Mood related insights : functional and structural MRI studies in depression and anxiety disorders

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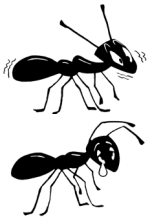

CHAPTER 6

REDUCED MEDIAL PREFRONTAL CORTEX VOLUME IN ADULTS REPORTING CHILDHOOD EMOTIONAL MALTREATMENT

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SUMMARY

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 dorsal 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 dorsal 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.

INTRODUCTION

Every year, approximately one in ten children growing up in Western societies experiences childhood emotional maltreatment (CEM) (Gilbert et al., 2009). 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 and has been associated with a profound and enduring negative impact on behavioral, emotional, and social functioning (Egeland, 2009; Gilbert et al.,2009). For instance, CEM is associated with maladaptive emotional functioning in adulthood (Teicher, Samson, Polcari, & McGreenery, 2006), which in turn is a key vulnerability factor for the development of psychiatric disorders when faced with stressors in later life (Beck, 2008). In line with this, CEM is an important predictor for the development of depressive and anxiety disorders in adulthood (Gibb, Chelminski, & Zimmerman, 2007; Spinhoven et al., 2010). 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 (Sanchez, Ladd, & Plotsky, 2001). 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) (Arnsten, 2009; Lupien, McEwen, Gunnar, & Heim, 2009; McEwen, 2008; Sanchez et al., 2001). In line with this, human studies examining the neuroanatomical correlates of childhood maltreatment in adults found decreased gray matter volume in the hippocampus (Kitayama, Vaccarino, Kutner, Weiss, & Bremner, 2005; Vythilingam et al., 2002) and medial PFC (Andersen et al., 2008; Cohen et al., 2006; Frodl, Reinhold, Koutsouleris, Reiser, & Meisenzahl, 2010; Tomoda et al., 2009; Treadway et al., 2009). However, these studies focused mainly on the impact of sexual (Andersen et al., 2008; Kitayama et al., 2005; Vythilingam et al., 2002) and/or physical abuse (Tomoda et al., 2009) or did not exclude co-occurence of different types of abuse (Cohen et al., 2006; Frodl et al., 2010; Treadway et al., 2009).

One way through which chronic stress may lead to structural changes is through enhanced activation of neuroendocrine systems (McEwen, 2008). 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 (McEwen, 2008; Nestler et al., 2002). In this way, chronic stress may inhibit cytogenesis and increase vulnerability to attrition within the hippocampus, amygdala, or PFC (Lupien et al., 2009; McEwen, 2008). In line with these findings, childhood maltreatment has been linked to enhanced cortisol reactivity to psychosocial

stress in patients with depression and anxiety disorders (Elzinga, Spinhoven, Berretty, de Jong, & Roelofs, 2010; Heim et al., 2000; Heim et al., 2002) and to blunted cortisol reactivity in healthy subjects (Carpenter et al., 2007; Elzinga et al., 2008). Additionally, altered patterns of cortisol reactivity during stress have been found in individuals reporting CEM (Carpenter et al., 2009). Furthermore, white matter tract abnormalities were found in a small sample of young adults reporting CEM (n =16) (Carpenter et al., 2009; Choi, Jeong, Rohan, Polcari, & Teicher, 2009). However, it is unknown whether CEM is similarly associated with structural gray matter abnormalities in adulthood. Given the important role of the limbic brain regions (hippocampus and amygdala) and the medial PFC in the perception and regulation of emotional behavior and stress response (Arnsten, 2009; Cardinal, Parkinson, Hall, & Everitt, 2002; Lupien et al., 2009; McEwen, 2008; Sanchez et al., 2001), gray matter 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 controls. We used high-resolution magnetic resonance imaging (MRI) and a whole-brain optimized voxel-based morphometry (VMB) analysis approach, specifying the amygdala, hippocampus, and medial PFC (including the anterior cingulate gyrus) as regions of interest. We examined whether adult patients and controls reporting multiple incidents of CEM before age 16 (n= 84) displayed structural brain changes in compared with patients and controls 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

PARTICIPANTS

Participants were drawn from the Netherlands Study of Depression and Anxiety (NESDA), (n= 2981), a large cohort study (Penninx et al., 2008). A subset of the NESDA participants (both patients and controls) 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 and/or social anxiety disorder and/or generalized anxiety disorder in the past six months according to DSM-IV criteria). Diagnoses were established using the structured Composite International Diagnostic Interview (Robins et al., 1988), administered by a trained interviewer. Exclusion criteria were the presence of Axis I disorders other than MDD, panic disorder, social anxiety disorder, or generalized anxiety disorder; 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

controls were the presence or history of major internal orneurological 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 healthy control participants had no lifetime depressive or anxiety disorders and were not taking any psychotropic drugs. Thus, 301 native Dutch-speaking participants (233 patients and 68 controls) were included and underwent MRI at one of the three participating centers (i.e., Leiden University Medical Center, Academic Medical Center Amsterdam, 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 (De, Bijl, Smit, Vollebergh, & Spijker, 2002). 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) (Brugha, Bebbington, Tennant, & Hurry, 1985). In addition, at the day of scanning, depression and anxiety severity was measured using the Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979) and the Beck Anxiety Inventory (BAI) (Beck et al., 1988).

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) (Muller et al., 2000). For this study, individuals using selective serotonin reuptake inhibitors were excluded (n= 79) given their potential effect on neuronal plasticity (Dranovsky & Hen, 2006). 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 re- porting 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 controls, 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 controls, 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 ACQUISITION

Imaging data were acquired using Philips 3-tesla 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 (Academic Medical Center) channel head coil. For each subject, an anatomical image was obtained using a sagittal 3-dimensional gradient-echo T1-weighted sequence (repetition time: 9 msec; echo time: 3.5 msec; matrix 256x256; voxel size: 1x1x1mm; 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), have been reported elsewhere (van Tol et al., 2010).

IMAGE PROCESSING

An optimized VBM approach following the Diffeomorphic Anatomical Registration through Exponentiated Lie algebra (DARTEL) (Ashburner, 2007) was performed using SPM5 (Statistical Parametric Mapping software; http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab 7.1.0 (The MathWorks Inc., Natick, MA, USA). 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

TABLE 1:
CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF PARTICIPANTS REPORTING CHILDHOOD EMOTIONAL MALTREATMENT VS. NO ABUSE

Childhood Emotional Maltreatment (CEM), ANX=Anxiety Disorder(s), MDD=Major Depressive Disorder, CDA=Comorbid Depression Anxiety, A=Academic Medical Center Amsterdam, L=Leiden University Medical Center, G=University Medical Center Groningen, MADRS=Montgomery Asberg Depression Rating Scale, BAI=Beck Anxiety Inventory, U, X2=Mann Whitney U, and Chi-square test statistics of CEM vs No Abuse comparisons, SEM=Standard Error of Mean.

		No Abuse (*n* =97)	CEM (*n* =84)	*U*	X^2	*p*
Gender	% M/F	33/67	34.5/65.5		.05	.83
Age	Mean (SEM)	36.57 (1.09)	38.68 (1.09)	3612		.19
Education	Mean (SEM)	13.27 (0.29)	12.81 (0.35)	3706.5		.29
Handedness	% L/R	11/89	5/95		2.56	.11
Current diagnosis	*n* MDD	22	20		.09	.76
	n ANX	22	21		.02	.88
	n CDA	12	30		6.72	.01
	n HC	40	13		13.75	.00
Liefetime 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
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)	3604		.18
White Matter	Mean (SEM)	491.33 (6.94)	494.69 (6.53)	3884		.59

fields are warped (and modulated) to match this template.), and 4) smoothing of the gray matter and white matter images using an 8-mm, full-width-at-half-maximum Gaussian kernel to increase the signal-to-noise ratio. In the resulting gray matter images, each voxel represents an absolute amount of gray matter volume, equivalent to the gray matter volume per unit before normalization.

VBM ANALYSIS

Gray matter (or white matter) segments in native space were used to calculate absolute total gray matter (white matter) volumes. Next, smoothed gray matter (white matter) density images were entered into a voxel-by-voxel analysis of variance for between-group comparisons, with age and total absolute gray matter (white matter) 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-gray matter (-white matter) tissue, voxelwise comparisons were masked using a comparison-specific explicit optimal threshold gray matter (white matter) mask created using the Masking toolbox (http://www.cs.ucl.ac.uk/staff/g.ridgway/masking) (Ridgway et al., 2009).

For the a priori–set regions of interest (medial PFC, anterior cingulate cortex, 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 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 per subject to SPSS. Clinical and demographic group differences were analyzed using SPSS-17 (http://www.spss.com), and in all analyses, age, total gray matter (white matter) 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 gray matter density maps/images of individuals reporting CEM (n= 84) with gray matter density maps of the No Abuse group (n= 97). These analyses revealed that CEM was associated with a 5.14% reduction in the left dorsal medial PFC ([x=-11, y=23, z=40], Brodmann area 8, cluster size/number of voxels (K)= 263, Z =3.80, $p< .05$ (small volume corrected; 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 gray matter volumes. Finally, CEM was not associated with white matter reductions in or surrounding our regions of interest or with increased regional white matter volume.

To explore possible interactions among CEM, current diagnosis, and sex, a 2 (CEM) x 4 (diagnosis: MDD, ANX, CDA, and controls) x 2 (sex) univariate analysis of covariance (ANCOVA) was performed, with local dorsal medial PFC volume (milliliters [ml]) as a dependent factor. Again, individuals from the CEM group had smaller dorsal medial PFC volumes than the No Abuse group ([CEM (M ± 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 dorsal medial PFC 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 controls, $F_{1,45}$= 1.85, p= .09, d=.44). In addition, there was no interaction between CEM and sex ($F_{1,161}$= 2.01, p= .99, d= .21). Taken together, these results indicate that reduced dorsal medial PFC volume was present in all CEM groups (i.e., male and female subjects with MDD, ANX, CDA, and in the control 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.

1 Four participants were missing because of incomplete depression or anxiety data (one reported 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 gray matter density maps of individuals reporting only CEM (n= 48, i.e. MDD, n= 13, ANX, n= 12, CDA, n= 13, and controls, n= 10; Table S-1 in the supplemental material 1) with individuals reporting No Abuse (n= 97). n 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 [small volume corrected]; Table 2), extending into the anterior medial PFC 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 white matter reductions in or surrounding our regions

TABLE 2:
THE NEUROANATOMICAL CORRELATES OF CHILDHOOD EMOTIONAL MALTREATMENT VS. NO ABUSE

Childhood Emotional Maltreatment (CEM), R=right sided, L=left sided, BA=Brodmann Area, K=cluster size (number of voxels), **p<.05, SVC 16 mm FWE corrected.

CEM (n=84) < No Abuse (n=97)

				DARTEL-coordinate			
R/L	BA	region	k	x	y	z	z-value
L	8	Medial prefrontal gyrus	263	-11	23	40	3.80 **
L+R	8	medial prefrontal gyrus	767	-11	21	40	4.37 **
				-5	9	42	

Only CEM (n=48) < No abuse (n=97)

				DARTEL-coordinate			
R/L	BA	region	k	x	y	z	z-value
R	9/32	cingulate gyrus/medial prefrontal gyrus	87	6	18	36	
R	10/32	cingulate gyrus/medial prefrontal gyrus		9	44	16	3.53 **
				11	47	9	

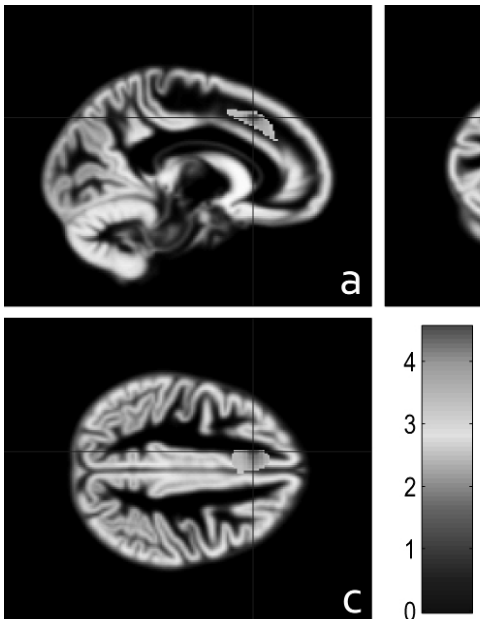


FIGURE 1 :

The medial PFC region showing 7.2 % volume reduction amongst individuals reporting only childhood emotional maltreatment displayed on a sagittal (A),coronal (B) and transversal (C) plane.

A full-color image can be found on the supplementary sheet.

of interest or with increased regional gray matter of white matter volume.

An ANCOVA confirmed the main effect of CEM (CEM: M ± SEM: 4.78 ± .07 ml; No Abuse: 5.15 ± .06 ml; $F_{1,125}$= 15.15, p< .001, d= .69). Moreover, the reduced dorsal medial PFC 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 dorsal medial PFC 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 controls, $F_{1,42}$= 1.96, p= .08, d= .51), and CEM did not interact with sex ($F_{1,125}$=.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

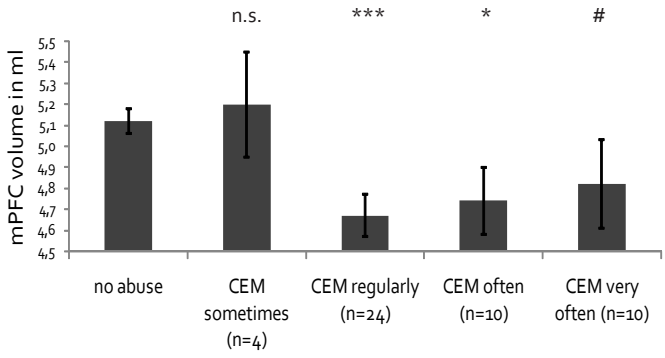
To investigate whether the dorsal medial PFC volume reductions were dependent on CEM frequency, we performed a 5 (frequency of CEM: No Abuse, sometimes, regularly, often, and very often) x 4 (diagnosis: MDD, ANX, CDA, and controls) ANCOVA, with local dorsal medial PFC volume (ml) as a dependent factor. The analysis revealed a main effect of frequency of CEM on dorsal medial PFC volume [$F_{4,120}$= 4.89, p< .001, d= .39][3] which did not interact with psychopathology [$F_{12,120}$= .93, p= .52, d= .17]. As is illustrated in Figure 2, dorsal medial PFC 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 dorsal medial PFC 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.

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), F1,124= 1.76, P=.19, nor did it have an impact on the main effect of CEM on dorsal medial PFC volume, F1,124= 15.98, p< .001, 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 dorsal medial PFC volume [F1,120= 15.8, p<.001, d= .73].

FIGURE 2:

Estimated Marginal Means and Standard Error of Mean (SEM) of medial PreFrontal Cortex (mPFC) volume amongst the different frequencies of Childhood Emotional Maltreatment (CEM), and contrast results of EM frequencies vs. the No Abuse group. ***= p <.000, * = p<.05, # = p =.056, n.s. = not significant (two-sided).



In this study, self-reported CEM was found to be associated with a significant reduction in predominantly left dorsal medial PFC gray matter volume, independent of sex, and psychiatric status, at least in individuals who reported CEM occurring regularly or more frequently. Furthermore, the dorsal medial PFC gray matter 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 dorsal medial PFC is highly sensitive to the effects of chronic stress in childhood (Arnsten, 2009; Lupien et al., 2009; Sanchez et al., 2001). The medial PFC is one of the brain regions that undergo major developmental changes during childhood and adolescence (Lupien et al., 2009; Sanchez et al., 2001)). 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 medial PFC (Arnsten, 2009; Heim et al., 2000; Lupien et al., 2009; Sanchez et al., 2001). 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 medial PFC (Levine et al., 2008; Sanchez et al., 2007), in comparison with the hippocampus and amygdala (Schubert, Porkess, Dashdorj, Fone, & Auer, 2009). For example, in animals, it has been shown that architectural changes in prefrontal dendrites can be observed after only one week of stress or even after a single stressful incident (Arnsten, 2009). In contrast, structural changes in the hippocampus only appear after several weeks of stress, which might be an indication that the medial PFC is more sensitive to the detrimental effects of stress (Arnsten, 2009).

The finding that CEM is associated with (predominantly left) dorsal medial PFC reduction is of particular interest considering that the medial PFC plays an important role in emotion regulation (Cardinal et al., 2002; Phillips et al., 2003a). Moreover, reduced activity in the left PFC in particular has been associated with negative emotional states (Demaree, Everhart, Youngstrom, & Harrison, 2005). Furthermore, the dorsal medial PFC is essential for the regulation of autonomic and neuroendocrine stress response and arousal associated with emotional states and behavior, whereas the ventral medial PFC has been implicated in generating these emotional states as well as behavior (Drevets et al., 2008; Phillips et al., 2003a). The dorsal and ventral medial PFC are reciprocally functionally related, and abnormalities in the function of either, or both, may be associated with abnormalities in emotional behavior and regulation (Phillips et al., 2003a). In line with these findings, decreased blood flow in the dorsal medial PFC has been associated with increased autonomic responsiveness, anxiety,

and sad mood (Phillips et al., 2003a) In addition, dorsal medial PFC dysfunctions have been implicated in many psychiatric disorders, including depressive disorders (Drevets et al., 2008) and anxiety disorders (Zhao et al., 2007). Taken together, these results suggest that the reduced dorsal medial PFC volume may (in part) underlie the enhanced emotional sensitivity associated with CEM. It should be noted that, contrary to our predictions, the reduced medial PFC volume associated with CEM was independent of psychopathological status, indicating that the reduced medial PFC volume was present not only in individuals with psychopathology but also in controls who never developed a depression or anxiety disorder (although the number of controls with reported CEM is relatively small, and effect sizes of medial PFC reductions were also smaller in the controls than in individuals with depression and/or anxiety). Therefore, reduced medial PFC 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 (Frodl et al., 2010; Gatt et al., 2009; Joffe et al., 2009) 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 (Beck,2 008; Caspi & Moffitt, 2006). 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 controls 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 (Ridgway et al., 2008), although recent studies (McLaren, Kosmatka, Kastman, Bendlin, & Johnson, 2010; Yassa & Stark, 2009) 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 (Bergouignan et al., 2009). 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 diagnosis was an exclusion criterion for NESDA, unidentified current or lifetime posttraumatic stress disorder symptoms may still have been present, which may have influenced our findings. However, CEM-related medial PFC gray matter reductions were also present among controls who had never developed a depressive or anxiety disorder; therefore, it is unlikely that current or lifetime posttraumatic stress disorder 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 over-report, whereas controls

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 (Spinhoven et al., 2010). Finally, our findings are based on a cross-sectional study. Whereas the idea that CEM is associated with dorsal medial PFC gray matter volume reductions fits well with numerous preclinical studies, the possibility of reversed causality cannot be excluded. For instance, individuals with reduced dorsal medial PFC volume might report more CEM as a result of impaired emotion regulation. Another explanation may be that the reduced dorsal medial PFC volume was preexistent and that inadequate emotion regulation associated with reduced dorsal medial PFC 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 dorsal medial PFC volume. Nevertheless, presence of life stressors (yes or no) was not associated with medial PFC volume ($F_{1,109}$= .09, p= .76, d= .05], and the impact of CEM on medial PFC 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 aetiology 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 dorsal medial PFC gray matter volume. In line with an accumulating number of animal studies (Caspi & Moffitt, 2006; Levine et al., 2008; Sanchez et al., 2007; Sanchez et al., 2001), 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 (Carpenter et al., 2009; Elzinga et al., 2008) and that CEM is an important predictor for the development of depressive and anxiety disorders in adulthood (Gibb et al., 2007; Spinhoven et al., 2010). Given the important role of the mPFC in the perception and regulation of emotional behavior and stress responses (Arnsten, 2009; Cardinal et al., 2002; Lupien et al., 2009; McEwen, 2008; Radley, Williams, & Sawchenko, 2008; Sanchez et al., 2001), our finding might provide an important link in understanding the increased emotional sensitivity in individuals reporting CEM.

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TABLE S-1.
CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF PARTICIPANTS REPORTING ONLY CHILDHOOD EMOTIONAL MALTREATMENT VS. NO ABUSE.

Childhood Emotional Maltreatment (CEM), ANX= Anxiety Disorder, MDD= Major Depressive Disorder, CDA= comorbid major depressive disorder and anxiety disorder, S=sometimes, R=regularly, O=often, V= very Often, A= Amsterdam Medical Center, L= Leiden University Medical Center, G= University Medical Center Groningen, MADRS= Montgomery Åsberg Depression Rating Scale, BAI= Beck anxiety inventory, F, U, X^2 =F ratio, Mann Whitney U, and Chi-square test statistics, SEM= Standard Error of Mean.

		No abuse (n=97)	only CEM (n=48)	U	X^2	*p*
Gender	% M/F	33/67	42/58		1.05	.30
Age	Mean (SEM)	36.57 (1.09)	37.6 (1.60)	2204.5		.60
Education	Mean (SEM)	13.27 (0.29)	13.56 (0.41)	2229		.67
Handedness	% L/R	11/89	6/94		.95	.33
Current diagnosis	*n* MDD	22	12		2.31	.13
	n ANX	22	12		2.94	.09
	n CDA	12	13		.00	1
	n HC	40	10		18.00	.00
Liefetime diagnosis	% MDD	43.29	72.92		11.31	.00
	% ANX	41.24	60.42		4.74	.00
MADRS	Mean (SEM)	7.10 (.94)	12.30 (0.16)	1428		.00
BAI	Mean (SEM)	8.79 (1.04)	11.91 (1.41)	1603		.01
Scan location	% A/L/G*	28.9 /41.2/29.9	37.5/39.6/22.9		1.34	.51
Gray Matter	Mean (SEM)	740.40 (7.98)	739.73 (8.79)	2260		.76
White Matter	Mean (SEM)	491.33 (6.94)	499 (9.57)	2145		.44