression and anxiety severity were added as covariates [$F(1,116) = 15.72$, $p < .001$, $d = .70$].[2]

Associations Between Frequency of Emotional Maltreatment and mPFC Volume

To investigate whether the mPFC volume reductions were dependent on CEM frequency, we performed a 5 (frequency of CEM: No Abuse, sometimes, regularly, often, and very often) × 4 (diagnosis: MDD, ANX, CDA, and HC) ANCOVA, with local mPFC volume (mL) as a dependent factor. The analysis revealed a main effect of frequency of CEM on mPFC volume [$F(4120 = 4.89$, $p < .001$, $d = .39$],[3] which did not interact with psychopathology [$F(12,120 = .93$,

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[1]Four participants were missing because of incomplete depression or anxiety data (one reported CEM).

[2]History of alcoholism (abuse or dependence as measured with the Composite International Diagnostic Interview) did not affect the results (i.e., history of alcoholism [yes or no] was not a significant covariate in the analysis), $F(1,124) = 1.76$, $p = .19$, nor did it have an impact on the main effect of CEM on mPFC volume, $F(1,124) = 15.98$, $p < .000$, $d = .71$).

[3]Exclusion of the "sometimes" group ($n = 4$), due to its small size, did not affect the results, including the main effect of CEM on mPFC volume volume [$F(1,120) = 15.8$, $p < .000$, $d = .73$].
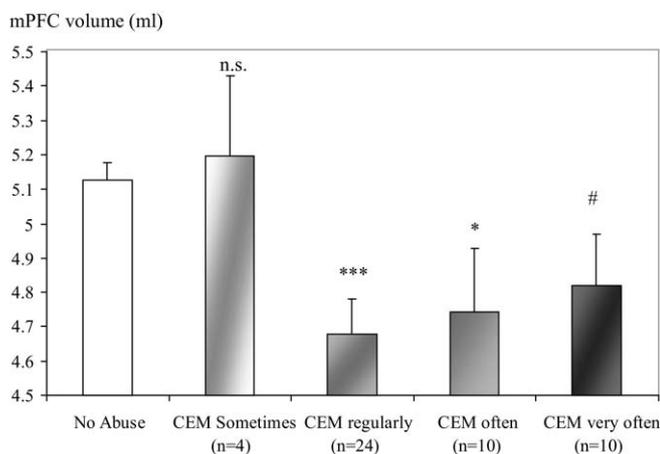
mPFC volume (ml)

Figure 2. Estimated marginal means and SEM of medial prefrontal cortex (mPFC) volume among the different frequencies of childhood emotional maltreatment (CEM) and contrast results of CEM frequencies versus the No Abuse group. ***α < .000; *α < .05; #p = .056; n.s., not significant (two-sided).

$p = .52$, $d = .17$]. As is illustrated in Figure 2, mPFC volumes were reduced in individuals who reported that CEM happened regularly or more often. Individuals reporting CEM occurred "sometimes" did not have a significantly lower mPFC volume compared with the no abuse group; however, this group was extremely small ($n = 4$), and therefore caution is warranted when interpreting the findings of these individuals.

Discussion

In this study, self-reported CEM was found to be associated with a significant reduction in predominantly left dorsal mPFC GM volume, independent of gender, and psychiatric status, at least in individuals who reported CEM occurring regularly or more frequently. Furthermore, the mPFC GM volume reduction was not due to concomitant childhood physical and/or sexual abuse, because the reductions were also found when CEM was experienced in absence of concurrent childhood physical and/or sexual abuse.

These findings provide an important clinical extension of preclinical observations that the mPFC is highly sensitive to the effects of chronic stress in childhood (7–9). The mPFC is one of the brain regions that undergo major developmental changes during childhood and adolescence (7,9). Exposure to emotionally abusive episodes during this developmental period may increase secretion of glucocorticoids, which may interfere with the transcriptional mechanisms that control the expression of brain-derived neurotrophic factor and may thereby inhibit cytogenesis and increase vulnerability to attrition within the mPFC (7–9,18). Moreover, the fact that reductions in hippocampal volume were only observed at a very low threshold and no significant changes were observed in the amygdala, concurs with findings of animal models on isolation rearing or maternal separation that indicate a specific and profound impact on the mPFC (40,41), in comparison with the hippocampus and amygdala (42). For example, in animals, it has been shown that architectural changes in prefrontal dendrites can be observed after only 1 week of stress or even after a single stressful incident (8). In contrast, structural changes in the hippocampus only appear after several weeks of stress, which might be an indication that the mPFC is more sensitive to the detrimental effects of stress (8).

The finding that CEM is associated with (predominantly left) dorsal mPFC reduction is of particular interest considering that the

mPFC plays an important role in emotion regulation (26,43). Moreover, reduced activity in the left PFC in particular has been associated with negative emotional states (44). Furthermore, the dorsal mPFC is essential for the regulation of autonomic and neuroendocrine stress response and arousal associated with emotional states and behavior, whereas the ventral mPFC has been implicated in generating these emotional states as well as behavior (43,45). The dorsal and ventral mPFC are reciprocally functionally related, and abnormalities in the function of either, or both, may be associated with abnormalities in emotional behavior and regulation (43). In line with these findings, decreased blood flow in the dorsal mPFC has been associated with increased autonomic responsiveness, anxiety, and sad mood (43). In addition, mPFC dysfunctions have been implicated in many psychiatric disorders, including depressive disorders (46) and anxiety disorders (47). Taken together, these results suggest that the reduced dorsal mPFC volume may (in part) underlie the enhanced emotional sensitivity associated with CEM. It should be noted that, contrary to our predictions, the reduced mPFC volume associated with CEM was independent of psychopathological status, indicating that the reduced mPFC volume was present not only in individuals with psychopathology but also in HCs who never developed a depression or anxiety disorder (although the number of HCs with reported CEM is relatively small, and effect sizes of mPFC reductions were also smaller in the HCs than in individuals with depression and/or anxiety). Therefore, reduced mPFC volume does not seem to be directly linked to the development of depressive or anxiety disorders in individuals reporting CEM. This finding is more consistent with the idea that additional risk factors, such as genetic makeup (48–50) alone or in interaction with exposure to stressful life events during adulthood may additionally determine who will subsequently develop a depressive and/or anxiety disorder (4,39). In line with this suggestion, individuals with current depressive and/or anxiety disorder reporting CEM ($n = 65$) indeed reported more negative life events (mean ± SEM: 5.96 ± .55) than HCs reporting CEM [$n = 13$; $4.62 ± .24$, $t(76) = -2.26$, $p < .05$].

Although our results are compelling, several potential limitations must be taken into account. The use of the DARTEL VBM approaches is not without its limitations (51), although recent studies (53,54) demonstrated that it is an improvement to standard voxel-based approaches. In addition, the sensitivity of the DARTEL approach for detecting hippocampal atrophy has been demonstrated in MDD patients (52). Nevertheless, manual tracing or shape-based analyses techniques, as have been used in most previous studies on hippocampal structural abnormalities, might be more sensitive in detecting deformations compared with an automated segmentation approach. Furthermore, although a clinically diagnosed posttraumatic stress disorder (PTSD) diagnosis was an exclusion criterion for NESDA, unidentified current or lifetime PTSD symptoms may still have been present, which may have influenced our findings. However, CEM-related mPFC GM reductions were also present among HCs who had never developed a depressive or anxiety disorder; therefore, it is unlikely that current or lifetime PTSD may have confounded our results. In addition, history of childhood maltreatment was retrospectively assessed by means of an interview, and it is important to acknowledge the inherent subjectivity of self-reported CEM. For instance, the retrospective assessment of CEM may be subject to recollection bias, so that individuals with current psychopathology may overreport, whereas HCs may underreport, a history of childhood maltreatment. However, in the NESDA sample, current affective state did not moderate the association between CEM and lifetime affective disorder, indicating that recall of CEM in the current sample was not critically affected by

current mood state (6). Finally, our findings are based on a cross-sectional study. Whereas the idea that CEM is associated with mPFC GM volume reductions fits well with numerous preclinical studies, the possibility of reversed causality cannot be excluded. For instance, individuals with reduced mPFC volume might report more CEM as a result of impaired emotion regulation. Another explanation may be that the reduced mPFC volume was preexistent and that inadequate emotion regulation associated with reduced mPFC volume might increase children's risk for exposure to CEM. Following this line of thought, one would expect that reports of presence or absence of life stressors later in life would also be related to mPFC volume. Nevertheless, presence of life stressors (yes or no) was not associated with mPFC volume [$F(1,109) = .09$, $p = .76$, $d = .05$], and the impact of CEM on mPFC volume remained unchanged when adding presence of life events into the analysis [$F(1,109) = 9.08$, $p < .01$, $d = .54$]. Theoretically, longitudinal studies examining neuroanatomical developmental changes over time among individuals reporting CEM are needed to shed more light on the etiology of our findings. To the best of our knowledge, such studies have not yet been conducted, and from an ethical point of view, it would be highly problematic to prospectively follow children who are known to be exposed to CEM without interfering in their situation.

In summary, we found in a large sample of unmedicated adults that self-reported CEM is associated with a substantial reduction in mPFC GM volume. In line with an accumulating number of animal studies (7,39–41), our finding suggest that sustained inhibition of growth, or even structural damage, can occur after exposure to emotional maltreatment in childhood. In addition, previous studies have shown that CEM is associated with altered hypothalamic-pituitary-adrenal axis reactivity to stress (23,24) and that CEM is an important predictor for the development of depressive and anxiety disorders in adulthood (5,6). Given the important role of the mPFC in the perception and regulation of emotional behavior and stress responses (7–10,26,45), our finding might provide an important link in understanding the increased emotional sensitivity in individuals reporting CEM.

Supplementary material cited in this article is available online.

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