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Hypoactive medial Prefrontal Cortex functioning in adults reporting Childhood Emotional Maltreatment

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ABSTRACT

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 fMRI, 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, nor 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.

INTRODUCTION

Childhood emotional maltreatment (CEM; emotional abuse and/or emotional neglect) is experienced by one out of ten children growing up in western societies every year (Gilbert, Widom, 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 (Egeland, 2009; Gilbert, Widom, et al., 2009; Hart & Rubia, 2012; Pollak et al., 2008; Schechter, 2012; Spinhoven et al., 2010). After chronic exposure to CEM, individuals may develop sustained negative self-associations (Van Harmelen et al., 2010), which may bias attention towards 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 (Iffland et al., 2012; Spinhoven et al., 2010).

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; Danese & McEwen, 2012; Hart & Rubia, 2012; Lupien et al., 2009; McCrory et al., 2012; McEwen et al., 2012). In line, we reported CEM related smaller mPFC volume (Van Harmelen, Van Tol, et al., 2010), and amygdala hyperactivation during the processing of emotional faces in patients and healthy controls (HC) (Van Harmelen et al., 2012); see also (Bogdan, Ph, Williamson, & Hariri, 2012; Dannlowski, Kugel, et al., in press; Dannlowski, Stuhrmann, et al., 2012; McCrory et al., 2011). The mPFC is crucial for emotional -processing, -memory, and modulates the stress response (Cardinal et al., 2002; Etkin et al., 2011; Phillips et al., 2003). The dorsal mPFC plays a vital role in the (re-) appraisal of emotional stimuli, while the ventral mPFC dampens fear responses through its regulation of the amygdala (Etkin et al., 2011; Phillips et al., 2003). 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 (Etkin et al., 2011; Phillips et al., 2003). The mPFC is also crucial for understanding other people's beliefs, feelings, and motivations (i.e. mentalizing) (Denny et al., 2012; Frith & Frith, 2006; Frith & Frith, 2003; Meyer et al., 2012; Mitchell, Macrae, & Banaji, 2006). 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' subcortical 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 & Whalen, 2001; Hermans et al., 2011; Oei et al., 2012; Todd, Evans, Morris, Lewis, & Taylor, 2011; Whalen, 2007). 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 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), Comorbid 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 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 2 doses of 10 mg of oxazepam 3 times per week or use within 48 hrs 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, Bijl, Smit, Vollebergh, & Spijker, 2002), Participants were asked whether they had experienced emotional neglect, emotional abuse, physical abuse, or sexual abuse before the age of 16, 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 (>once) of emotional neglect and/or emotional abuse (In line with our previous studies e.g. van Harmelen, van Tol et al., 2010, van Harmelen et al., 2013). In the final sample (N=194, Table 1; additional exclusion criteria in supplement), 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, Van Tol, et al., 2010), 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; Bebbington, Tennant, & Hurry, 1985), and Neuroticism with the NEO Five-Factor Inventory (Costa & 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. At the day of scanning (Approx. 8 weeks following NESDA baseline assessment), severity of depression and anxiety (last two weeks) was assessed using the Beck Anxiety Inventory (BAI; Beck, Epstein, Brown, & Steer, 1988) and the Montgomery Åsberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979).

TASK PARADIGM

The word-encoding and -recognition task was event-related, subject-paced (max 5s) (Daselaar, Veltman, Rombouts, Raaijmakers, & Jonker, 2003), supplement). 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 ten minute 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]=2300ms; echo time [TE]=30ms [UMCG: 28 ms], matrix size: 96×96 [UMCG: 64×64], 35 axial slices [UMCG: 39], interleaved acquisition, 2.29×2.29mm in-plane resolution [UMCG: 3×3mm], 3mm slice thickness). Anatomical imaging included a sagittal 3-dimensional gradient-echo T1-weighted sequence (TR=9ms, TE=3.5ms; matrix 256×256; voxel size: 1×1×1mm; 170 slices).

IMAGING DATA

Functional imaging data were preprocessed in Statistical Parametric Mapping software (SPM5) in Matlab7.1 (www.mathworks.co.uk), and analyzed using SPM8 in Matlab7.8. Preprocessing 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 3×3×3mm voxels and spatial smoothing using an 8-mm FWHM Gaussian kernel. Next, data were analyzed in the context of the General Linear Model. Haemodynamic responses to each stimulus were modeled with a delta function convolved with a synthetic haemodynamic response function and modulated using RT. The model included regressors for encoding[1] and recognition[2] 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: 128s) 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 (Hart & Rubia, 2012; Iidaka et al., 2002), 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. Because only 9 HC reported CEM, we were unable to perform group (MDD, ANX, CDA, HC)×CEM (No Abuse, CEM) RMANOVAs, 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

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

University (WFU)-Pickatlas (Maldjian, Laurienti, Kraft, & Burdette, 2003). The main effects of task are reported at P<.05, Family Wise Error (FWE) (voxel level). Activations outside our ROIs were examined using whole-brain analyses at P<.05 FWE corrected, while masking for the main effect of task (P<.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, Valabregue, & Poline, 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<.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<.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.

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<.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, nor RTs, between the CEM and No Abuse groups (Tables 1 & S1).

[3]For the word classification task, data from 16 individuals was missing (6 reported No Abuse).

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) & (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) & (K= 38, x=-39, y=36, z=30, Z=6.45). 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)×Words (Positive, Negative, Neutral)×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, nor interaction effects of CEM [Amygdala (F's<1.41, all P's>.24) & Hippocampus (F's< 2.69, P's>.10), details in Supplement].

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, Psvc=.024, Figure 1)[4]. No other clusters were found in, or outside, our ROIs (Table 2).

A CEM (No Abuse, CEM)×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=.001), a marginal main effect of Words (F(2, 372) =2.78, P=.06). Positive words elicited more mPFC activation (M=.28, SE=.04) compared to neutral (M=.16, SE=.05; P<.01), but not negative words (M=.25, SE=.04, P=.70). No other differences were found (P's>.11). There was no Words×CEM interaction nor other significant main or interaction effects (F's< 2.19,P's>.13). Current psychiatric status had a main effect on mPFC activation (F(1,186)=7.93, P=.01); HC had more mPFC activations than patients (t's>2.75,P's<.007).

[4] The 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.

Additional covariance analyses showed that the main effect of CEM remained significant when we covaried 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 Supplement).

Finally, to investigate the functional connectivity of this mPFC cluster (x=-3 y=45 z=33) in individuals with CEM (compared to No Abuse), we performed a Psycho–Physiological interaction (PPI) analysis (specifics in Supplement; 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, Psvc<.004), and left hippocampus (K=17, x=-24, y=-12, z=-18, Z=3.97, Psvc<.02). No negative connectivity was found with our ROIs. However, no differential connectivity was found for the CEM versus No abuse groups within our ROIs (Supplement and 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 not with amygdala, nor hippocampal activations. 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 (see Table 2).

Next, we performed a CEM (CEM vs. No Abuse)×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<.001), there was no main effect of Words (F(2, 372)=.04, P=.96). Psychiatric status did have a main effect (F(1,186)=9.25, P=.003), with HCs having higher mPFC activations than patients (t's>3.54, P's<.001). Furthermore, gender had a marginal main effect (F(1,186)=3.53, P=.06), with males having marginally more mPFC

[5] Due to technical problems with fMRI data of 3 participants (1 reported CEM), we could not include these participants in the PPI analyses.

activation than females for positive words (t=1.74, P=.08), but not for negative or neutral words (t's<1.48, Ps>.14). Location had a significant main effect (i.e. AMC=(F(1,186)=5.24, P=.02) & LUMC=(F(1,186)=3.62, P=.06). Participants scanned at the AMC had marginally more mPFC activation for negative words (t=1.90, P=.06), but not for positive or neutral words (ts>1.14, Ps>.26). Post-hoc t-tests showed that participants scanned in Leiden did not have more mPFC activation (all ts>1.40, all ps>.16). There was no Words×CEM interaction, nor other main, or interaction effects (Fs < 1.82, P's>.16).

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, nor mPFC volume (Supplement).

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, Psvc<.009), and left hippocampus (K=22, x=-21, y=-12, z=-24, Z=4.98, Psvc<.005), but no negative connectivity with the mPFC, across participants. Finally, no CEM related differential connectivity was found within our ROIs (see Supplement and 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, nor smaller mPFC volume (Van Harmelen, Van Tol, et al., 2010). In addition, the mPFC hypoactivations were not accounted for by psychiatric status, nor by higher depressive or anxiety symptoms, despite the fact that the CEM group contained more patients, and that patients showed mPFC hypoactivation compared to 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 (Bogdan et al., 2012; Dannlowski, Kugel, et al., in press; Dannlowski, Stuhrmann, et al., 2012; McCrory et al., 2011, 2013; Van Harmelen et al., 2012), 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 has been reported in depressed individuals (see for an overview: Groenewold, Opmeer, De Jonge, Aleman, & Costafreda, 2013), and in post-traumatic stress disorder (PTSD) (see for an overview: Brown & 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 (ten minute) 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 (Denny, Kober, Wager, & Ochsner, 2012; Frith & Frith, 2006; Frith & Frith, 2003; Meyer et al., 2012; Mitchell, Macrae, & Banaji, 2006). 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 (Brewin, 2007; Hardt & Rutter, 2004), 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., 2010). 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, Bernstein, Lobbestael, & Arntz, 2009), which is a well validated and reliable questionnaire on childhood trauma (Thombs, Bernstein, Lobbestael, & Arntz, 2009) (Spinhoven et al., submitted). In addition, compared to 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).

Second, IQ was not assessed as a potential confound in our analyses. However, education level, which is highly correlated with IQ (r=.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 versus 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., 2012) 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 be a predisposing 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 predisposing 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, nor by mPFC volume. Together with previous findings of CEM related smaller mPFC volume (Van Harmelen, Van Tol, et al., 2010), and amygdala hyperactivity to facial expressions (Bogdan et al., 2012; Dannlowski, Kugel, et al., in press; Dannlowski, Stuhrmann, et al., 2012; McCrory et al., 2011, 2013; Van Harmelen et al., 2012), these findings suggest that CEM increases individuals risk to the development of psychopathology (Iffland et al., 2012; Spinhoven et al., 2010) 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.

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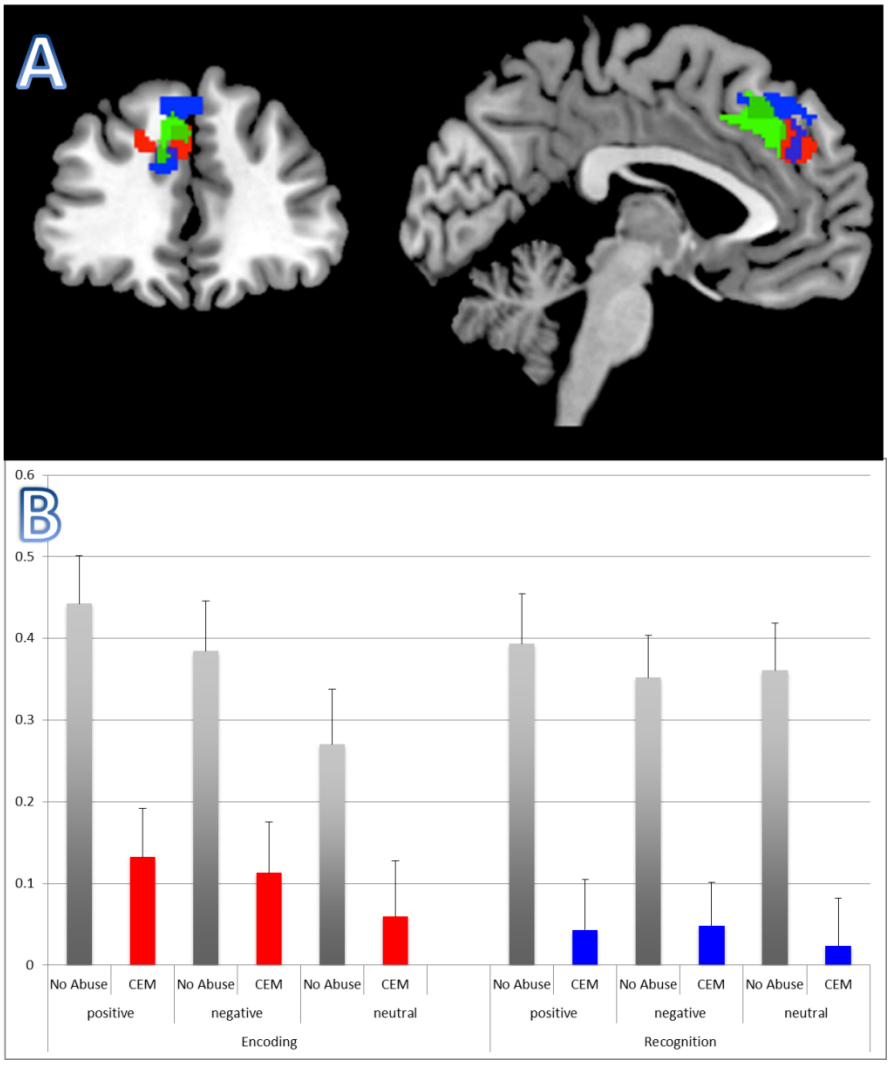
Figure 1. Medial prefrontal cortex activations during encoding, and recognition of positive, negative and neutral words in adults reporting Childhood Emotional Maltreatment (CEM; N=96) vs. No Abuse (N=98).



Note. Figure 1a depicts the main effect of CEM on medial prefrontal cortex activation during encoding (Red), and recognition (Blue) at P<.005 K>5 uncorrected. The green blob depicts the region that has been found to be smaller in adults reporting CEM (van Harmelen van Tol et al., 2010). Figure 1b 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 1. Demographics, clinical characteristics and memory performance of the No Abuse and CEM groups.

	No Abuse (N=98)		**CEM (N=96)**				
	Mean	SD	Mean	SD	X^2	*F*	*P*
Age	36.48	10.56	38.11	9.52		1.28	0.26
Gender (male/female)(n)	32/66		37/59		.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		.50		0.78
Diagnosis (yes/no) (n)	65/33		87/9		16.88		<.001
Diagnosis (MDD/CDA/ANX/HC) (n)	24/19/22/33		20/40/27/9		22.04		<.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	<.001
Neuroticism	34.31	7.93	41.81	9.34		36.31	<.001
MADRS	8.19	9.29	15.08	9.99		26.81	<.001
BAI	9.29	9.62	12.82	9.04		6.63	<.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 sensitivit negative words	0.52	0.12	0.54	0.14		1.40	0.24
Discriminant sensitivit neutral words	0.63	0.16	0.65	0.17		1.37	0.24

Table 2. Main effect of CEM at p<.005, K>5

		K	F	Z	p(unc)	x,y,z {mm}
Encoding	Medial Frontal Gyrus	28	15.31	3.71	<.001	-3 45 33
	Superior Temporal Gyrus	22	13.53	3.47	<.001	57 -51 9
	Inferior Frontal Gyrus	10	13.26	3.43	<.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	<.001	-6 48 39
			15.49	3.74	<.001	-3 33 45
			12.04	3.26	0.001	-12 39 24
	Putamen	5	12.41	3.31	<.001	-30 -3 -6
	Inferior Parietal Lobe	8	10.52	3.02	0.001	-24 57 15