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Hypoactive medial prefrontal cortex functioning in adults reporting childhood emotional maltreatment

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Childhood emotional maltreatment (CEM) has adverse effects on medial prefrontal cortex (mPFC) morphology, a structure that is crucial for cognitive functioning and (emotional) memory and which modulates the limbic system. In addition, CEM has been linked to amygdala hyperactivity during emotional face processing. However, no study has yet investigated the functional neural correlates of neutral and emotional memory in adults reporting CEM. Using functional magnetic resonance imaging, we investigated CEM-related differential activations in mPFC during the encoding and recognition of positive, negative and neutral words. The sample (N = 194) consisted of patients with depression and/or anxiety disorders and healthy controls (HC) reporting CEM (n = 96) and patients and HC reporting no abuse (n = 98). We found a consistent pattern of mPFC hypoactivation during encoding and recognition of positive, negative and neutral words in individuals reporting CEM. These results were not explained by psychopathology or severity of depression or anxiety symptoms, or by gender, level of neuroticism, parental psychopathology, negative life events, antidepressant use or decreased mPFC volume in the CEM group. These findings indicate mPFC hypoactivity in individuals reporting CEM during emotional and neutral memory encoding and recognition. Our findings suggest that CEM may increase individuals' risk to the development of psychopathology on differential levels of processing in the brain; blunted mPFC activation during higher order processing and enhanced amygdala activation during automatic/lower order emotion processing. These findings are vital in understanding the long-term consequences of CEM.

Keywords: Anxiety; childhood abuse; depression; emotional maltreatment; magnetic resonance imaging (MRI); medial prefrontal cortex (PFC)

INTRODUCTION

Childhood emotional maltreatment (CEM; emotional abuse and/or emotional neglect) is experienced by one out of 10 children growing up in Western societies every year (Gilbert *et al.*, 2009). CEM is the most prevalent type of child-maltreatment and has a profound negative impact on social, cognitive, behavioral and emotional functioning (Pollak *et al.*, 2009; Egeland, 2009; Gilbert *et al.*, 2009; Hart and Rubia, 2012; Spinhoven *et al.*, 2010; Schechter, 2012). After chronic exposure to CEM, individuals may develop sustained negative self-associations (Van Harmelen *et al.*, 2010a), which may bias attention toward negative information about the self and others. Even as adults, this may result in negative interpretations when engaged in stressful interpersonal situations, or when retrieving memories of such situations (Beck, 2008). In line, individuals with CEM are more prone to develop depressive and anxiety disorders (Spinhoven *et al.*, 2010; Iffland *et al.*, 2012).

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Chronic childhood stress is associated with structural and functional changes in the brain, especially within the (medial) prefrontal cortex [(m)PFC], hippocampus and the amygdala [see overviews and mechanisms; (Arnsten, 2009; Lupien *et al.*, 2009; Danese and McEwen, 2012; Hart and Rubia, 2012; McCrory *et al.*, 2012; McEwen *et al.*, 2012)]. In line, we reported CEM-related smaller mPFC volume (Van Harmelen *et al.*, 2010b) and amygdala hyperactivation during the processing of emotional faces in patients and healthy controls (HC) (Van Harmelen *et al.*, 2013); see also Bogdan *et al.* (2012); Dannlowski *et al.* (2012a; 2012b) and McCrory *et al.* (2011). The mPFC is crucial for emotional processing, memory and modulates the stress response (Cardinal *et al.*, 2002; Phillips *et al.*, 2003; Etkin *et al.*, 2011). The dorsal mPFC plays a vital role in the (re-) appraisal of emotional stimuli, whereas the ventral mPFC dampens fear responses through its regulation of the amygdala (Phillips *et al.*, 2003; Etkin *et al.*, 2011). The dorsal and ventral mPFC are functionally inextricably intertwined, therefore abnormalities in either or both may be associated with abnormalities in emotional processing, memory and stress response (Phillips *et al.*, 2003; Etkin *et al.*, 2011). The mPFC is also crucial for understanding other people's beliefs, feelings and motivations (i.e. mentalizing) (Frith & Frith, 2003; Frith and Frith, 2006; Mitchell *et al.*, 2006; Denny *et al.*, 2012; Meyer *et al.*, 2013). In children, a smaller PFC volume has been found to mediate the link between childhood stress and reduced cognitive functioning (Hanson *et al.*, 2012). However, the neural correlates of cognitive functioning in adults reporting CEM are unknown.

During and immediately after acute interpersonal stress, brain activity shifts from higher cortical (e.g. mPFC) regions to 'lower' sub-cortical regions (e.g. amygdala, hippocampus) (Hermans *et al.*, 2011; Oei *et al.*, 2012). Stress activates the amygdala as part of a 'salience

network' for vigilant attentional reorienting, strengthening of emotional memory traces and autonomic-neuroendocrine control, facilitating the processing/encoding of emotional information, at the detriment of higher order cognitive functions (Davis and Whalen, 2001; Whalen, 2007; Hermans *et al.*, 2011; Todd *et al.*, 2011; Oei *et al.*, 2012). In HCs, exposure to acute psychosocial stress increases coupling of mPFC and amygdala activations, which persists even some time after the stress has waned (Veer *et al.*, 2011). To investigate whether CEM is related to a reduction in higher order cognitive functioning, the functional neural correlates of CEM during cognitive tasks that are known to engage frontal regions need to be examined.

Here, we examined the neural correlates of CEM during the encoding and recognition of (positive, negative and neutral) words in a large sample ($N=194$), by comparing patients and HC reporting CEM [$n=96$; i.e. patients with major depressive disorder (MDD; $n=20$), anxiety disorder (ANX; $n=27$), co-morbid depression and anxiety disorder (CDA; $n=40$) and HC ($n=9$)], with those reporting no abuse [$n=98$; [i.e. MDD ($n=24$), ANX ($n=22$), CDA ($n=19$) and HC ($n=33$)]. We expected that self-reported CEM was associated with a memory bias (i.e. relative enhanced recognition) with respect to negative stimuli and limbic (amygdala and hippocampal) hyperactivations during encoding and recognition of negative words, but not for positive or neutral words. In addition, we expected a general reduction in cognitive functioning in individuals with CEM, associated with overall reduced mPFC activations (across valence).

METHOD

Participants

Participants were a subset from the Netherlands Study of Depression and Anxiety [NESDA; $N=2981$; (Penninx *et al.*, 2008)], consisting of

233 patients with MDD and/or ANX and 68 HC. Participants underwent magnetic resonance imaging (MRI) scanning in the Leiden University Medical Center (LUMC), Academic Medical Center Amsterdam (AMC) or University Medical Center Groningen (UMCG). Trained interviewers established diagnoses using the structured Composite International Diagnostic Interview (Wittchen *et al.*, 1991). Patients were included when they had a diagnosis <6 months recency of current DSM-IV MDD and/or ANX (panic disorder and/or social anxiety disorder). Patients were excluded if they were taking any psychotropic medication other than stable use of selective serotonin reuptake inhibitors (SSRIs) or infrequent benzodiazepine use (i.e. equivalent to two doses of 10 mg of oxazepam three times per week or use within 48 h prior to scanning). HCs had no lifetime MDD or ANX and were not taking any psychotropic drugs. Ethical Review Boards of each participating center approved this study, and after complete description of the study, written informed consent was obtained.

Childhood maltreatment

Childhood maltreatment was assessed through the NEMESIS trauma interview (De Graaf *et al.*, 2002). Participants were asked whether they had experienced emotional neglect, emotional abuse, physical abuse or sexual abuse before the age of 16 years, and if so, how often it occurred ('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'. Emotional 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

Table 1 Demographics, clinical characteristics and memory performance of the No Abuse and CEM groups

Characteristics and performance	No Abuse ($N=98$) Mean (s.d.)	CEM ($N=96$) Mean (s.d.)	χ^2	F-value	P-value
Age	36.48 (10.56)	38.11 (9.52)		1.28	0.26
Gender (male/female) (n)	32/66	37/59	0.73		0.39
Education level (attained in years)	13.16 (2.88)	12.5 (3.28)		2.24	0.14
Scan location (A/L/G) (n)	30/37/31	32/38/26	0.50		0.78
Diagnosis (yes/no) (n)	65/33	87/9	16.88		<0.001
Diagnosis (MDD/CDA/ANX/HC) (n)	24/19/22/33	20/40/27/9	22.04		<0.001
Type of abuse (CEM + S / CEM + P/ CEM + S&P) (n)		56/16/13/11			
Frequency of CEM (Som/Reg/Often/very Often) (n)		15/27/19/35			
SSRI use (yes/no) (n)	21/77	29/67	1.95		0.16
Parental psychopathology (yes/no) (n)	38/25	54/18	3.37		0.07
Negative life events	4.06 (1.97)	5.43 (2.17)		20.99	<0.001
Neuroticism	34.31 (7.93)	41.81 (9.34)		36.31	<0.001
MADRS	8.19 (9.29)	15.08 (9.99)		26.81	<0.001
BAI	9.29 (9.62)	12.82 (9.04)		6.63	<0.011
Anxiety score (VAS) before encoding	34.12 (24.71)	34.94 (27.27)		0.05	0.83
Anxiety score (VAS) after encoding	29.54 (21.66)	30.13 (24.75)		0.03	0.86
Word classification					
Proportion words classified as positive	98.94 (24.04)	98.37 (22.35)		0.03	0.87
Proportion words classified as negative	96.97 (5.68)	96.07 (11.39)		0.45	0.51
Proportion words classified as neutral	103.14 (24.52)	102.77 (25.03)		0.01	0.92
Memory					
Proportion correctly recognized positive words	0.73 (0.13)	0.73 (0.15)		0.01	0.93
Proportion correctly recognized negative words	0.69 (0.13)	0.69 (0.16)		0.07	0.80
Proportion correctly recognized neutral words	0.69 (0.15)	0.71 (0.17)		1.41	0.24
Proportion false alarms positive words	0.12 (0.10)	0.11 (0.09)		0.03	0.85
Proportion false alarms negative words	0.17 (0.11)	0.15 (0.10)		1.27	0.26
Proportion false alarms neutral words	0.06 (0.06)	0.06 (0.05)		0.00	0.97
Discriminant sensitivity positive words	0.61 (0.16)	0.62 (0.15)		0.04	0.85
Discriminant sensitivity negative words	0.52 (0.12)	0.54 (0.14)		1.40	0.24
Discriminant sensitivity neutral words	0.63 (0.16)	0.65 (0.17)		1.37	0.24

abuse (in line with our previous studies, e.g. van Harmelen *et al.*, 2010b, 2013). In the final sample ($N=194$, Table 1; additional exclusion criteria in Supplementary Data), 96 adults reported CEM ($n=20$ MDD, $n=27$ ANX, $n=40$ CDA, $n=9$ HC) and 98 reported no abuse ($n=24$ MDD, $n=22$ ANX, $n=19$ CDA, $n=33$ HC). This is largely the same cohort in whom we found CEM-related reduced mPFC volume (Van Harmelen *et al.*, 2010b) and enhanced amygdala responses (Van Harmelen *et al.*, 2013). In the CEM group, participants reported isolated emotional neglect ($n=46$, 47.9%), isolated emotional abuse ($n=3$, 3.1%) or both emotional neglect and emotional abuse ($n=47$, 49.0%) in childhood. In addition, 95 participants (99.0%) reported their biological parents as perpetrators, one person (1.0%) reported a stepfather as perpetrator.

Additional assessments

In the NESDA study, we assessed lifetime negative life events with the List of Threatening Events Questionnaire (Brugha *et al.*, 1985) and Neuroticism with the NEO Five-Factor Inventory (Costa and McGrae, 1992). Parental psychopathology was assessed using a family tree approach interview, assessing whether a member of their family had experienced anxiety, depression or other psychopathological problems, and if so, which member of their family. On the day of scanning (~8 weeks following NESDA baseline assessment), severity of depression and anxiety (last 2 weeks) was assessed using the Beck Anxiety Inventory (BAI; Beck *et al.*, 1988) and the Montgomery Åsberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979).

Task paradigm

The word-encoding and -recognition task was event-related, subject-paced (max 5 s) (Daselaar *et al.*, 2003) (Supplementary Data). During encoding, participants were asked to classify 40 positive, 40 negative and 40 neutral words according to their valence. During a baseline control condition, participants viewed the words 'left', 'middle' or 'right' and were instructed to press the corresponding key. After a 10 min retention interval, participants indicated whether they had 'seen' (i.e. remembered), 'probably had seen' (i.e. know), or 'hadn't seen' (i.e. rejection) 120 old encoding target words, 120 new distracter words and 40 baseline control trials. Trial presentation was pseudo-randomized. We recorded response accuracy and times (RT). Anxiety levels were recorded before and after word encoding and recognition using a Visual Analogue Scale (0–100; Huskisson, 1993).

Image acquisition

Imaging data were acquired using Philips 3-Tesla MRI-systems (Best, The Netherlands) located at the LUMC, AMC and UMCG, equipped with SENSE-8 (LUMC, UMCG) and SENSE-6 (AMC) channel head coils. Echo-planar images were obtained using a T2*-weighted gradient echo sequence [repetition time (TR)=2300 ms; echo time (TE)=30 ms (UMCG: 28 ms), matrix size: 96 × 96 (UMCG: 64 × 64), 35 axial slices (UMCG: 39), interleaved acquisition, 2.29 × 2.29 mm in-plane resolution (UMCG: 3 × 3 mm), 3 mm slice thickness]. Anatomical imaging included a sagittal three-dimensional gradient-echo T1-weighted sequence (TR=9ms, TE=3.5 ms; matrix 256 × 256; voxel size: 1 × 1 × 1 mm; 170 slices).

Imaging data

Functional imaging data were pre-processed in Statistical Parametric Mapping software (SPM5) in Matlab7.1 (www.mathworks.co.uk) and analyzed using SPM8 in Matlab7.8. Pre-processing of the imaging data included reorientation of the functional images to the anterior

commissure, slice time correction, image realignment, registration of the T1 scan to the mean image, warping to Montreal Neurological Institute (MNI)-space as defined by the SPM5 T1-template, reslicing to 3 × 3 × 3 mm voxels and spatial smoothing using an 8 mm FWHM Gaussian kernel. Next, data were analyzed in the context of the General Linear Model. Hemodynamic responses to each stimulus were modeled with a delta function convolved with a synthetic hemodynamic response function and modulated using RT. The model included regressors for encoding¹ and recognition² parameters. In addition, filler words, error- and no-response trials were included as a regressor of no interest. Low-frequency noise was removed by applying a high-pass filter (cut-off: 128 s) to the fMRI time-series at each voxel. Owing to the small proportion of 'know responses' on the recognition trials, these responses were treated as 'remembered' and added to either correct recognition (CREC) or false alarms (FA).

Contrast images for subsequently correctly recognized (SCR) words during encoding (SCR_pos > baseline, SCR_neg > baseline, SCR_neu > baseline) and CREC words during recognition (CREC_pos > baseline, CREC_neg > baseline and CREC_neu > baseline) were calculated per subject on a voxel-by-voxel basis and entered into second-level analyses for between-group comparisons.

We next set up CEM (No Abuse, CEM) × Words (Positive, Negative, Neutral) RM ANCOVAs for the encoding and recognition task separately. Age, gender and education level were specified as covariates (Iidaka *et al.*, 2002; Hart and Rubia, 2012) and two dummy variables were added as covariates to control for variation caused by the different scanning locations. To examine if CEM-related word encoding and recognition was confounded by individual's psychiatric status, we also added a dummy for current MDD, ANX (yes/no), demeaned within the CEM and No Abuse group to control for variation caused by psychopathology. As only nine HC reported CEM, we were unable to perform group (MDD, ANX, CDA, HC) × CEM (No Abuse, CEM) RM ANOVAs, as these analyses would be seriously underpowered. For the specific effects of MDD, ANX and HC on word encoding and recognition in largely the same sample, see van Tol *et al.* (2012).

We defined the following ROIs: hippocampus, amygdala, and mPFC. Because the anatomical location of the mPFC is less well defined than that of the hippocampus and amygdala, we focused on the mPFC in the broadest sense (i.e. dorsal mPFC (Brodmann area (BA) 8 and 9), ventral mPFC (BA 10), dorsolateral mPFC (BA 8, 9, and 46), and the dorsal and pregenual ACC (BA 32,24), using the AAL toolbox implemented in the Wake Forest University (WFU)-Pickatlas (Maldjian *et al.*, 2003). The main effects of task are reported at $P < 0.05$, Family Wise Error (FWE) (voxel level). Activations outside our ROIs were examined using whole-brain analyses at $P < 0.05$ FWE corrected, while masking for the main effect of task ($P < 0.05$ uncorrected). All results are reported in MNI space.

Bilateral Amygdala (131 voxels) and hippocampal (536 voxels) activations were examined by extracting their activations for the main effect of task (F) to SPSS using Marsbar (Brett *et al.*, 2002) and binary masks using WFU-Pickatlas. MPFC activations were examined using CEM vs No Abuse (F) analysis at $P < 0.005$, uncorrected and post hoc t -tests had to meet $P < 0.05$ FWE corrected for the spatial extend of the activated region with an initial height threshold of $Z > 3.09$, and $K > 5$ voxels, while masking for the main effect of task ($P < 0.05$ uncorrected). For this small volume correction (P_{SVC}) we used the WFU-pickatlas and to extract significant mPFC activations for the main effect of task to SPSS we used the Marsbar Toolbox.

¹SCR_pos, SCR_neg, SCR_neu, SMISS_pos, SMISS_neg, SMISS_neu, BL. (SCR = subsequently correct; SMISS = subsequently missed).

²CREC_pos, CREC_neg, CREC_neu, CREJ_pos, CREJ_neg, CREJ_neu, FA_pos, FA_neg, FA_neu, MISS_pos, BL. (CREC = Correct recognition; CREJ = correct rejections; MISS = misses).

Behavioral analyses

Psychometric and performance data were analyzed with SPSS-19. Proportions (p) Correctly Recognized words (pCREC), False Alarms (pFA) and old/new discriminant accuracy ($d' = pCREC - pFA$) were calculated for positive, negative and neutral words. For all tests, significance was set at $P < 0.05$ two-tailed, Bonferroni-corrected.

RESULTS

CEM vs No Abuse group characteristics and memory performance

The CEM vs No Abuse groups did not differ in age, education, gender, SSRI-use, scan location and anxiety levels before and after the task. The CEM group included more patients, reported higher depressive and anxious symptomatology, higher neuroticism scores, more lifetime negative life events and slightly more parental psychopathology (Table 1). RM ANOVAs revealed no differences in valence classification,³ memory performance or RTs, between the CEM and No Abuse groups (Table 1 and Supplementary Table S1).

Imaging results

Main effect of task during word encoding

The main effect of task during encoding was associated with bilateral amygdala [$K=6$, $x=-18$, $y=-6$, $z=-18$, Z -score (Z)=6.73] and ($K=1$, $x=24$, $y=-9$, $z=-15$, $Z=5.38$), hippocampal, ($K=174$, $x=-21$, $y=-15$, $z=-18$, $Z>8$, $K=60$, $x=-21$, $y=-15$, $z=-21$, $Z=6.97$), ($K=31$, $x=21$, $y=-12$, $z=-18$, $Z=6.93$) and mPFC activations ($K=740$, $x=-6$, $y=60$, $z=30$, $Z>8$); ($K=57$, $x=-27$, $y=0$, $z=57$, $Z=7.67$) and ($K=38$, $x=-39$, $y=36$, $z=30$, $Z=6.45$). Supplementary Table S2 depicts main effect of task activations outside our ROIs.

CEM and word encoding: amygdala and hippocampus

Extracted amygdala and hippocampal activations for the main effect of task (SCR_pos > baseline, SCR_neg > baseline and SCR_neu > baseline) were analyzed in a CEM (No Abuse, CEM) \times Words (Positive, Negative, Neutral) \times Lateralization (Left, Right) RM ANCOVA, with psychiatric status (demeaned within group), age, gender, education level and dummies for location as covariates. Contrary to our expectations, there were no significant main or interaction effects of CEM [amygdala (F -values < 1.41 , all P -values > 0.24) and hippocampus (F -values < 2.69 , P -values > 0.10), details in Supplementary Data].

CEM and word encoding: mPFC

A CEM vs No Abuse analysis showed CEM-related mPFC hypoactivation during the encoding of positive, negative and neutral words ($K=26$, $x=-3$, $y=45$, $z=33$, $Z=3.91$, $P_{svc}=0.024$; Figure 1).⁴ No other clusters were found in or outside our ROIs (Table 2).

A CEM (No Abuse, CEM) \times Words (positive, negative, neutral) RM ANCOVA on extracted mPFC activations in this cluster, with psychiatric status (demeaned within group), age, gender, education level and dummies for location as covariates showed, besides the main effect of CEM [$F(1, 186) = 11.26$, $P = 0.001$], a marginal main effect of Words [$F(2, 372) = 2.78$, $P = 0.06$]. Positive words elicited more mPFC activation (mean = 0.28, s.e. = 0.04) compared with neutral (mean = 0.16, s.e. = 0.05; $P < 0.01$), but not negative words (mean = 0.25, s.e. = 0.04, $P = 0.70$). No other differences were found (P -values > 0.11). There

was no Words \times CEM interaction neither other significant main nor interaction effects (F -values < 2.19 , P -values > 0.13). Current psychiatric status had a main effect on mPFC activation [$F(1, 186) = 7.93$, $P = 0.01$]; HC had more mPFC activations than patients (t -values > 2.75 , P -values < 0.007).

Additional covariance analyses showed that the main effect of CEM remained significant when we co-varied for depression or anxiety severity, neuroticism scores, parental psychopathology, negative life events, concurrent physical and/or sexual abuse, antidepressant medication use or mPFC volume in the CEM group (see Supplementary Data).

Finally, to investigate the functional connectivity of this mPFC cluster ($x = -3$, $y = 45$, $z = 33$) in individuals with CEM (compared with No Abuse), we performed a psycho-physiological interaction (PPI) analysis (specifics in Supplementary Data; Friston *et al.*, 1997).⁵ Across participants, the PPI showed positive connectivity with the right amygdala ($K=9$, $x=21$, $y=0$, $z=-15$, $Z=3.87$, $P_{svc}<0.004$) and left hippocampus ($K=17$, $x=-24$, $y=-12$, $z=-18$, $Z=3.97$, $P_{svc}<0.02$). No negative connectivity was found with our ROIs. However, no differential connectivity was found for the CEM vs No Abuse groups within our ROIs (Supplementary Data and Supplementary Table S3).

Recognition

Main effect of task during word recognition.

The main effect of task during recognition was associated with mPFC activations ($K=129$, $x=-3$, $y=27$, $z=48$, $Z=6.85$); ($K=54$, $x=-30$, $y=-3$, $z=57$, $Z=6.71$); ($K=45$, $x=3$, $y=63$, $z=3$, $Z=6.57$); ($K=51$, $x=33$, $y=48$, $z=30$, $Z=6.46$), ($K=5$, $x=0$, $y=9$, $z=39$, $Z=4.79$), but neither with amygdala nor hippocampal activations. Supplementary Table S2 displays task activations outside our ROIs.

Impact of CEM on word recognition in the mPFC

A CEM vs No Abuse analysis showed CEM-related mPFC hypoactivation during the correct recognition of positive, negative and neutral words ($K=152$, $x=-6$, $y=48$, $z=39$, $Z=4.18$, $P_{svc}=0.007$, Figure 1). No other significant clusters were found in or outside our ROIs (Table 2).

Next, we performed a CEM (CEM vs No Abuse) \times Words (Positive, Negative, Neutral) RM ANCOVA on extracted mPFC activations, with psychiatric status (demeaned within group), age, gender, education level and dummies for location as covariates. Besides the main effect of CEM [$F(1, 186) = 18.34$, $P < 0.001$], there was no main effect of Words [$F(2, 372) = 0.04$, $P = 0.96$]. Psychiatric status did have a main effect [$F(1, 186) = 9.25$, $P = 0.003$], with HCs having higher mPFC activations than patients (t -values > 3.54 , P -values < 0.001). Furthermore, gender had a marginal main effect [$F(1, 186) = 3.53$, $P = 0.06$], with males having marginally more mPFC activation than females for positive words ($t = 1.74$, $P = 0.08$), but not for negative or neutral words (t -values < 1.48 , P -values > 0.14). Location had a significant main effect [i.e. AMC = [$F(1, 186) = 5.24$, $P = 0.02$] and LUMC = [$F(1, 186) = 3.62$, $P = 0.06$]]. Participants scanned at the AMC had marginally more mPFC activation for negative words ($t = 1.90$, $P = 0.06$), but not for positive or neutral words (t s > 1.14 , P -values > 0.26). Post hoc t -tests showed that participants scanned in Leiden did not have more mPFC activation (all t s > 1.40 , all P -values > 0.16). There was no Words \times CEM interaction, neither other main nor interaction effects (F s < 1.82 , P -values > 0.16).

³For the word classification task, data from 16 individuals were missing (six reported No Abuse).

⁴The mPFC activations for encoding and recognition were small-volume corrected using a mask based on the left superior frontal medial cortex, 584 voxels, region based on AAL toolbox.

⁵Due to technical problems with fMRI data of three participants (one reported CEM), we could not include these participants in the PPI analyses.

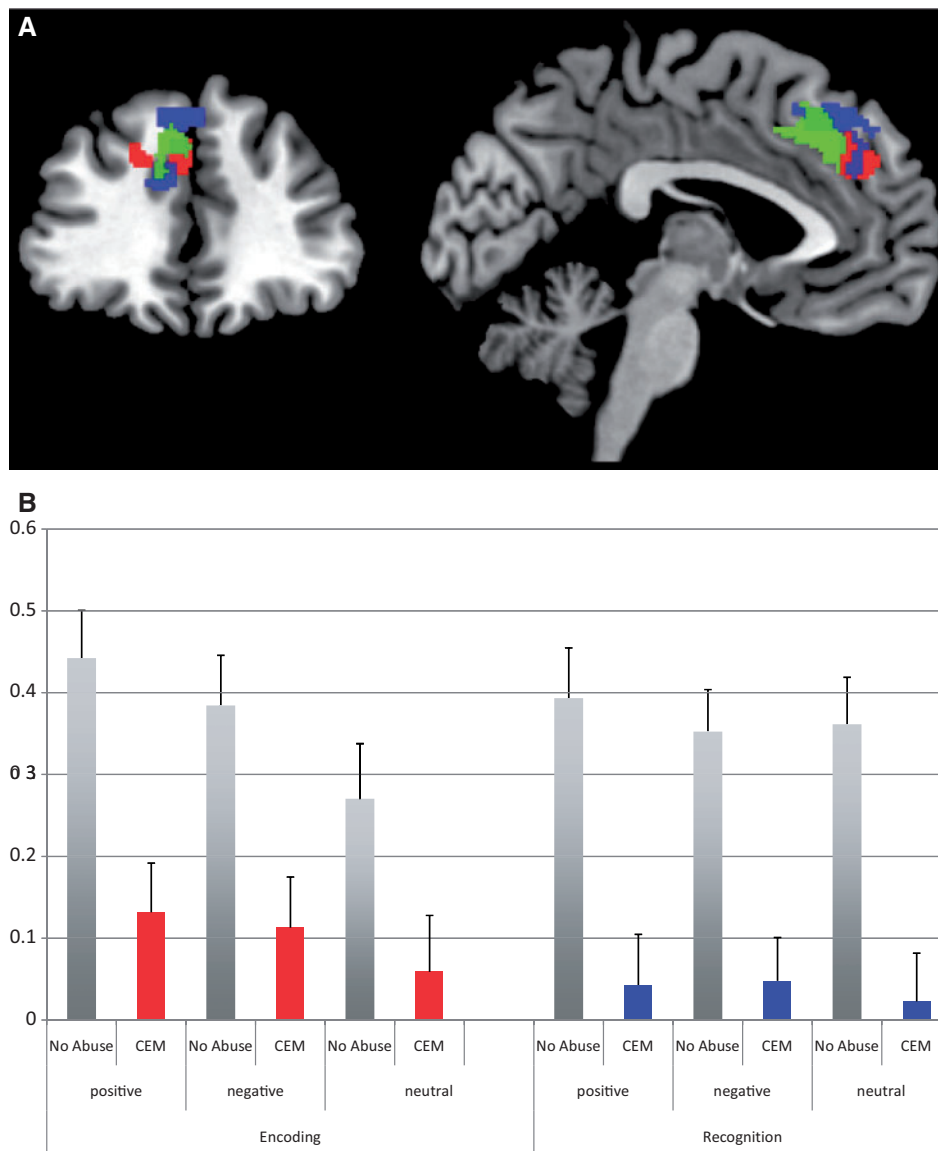


Fig. 1 Medial prefrontal cortex activations during encoding and recognition of positive, negative and neutral words in adults reporting CEM ($N = 96$) vs No Abuse ($N = 98$). (A) Depicts the main effect of CEM on medial prefrontal cortex activation during encoding (red) and recognition (blue) at $P < 0.005$ $K > 5$ uncorrected. The green blob depicts the region that has been found to be smaller in adults reporting CEM (van Harmelen et al., 2010b). (B) Depicts the medial prefrontal cortex activations (BOLD signal change) during encoding (red) and recognition (blue) of positive, negative and neutral words in adults reporting CEM vs No Abuse.

Table 2 Main effect of CEM at $P < 0.005$, $K > 5$

Main effects CEM	K-values	F-values	Z-values	P(unc)	x, y, z (mm)
Encoding					
Medial frontal gyrus	28	15.31	3.71	<0.001	-3, 45, 33
Superior temporal gyrus	22	13.53	3.47	<0.001	57, -51, 9
Inferior frontal gyrus	10	13.26	3.43	<0.001	-51, 30, 0
Insula	12	12.14	3.27	0.001	39, -27, 6
		10.36	3	0.001	39, -27, 18
Middle temporal gyrus	5	10.73	3.06	0.001	-54, -9, -15
	6	9.78	2.9	0.002	54, 3, 39
Recognition					
Medial frontal gyrus	129	17.76	4.02	<0.001	-6, 48, 39
		15.49	3.74	<0.001	-3, 33, 45
		12.04	3.26	0.001	-12, 39, 24
Putamen	5	12.41	3.31	<0.001	-30, -3, -6
Inferior parietal lobe	8	10.52	3.02	0.001	-24, 57, 15

Follow-up covariance analyses showed that CEM-related hypoactivation could not be explained by more depression or anxiety severity, neuroticism scores, parental psychopathology, negative life events, concurrent physical and/or sexual abuse, antidepressant medication use or mPFC volume (Supplementary Data).

Finally, a PPI analysis in this mPFC cluster ($x = -6, y = 48, z = 39$), revealed positive connectivity with the left amygdala ($K = 11, x = -27, y = 0, z = -18, Z = 3.64, P_{svc} < 0.009$) and left hippocampus ($K = 22, x = -21, y = -12, z = -24, Z = 4.98, P_{svc} < 0.005$), but no negative connectivity with the mPFC, across participants. Finally, no CEM-related differential connectivity was found within our ROIs (Supplementary Data and Supplementary Table S4).

DISCUSSION

We show consistent CEM-related mPFC hypoactivation during the encoding and recognition positive, negative and neutral words, a

task that requires higher order cognitive processing. Our findings cannot be explained by CEM-related higher levels of neuroticism, parental psychopathology, negative life events, concurrent physical and/or sexual abuse, antidepressant medication use or smaller mPFC volume (Van Harmelen *et al.*, 2010b). In addition, the mPFC hypoactivations were not accounted for by psychiatric status, or by higher depressive or anxiety symptoms, despite the fact that the CEM group contained more patients and those patients showed mPFC hypoactivation compared with HC.

Contrary to our predictions, limbic activations were not enhanced and PPI analyses showed no CEM-related differential mPFC–amygdala coupling either. Therefore, and together with findings of CEM-related amygdala hyperactivity to facial expressions (McCrorry *et al.*, 2011, 2013; Bogdan *et al.*, 2012; Dannlowski, *et al.* 2012a,b; Van Harmelen *et al.*, 2013), these findings suggest that individuals reporting CEM show hypoactive mPFC activation during cognitive processing/evaluation for meaning/content (subserved by the mPFC) and hyperactive amygdala activation in response to emotionally demanding tasks or contexts, which require amygdala processing. Interestingly, this pattern of findings resembles those of studies on the impact of acute stress exposure, showing that stress exposure induces a shift from higher cognitive to more habitual/emotional processes and related neural systems (PFC vs limbic regions) (Hermans *et al.*, 2011; Oei *et al.*, 2012).

Individuals reporting CEM showed similar response accuracy and RTs for positive, negative and neutral words. Thus, although enhanced negative stimuli processing and related brain activations have been reported in depressed individuals (see for an overview: Groenewold *et al.*, 2013), and in post-traumatic stress disorder (PTSD) (see for an overview: Brown and Morey, 2012), we did not find support for CEM-related biased processing of negative stimuli. It is unclear whether this reflects a lack of biased processing, or whether the task at hand was not sensitive enough to detect biases. The classification task did not assess appraisal of the words; hence, even though participants know how to accurately categorize the words they may still appraise them as more negative. In addition, recognition was assessed after a short (10 min) retention interval, making our task prone to performance ceiling effects that may obscure performance biases.

We found CEM-related mPFC hypoactivation across valence, however, on a behavioral level, we did not find similarly reduced cognitive processing. The CEM group was as accurate and fast in categorizing words as the No Abuse group. Hence, mPFC hypoactivation in individuals reporting CEM may resemble a more general blunting of cognitive processing in these individuals; individuals reporting CEM may require less cognitive and related mPFC processing in order to correctly recognize words later on. It is unknown whether this overall blunting of mPFC activation translates to other cognitive domains, which one might expect given that the mPFC is also implicated in self-referential processing and mentalizing (Frith *et al.*, 2003; Frith and Frith, 2006; Mitchell *et al.*, 2006; Denny *et al.*, 2012; Meyer *et al.*, 2013). Future studies are needed to investigate whether CEM-related mPFC hypoactivation is related to dysfunctions in these forms of social cognitive processing, as this may have important clinical implications.

Some limitations need to be taken into account. First, retrospective self-reported CEM is innately subjective and patients may over-report CEM histories. However, maltreatment history is more likely to be under- than over-reported (Hardt and Rutter, 2004; Brewin, 2007), and in the NESDA sample ($N=2981$), CEM recall was not affected by current mood state (Spinhoven *et al.*, 2010). Moreover, a history of maltreatment (including emotional abuse and emotional neglect) based on the NEMESIS trauma interview has been associated with an increased incidence and prevalence of psychiatric disorders, suggesting that the NEMESIS trauma interview has good construct

validity (e.g. de Graaf *et al.*, 2002; 2004; Wiersma *et al.*, 2009; Hovens *et al.*, 2010; Spinhoven *et al.*, 2010; van Harmelen *et al.*, 2010a). Furthermore, in a confirmatory factor analysis, type of abuse on the NEMESIS trauma interview showed loadings on latent constructs for abuse type comparable with the loading of analogous subscales of the childhood trauma questionnaire (CTQ, Thombs *et al.*, 2009), which is a well validated and reliable questionnaire on childhood trauma (Thombs *et al.*, 2009) (Spinhoven *et al.*, submitted for publication). In addition, compared with the CTQ, CEM is more likely to be under-reported than over-reported in the NEMESIS trauma interview and patients were shown to be somewhat more consistent in their reports than individuals without psychopathology (Spinhoven *et al.*, submitted for publication).

Second, IQ was not assessed as a potential confound in our analyses. However, education level, which is highly correlated with IQ ($r=0.88$; Gottfredson, 1997), did not explain our findings. Third, although the effects of CEM on brain functioning remain after regressing out important potential confounds such as psychopathology, parental psychopathology and neuroticism, comparing the CEM and No Abuse groups is intrinsically confounded by these factors and in the context of GLM, only linear components of such effects are addressed this way. Regressing out confounders cannot fully solve this problem and future studies may have to address this issue by directly comparing, for example, individuals with CEM and high levels of psychopathology vs individuals with CEM and no psychopathology. Fourth, contrary to our expectations, we did not find significant hippocampal or amygdala activations related to CEM during word encoding and retrieval. And although hippocampal and amygdala activations during word encoding and recognition in largely the same sample have been linked to psychopathology (van Tol *et al.*, 2012), we cannot rule out the possibility that our null findings regarding the impact of CEM in these regions may be due to the design of our study, namely a multi-site MRI collaboration. A multi-site MRI study may increase between-subject variability due to different scanner specifications and may therefore decrease sensitivity in detecting small effects. However, previous work on largely the same (multi-site) sample (see van Harmelen *et al.*, 2013) found CEM-related increased activation in the amygdala during emotional face processing. This suggests that our multi-site design is sensitive enough to identify overall group differences, and hence cannot fully explain the lack of effects in the amygdala and hippocampus in the context of word encoding. Fifth, our cross-sectional design obscures causality inferences; mPFC hypoactivation may have been present before CEM and may even been a pre-disposing factor that enhances parental risk to emotionally maltreat their children. However, continuing this line of reasoning, it might be expected that parental psychopathology is related to our findings, and it was not. Theoretically, only longitudinal studies can disentangle the impact of CEM from its pre-disposing factors. However, these studies are highly problematic from an ethical point of view, hence, our cross-sectional study with a large sample of patients and HCs and control of many potential confounds is a good alternative.

CONCLUSION

We found that CEM is related to mPFC hypoactivation during the encoding and recognition of positive, negative and neutral words. This was not explained by higher depression or anxiety symptoms, neuroticism, parental psychopathology, negative life events, antidepressant use or by mPFC volume. Together with previous findings of CEM-related smaller mPFC volume (Van Harmelen *et al.*, 2010b) and amygdala hyperactivity to facial expressions (McCrorry *et al.*, 2011, 2013; Bogdan *et al.*, 2012; Dannlowski *et al.*, 2012a,b, submitted for publishing; Van Harmelen *et al.*, 2012), these findings suggest that

CEM increases individuals' risk to the development of psychopathology (Spinhoven *et al.*, 2010; Iffland *et al.*, 2012) on differential levels of processing in the brain; mPFC hypoactivation during cognitive processing or more basal amygdala hyperactivation during emotion processing. Therefore, our findings add substantively to the understanding of the long-term impact of CEM.

SUPPLEMENTARY DATA

Supplementary data are available at SCAN online.

Conflict of Interest

None declared.

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