

# Enhanced amygdala reactivity to emotional faces in adults reporting childhood emotional maltreatment

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**In the context of chronic childhood emotional maltreatment (CEM; emotional abuse and/or neglect), adequately responding to facial expressions is an important skill. Over time, however, this adaptive response may lead to a persistent vigilance for emotional facial expressions. The amygdala and the medial prefrontal cortex (mPFC) are key regions in face processing. However, the neurobiological correlates of face processing in adults reporting CEM are yet unknown. We examined amygdala and mPFC reactivity to emotional faces (Angry, Fearful, Sad, Happy, Neutral) vs scrambled faces in healthy controls and unmedicated patients with depression and/or anxiety disorders reporting CEM before the age of 16 years ( $n = 60$ ), and controls and patients who report no childhood abuse ( $n = 75$ ). We found that CEM was associated with enhanced bilateral amygdala reactivity to emotional faces in general, and independent of psychiatric status. Furthermore, we found no support for differential mPFC functioning, suggesting that amygdala hyper-responsivity to emotional facial perception in adults reporting CEM may be independent from top-down influences of the mPFC. These findings may be key in understanding the increased emotional sensitivity and interpersonal difficulties, that have been reported in individuals with a history of CEM.**

**Keywords:** Amygdala; childhood emotional maltreatment; fMRI; mPFC; stress

## INTRODUCTION

Childhood Emotional maltreatment (CEM) 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 (Egeland, 2009; Gilbert *et al.*, 2009). One in 10 children growing up in Western societies experiences CEM per year (Gilbert *et al.*, 2009) and CEM has been associated with a cascade of negative outcomes on behavioral, emotional, and social functioning (Teicher *et al.*, 2006; Gibb *et al.*, 2007; Egeland, 2009; Gilbert *et al.*, 2009; Spinhoven *et al.*, 2010). For instance, CEM is associated with enhanced emotional sensitivity in adulthood, as evidenced by enhanced negative self-associations, depressive symptoms, and difficulties in interpersonal relationships (Spertus *et al.*, 2003; Egeland, 2009; Gilbert *et al.*, 2009; van Harmelen *et al.*, 2010a; Horner, in press).

In the context of chronic CEM, adequately responding to facial expressions is an important skill. Detecting when a parent is in a bad

mood may help a child to avoid a negative confrontation with that parent. However, over time, this adaptive response may lead to a persistent vigilance for negative facial expressions (Gibb *et al.*, 2009). The amygdala is a key brain region involved in the primary processing of emotional faces, and plays a crucial role in salience detection, fear conditioning, and emotional memory (Davis and Whalen, 2001; Bremner *et al.*, 2005; Todorov and Engell, 2008; Onur *et al.*, 2009; Kim *et al.*, 2011). In addition, adverse rearing environments in animals, such as maternal isolation, loss, and isolation rearing induce a cascade of long-term alterations on a behavioral and neurobiological level, with specific effects in the amygdala (Sanchez, 2001; McEwen *et al.*, 2012). For instance, maternal deprivation is associated with a lasting enhancement of contextual and cued fear conditioning (Oomen *et al.*, 2010), and anxious behavior in rats (Eiland and McEwen, 2010).

In humans, acute stress is associated with subsequent amygdala hypervigilance to emotional stimuli (van Marle *et al.*, 2010; Oei *et al.*, in press). In line with the findings of persistent vigilance in animals, greater left amygdala activation during the processing of negative emotional faces was observed in a small sample of youths who experienced severe emotional and physical neglect in foster care or orphanages (Maheu *et al.*, 2010), and in young adults reporting high childhood family stress (including CEM and physical abuse), while classifying the emotion of fearful and angry faces (Taylor *et al.*, 2006). Thus far, however, it is unknown whether CEM in isolation (i.e. without concomitant physical or sexual abuse) is related to enhanced amygdala activation for negative emotional faces. Furthermore, it is unknown whether CEM-related amygdala activation persists into adulthood, i.e. whether adults reporting CEM are characterized by enhanced amygdala response to negative emotional faces.

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Using fMRI, an emotional faces task (employing Angry, Fearful, Sad, Happy, Neutral and Scrambled faces) and applying a hypothesis driven region-of-interest (ROI) analysis approach, we examined amygdala functioning in a large sample ( $N=135$ ) of unmedicated outpatients (with major depressive disorder (MDD) and/or anxiety disorder (AD)) and healthy controls (HC). We investigated whether patients and HC reporting CEM ( $n=60$ ) showed enhanced amygdala reactivity to emotional faces compared to patients and HC reporting No Abuse ( $n=75$ ). In line with Maheu *et al.* (2010), we expected that individuals reporting CEM showed enhanced amygdala response to negative emotional faces (i.e. Angry, Fearful and Sad), but not to happy or neutral faces. In addition, our group recently reported reduced medial prefrontal cortex (mPFC) gray matter volume in adults reporting CEM (van Harmelen *et al.*, 2010b). However, it is unknown whether the reduced mPFC volume in these adults reporting CEM (van Harmelen *et al.*, 2010b) is also related to altered mPFC responsivity. Therefore, we also investigated differences between the CEM and No Abuse group with respect to mPFC reactivity to emotional faces.

In addition, to examine whether altered amygdala and mPFC activation in response to negative emotional faces are related to psychopathology, we investigated whether abnormal amygdala (and/or mPFC functioning) was more apparent in emotionally maltreated individuals with MDD and/or AD compared to HCs reporting CEM.

## METHODS

### Participants for the NESDA-MRI study

Participants were drawn from the Netherlands Study of Depression and Anxiety (NESDA,  $N=2981$ ). A subset of this large observational cohort study (Penninx *et al.*, 2008) were selected to undergo MRI scanning (233 patients and 68 HC). All participants underwent MRI in 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 center approved this study. After complete description of the study to the subjects, written consent was obtained.

Inclusion criteria for the NESDA-MRI patients were: current MDD and/or AD (panic and/or social AD) in the last 6 months according to Diagnostic and Statistical Manual-IV criteria. Diagnoses were established using the structured Composite International Diagnostic Interview (Wittchen *et al.*, 1991), administered by a trained interviewer.

Exclusion criteria for patients in the NESDA-MRI study were: the presence of axis-I disorders other than MDD, panic disorder or social AD (except generalized AD); any use of psychotropic medication other than a stable use of selective serotonin reuptake inhibitors (SSRI) or infrequent benzodiazepine use ( $3 \times 2$  tablets weekly or within 48 h prior to scanning), the presence of major internal or neurological disorders; dependence or past year abuse of alcohol and/or drugs; hypertension ( $>180/130$  mm Hg); heavy smoking ( $>5$  cigarettes/day); and general MRI contra-indications. Controls had no lifetime depressive or anxiety disorders and were not taking any psychotropic drugs.

In the current study, some additional exclusion criteria were formulated; patients using SSRI ( $n=79$ ) were excluded given its potential effect on face processing (Sheline *et al.*, 2001; Fu *et al.*, 2004). Moreover, we excluded 58 participants because of incomplete fMRI data ( $n=9$ ), technical difficulties ( $n=24$ ), or poor imaging quality ( $n=25$ ). See Supplementary Data for additional information on the excluded groups.

CEM was defined as emotional neglect and/or psychological abuse before the age of 16 years, as measured with the NEMESIS trauma interview (see below for more details concerning this interview). Since we did not expect that a single incident of CEM chronically alters brain

**Table 1** Clinical and demographic characteristics of participants reporting CEM vs No Abuse

| Variables                     | No Abuse<br>( $n=75$ ) | CEM<br>( $n=60$ ) | Analysis |          |       |
|-------------------------------|------------------------|-------------------|----------|----------|-------|
|                               |                        |                   | F        | $\chi^2$ | p     |
| Gender (Male/female)          | 26/49                  | 20/40             |          | 0.03     | 0.87  |
| Handedness (Left/right)       | 9/66                   | 4/56              |          | 1.09     | 0.30  |
| Scan centers (AMC/LUMC/UMCG)  | 16/32/27               | 14/28/18          |          | 0.54     | 0.76  |
| Age, Mean (SE)                | 34.91 (1.22)           | 38.22 (1.32)      | 3.36     |          | 0.07  |
| Education, Mean (SE)          | 13.32 (0.34)           | 12.52 (0.38)      | 2.49     |          | 0.12  |
| Neuroticism, Mean (SE)        | 32.69 (1.26)           | 39.53 (0.93)      | 14.83    |          | 0.001 |
| Recent Life events, Mean (SE) | 0.58 (0.11)            | 0.83 (0.16)       | 1.88     |          | 0.17  |
| Current diagnosis             |                        |                   |          | 8.73     | 0.03  |
| MDD                           | 18                     | 14                |          |          |       |
| AD                            | 17                     | 17                |          |          |       |
| Comorbid MDD and AD           | 11                     | 18                |          |          |       |
| HC                            | 29                     | 11                |          |          |       |
| Lifetime diagnosis            |                        |                   |          |          |       |
| MDD                           | 34                     | 44                |          | 10.71    | 0.001 |
| AD                            | 32                     | 38                |          | 5.70     | 0.013 |
| BAI                           | 9.19(1.22)             | 11.38(1.11)       | 1.69     |          | 0.19  |
| MADRS                         | 7.64(1.13)             | 12.88(1.32)       | 9.18     |          | 0.003 |
| Concurrent abuse              |                        |                   |          |          |       |
| Physical abuse                | 0                      | 7                 |          |          |       |
| Sexual abuse                  | 0                      | 11                |          |          |       |
| Physical and sexual abuse     | 0                      | 5                 |          |          |       |

Values are represented as  $n$  unless otherwise specified.

AMC = Amsterdam Medical Center, LUMC = Leiden University Medical Center, UMCG = University Medical Center Groningen, BAI = Beck Anxiety Inventory, MADRS = Montgomery Asberg Depression Rating Scale.

functioning, we excluded individuals reporting only a single incident of CEM ( $n=24$ ). Moreover, also individuals reporting childhood physical or sexual abuse without CEM ( $n=5$ ) were excluded. The final sample consisted of 135 participants (see Table 1 for all demographic and clinical characteristics). Individuals who reported emotional neglect or emotional abuse in childhood that had occurred more than once were included in the CEM group ( $n=60$ ); 30 individuals reported only emotional neglect, two reported only emotional abuse, and 28 reported both emotional neglect and abuse; 59 individuals reported their biological parents as perpetrators and one subject reported a sibling as the perpetrator). Individuals who did not report emotional, physical, and sexual maltreatment were included in the No Abuse group ( $n=75$ ; Table 1).

The CEM and No Abuse groups did not differ in years of education, recent life events, anxious symptomatology, gender, handedness, or scan location (Table 1). However, the CEM group was slightly older, had higher neuroticism scores, reported more depressive symptomatology, and consisted of more individuals with a current psychiatric diagnosis.

### Childhood maltreatment

Childhood maltreatment was assessed through the NEMESIS trauma interview (de Graaf *et al.*, 2002). In this interview, respondents were asked whether they had experienced emotional neglect, emotional abuse, physical abuse, and/or sexual abuse before the age of 16 years, how often this had 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, 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'.

Our definition of CEM (i.e. emotional neglect and/or emotional abuse before the age of 16 years) is based on the American Professional Society on the Abuse of Children (APSAC; Binggelli *et al.*, 2001; Egeland, 2009; Horner, in press). This definition states that emotional child maltreatment consists of acts of commission (emotional abuse, such as degrading, terrorizing, belittling, blaming, exploiting) and/or omission (emotional neglect such as isolation, rejection, denying emotional responsiveness), which conveys to the child that he/she is worthless, unloved, and unwanted, and are harmful to the child's emotional developmental needs.

#### Additional questionnaires

Recent life events (past year) were assessed using the List of Threatening Events Questionnaire (Brugha *et al.*, 1985). Neuroticism was measured with the NEO Five-Factor Inventory (Costa and McGrae, 1992). Furthermore, at the day of scanning, depression and anxiety severity (past week) were measured using the Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) and Beck's Anxiety Inventory (BAI) (Beck *et al.*, 1988).

#### The faces task

The faces paradigm was based on the event-related emotional paradigm used by Wolfensberger and colleagues (2008) that has been found to robustly activate the amygdala. Photographs of angry, fearful, sad, happy, neutral faces, and a control condition (scrambled faces) were presented to all participants. The photographs were selected from the Karolinska Directed Emotional Faces System (Lundqvist *et al.*, 1998) representing standardized facial expressions of emotions expressed by amateur actors. Twenty-four stimuli were selected for each of 5 facial expressions, comprising 12 female and 12 male faces. Each particular face was not presented more than four times. The scrambled faces were presented 80 times. The faces task was presented using E-prime software (Psychological Software Tools, Pittsburgh, PA, USA). In order to reduce anticipatory effects, an event-related design was employed. This entailed a pseudo-random presentation of a total of 200 stimuli against a black background. Each photograph was shown on the screen for 2.5 s, with an inter-stimulus (black screen) interval varying between 0.5 and 1.5 s. The images were projected onto a translucent screen at the end of the scanner bed, visible via a mirror above the participant's head. All participants were instructed to indicate each face's gender by pressing one of two buttons with the index finger of the left or right hand. During the presentation of scrambled faces, participants had to press left or right buttons in conformity with an arrow pointing to the left or to the right. The reaction times were recorded.

#### MRI acquisition

Imaging data were acquired using Philips 3T MR systems (Best, The Netherlands) located at the University Medical Centers in Leiden, Amsterdam and Groningen, equipped with a SENSE-8 (Leiden and Groningen) and a SENSE-6 (Amsterdam) channel head coil, respectively. For each subject, echo-planar images were obtained using a T2\*-weighted gradient echo sequence [repetition time (TR) = 2300 ms, echo time (TE) = 30 ms (Groningen: TE = 28 ms), matrix size: 96 × 96 (Groningen: 64 × 64), 35 axial slices (Groningen: 39 slices), interleaved acquisition, 2.29 × 2.29 mm in-plane resolution (Groningen: 3 × 3 mm), 3 mm slice thickness]. Echo-planar images were scanned parallel to the anterior-posterior commissure plane. To control for differences in scan sites, we added dummy variables for the different scan centers to all analyses. The faces paradigm was part of a functional scanning session utilizing multiple tasks, these results are reported elsewhere.

#### fMRI data preprocessing

Functional imaging data were preprocessed and analyzed using Statistical Parametric Mapping (SPM)-5 software implemented in Matlab 7.1.0 ([www.mathworks.co.uk](http://www.mathworks.co.uk)). Preprocessing, after extensive quality evaluation of the data, consisted of: manually reorienting the functional images to the anterior commissure, slice time correction, image realignment, registration of the T1-scan to the mean echo-planar 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 full-width half-maximum Gaussian kernel. Subject movement (>3 mm) resulted in exclusion of the data from further analysis.

#### fMRI data analysis

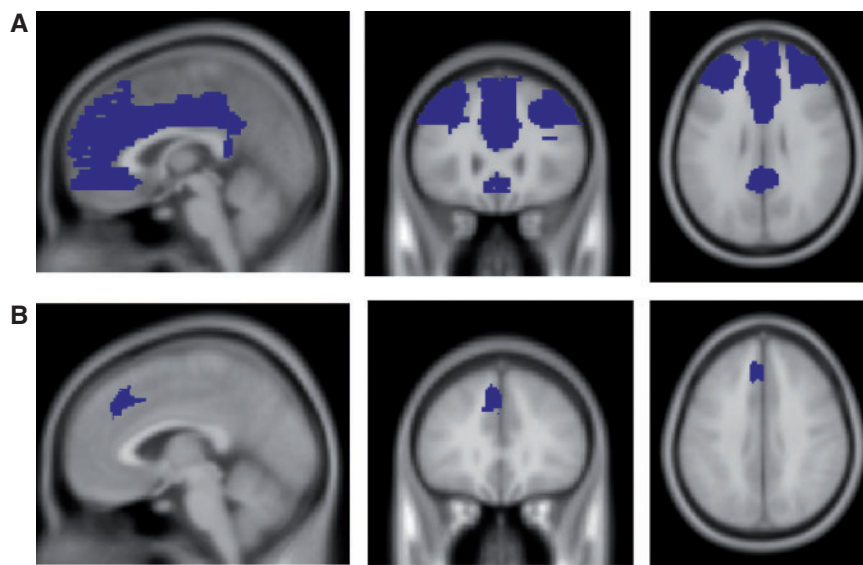
fMRI data were analyzed in the context of the General Linear Model. Hemodynamic responses to each stimulus were modeled with a delta function convolved with a synthetic hemodynamic response function. Low-frequency noise was removed by applying a high-pass filter (cut-off 128 s) to the fMRI time series at each voxel. Statistical parametric maps for each comparison of interest were calculated on a voxel-by-voxel basis.

For each subject, contrasts for facial expressions (Angry, Fearful, Sad, Happy, Neutral) *vs* scrambled faces were computed. We then conducted a facial expressions (Angry, Fearful, Sad, Happy, Neutral) × Group (CEM *vs* No Abuse) second level analysis, to examine the main effect of task in our ROIs (i.e. amygdala and mPFC). We specified dummy variables for the different scan centers and a weighted dummy for psychiatric status as covariates. In the weighted dummy for psychiatric status (with values 0 or 0.43), the value for the patient group ( $n=94$ ) was weighed according to the size of the control group ( $41/94=0.43$ ). In addition, because of findings of age and gender related differences in amygdala response to emotion processing (Iidaka *et al.*, 2002; Wager *et al.*, 2003), we also specified age and gender as covariates. All results are reported in MNI space, and significance threshold for the main effect of task was set at  $P < 0.05$  family-wise error (FWE) corrected for multiple comparisons. To investigate if there were any CEM-related activations outside our predefined ROIs, we performed a whole-brain analysis with at  $P < 0.05$  FWE corrected.

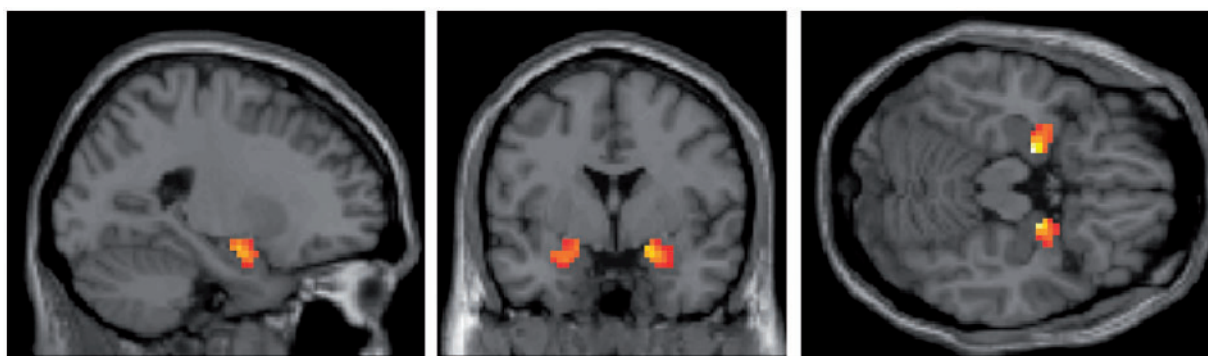
For the amygdala, we extracted activations for the main effect of task ( $F$ ) using the Marsbar ROI Toolbox, (Brett *et al.*, 2002). The binary mask in MNI space of the left and right amygdala was specified using the Wake Forest University (WFU) Pick Atlas software, SPM Toolbox (<http://fmri.wfubmc.edu>).

Since the anatomical region of the mPFC is less well defined than the amygdala, group differences ( $F$ ) in mPFC activations were examined using a facial expressions (Angry, Fearful, Sad, Happy, Neutral) × CEM (CEM *vs* No Abuse) voxel-wise ROI analysis, while masking for the main effect of task ( $F$ ). The ROI mask (Figure 1a) was based on the anatomical location of both dorsal and ventral mPFC (including the anterior cingulate cortex) in MNI space (using the WFU Pick Atlas toolbox). Dummy variables for the different scan centers, gender, age, and psychiatric status (weighted) were specified as covariates. Significance for group differences was set at  $P < 0.001$  uncorrected, with spatial extent threshold of five contiguous voxels.

Based on our previous findings of mPFC volume reductions in CEM in largely the same cohort (van Harmelen *et al.*, 2010b), group differences in activation within this region were also examined by extracting mean activation differences per valence type within this locus using a binary mask that was based on our earlier findings [ $(x = -11, y = 21, z = 44)$ ; see Figure 1b, van Harmelen *et al.*, 2010b].



**Fig. 1** ROI Masks for the mPFC. **A** = Cluster based on anatomical regions of the dorsal, ventral mPFC and the entire ACC. **B** = Cluster based on structural differences in CEM groups as reported in van Harmelen *et al.*, 2010b.



**Fig. 2** Amygdala activation for the main effect of task (emotional vs scrambled faces).

Following the extraction of Amygdala and mPFC activations (using MARSBAR), we ran correlation analyses to further investigate whether average Amygdala activation for all facial expressions was related to average mPFC activation for all facial expressions, within the No Abuse or CEM group.

#### SPSS data analysis

Psychometric and performance data were analyzed with SPSS 17. Based on the observed distribution of the data, the appropriate parametric ( $F$ ) or non-parametric chi-square ( $\chi^2$ ) test was performed. Since the CEM group was slightly older (Table 1), age was defined as a covariate in all SPSS analyses (however, all results remained the same when removing age as covariate). In addition, to investigate whether the results are dependent on psychiatric status, in all analyses, we added a weighted dummy for psychiatric status as a covariate. To further examine the exact impact of psychiatric status on emotional face processing in individuals reporting CEM, we finally performed an additional Diagnosis [MDD, AD, co-morbid MDD and AD (CDA), HC]  $\times$  CEM (No Abuse, CEM) analysis of variance.

Significance was set at  $P < 0.05$ , two-tailed, all tests were Bonferroni corrected for multiple comparisons.

## RESULTS

### Performance on faces task

Performance on faces was assessed using a facial expressions (Angry, Fearful, Sad, Happy, Neutral)  $\times$  CEM (CEM vs No Abuse) Repeated Measures (RM) Analyses of Covariance (ANCOVA) on the reaction times. Individuals reporting CEM had similar reaction times as individuals reporting No Abuse,  $F(1,130) = 0.002$ ,  $P = 0.96$ , and there was no CEM  $\times$  facial expressions interaction,  $F(4,520) = 1.03$ ,  $P = 0.39$ . There was a main effect of facial expressions,  $F(4,520) = 2.41$ ,  $P = 0.049$ , Cohen's  $d$  ( $d$ ) = 0.27. Compared to the other faces, participants were faster in labeling the gender of angry faces, all  $P$ 's  $< 0.001$ , independent of maltreatment-status,  $F(4,520) = 1.03$ ,  $P = 0.39$ . Moreover, age had a main effect,  $F(1,130) = 6.74$ ,  $P = 0.011$ ,  $d = 0.45$ , with older participants having longer reaction times. Psychiatric status did not affect reaction times,  $F(1,130) = 0.22$ ,  $P = 0.64$ .

### The main effect of task

A facial expressions (Angry, Fearful, Sad, Happy, Neutral)  $\times$  CEM (CEM vs No Abuse) analysis showed that the task was associated with significant activations in left and right amygdala,  $x = -18$ ,

**Table 2** Significant gray matter clusters of the main effect of task

| Clusters                        | Cluster level,<br>Number of voxels | Coordinates |                 |                 |          |          |          |
|---------------------------------|------------------------------------|-------------|-----------------|-----------------|----------|----------|----------|
|                                 |                                    | <i>F</i>    | <i>Z</i> -score | <i>P</i> -value | <i>x</i> | <i>y</i> | <i>z</i> |
| Right fusiform gyrus            | 271                                | 411.86      | >8              | <0.001          | 42       | -51      | -21      |
|                                 |                                    | 145.76      | >8              | <0.001          | 42       | -78      | -12      |
|                                 |                                    | 101.69      | >8              | <0.001          | 24       | -93      | -9       |
| Left fusiform gyrus             | 115                                | 200.84      | >8              | <0.001          | -39      | -51      | -21      |
|                                 |                                    | 198.59      | >8              | <0.001          | -27      | -90      | 9        |
| Left middle occipital gyrus     | 3555                               | 186.01      | >8              | <0.001          | 30       | -87      | 12       |
|                                 |                                    | 155.74      | >8              | <0.001          | -24      | -69      | -15      |
|                                 |                                    | 175.88      | >8              | <0.001          | 18       | -6       | -15      |
| Right amygdala                  | 263                                | 77.15       | >8              | <0.001          | 27       | 3        | -21      |
|                                 |                                    | 167.89      | >8              | <0.001          | -18      | -6       | -15      |
| Left amygdala                   | 236                                | 29.29       | 5.22            | <0.001          | -39      | 15       | -24      |
|                                 |                                    | 75.37       | >8              | <0.001          | 48       | 24       | 24       |
| Right superior frontal gyrus    | 350                                | 74.11       | >8              | <0.001          | 51       | 30       | 18       |
|                                 |                                    | 64.59       | 7.75            | <0.001          | 45       | 9        | 30       |
|                                 |                                    | 55.29       | 7.19            | <0.001          | -27      | 60       | 9        |
| Left superior frontal gyrus     | 83                                 | 53.20       | 7.05            | <0.001          | 54       | -48      | 39       |
| Right superior parietal lobe    | 149                                | 52.05       | 6.98            | <0.001          | -51      | -48      | 42       |
| Left superior parietal lobe     | 375                                | 50.92       | 6.90            | <0.001          | -45      | -48      | 48       |
|                                 |                                    | 45.93       | 6.56            | <0.001          | -60      | -39      | 36       |
|                                 |                                    | 44.10       | 6.43            | <0.001          | 66       | -21      | 9        |
| Right superior temporal gyrus   | 117                                | 26.33       | 4.95            | <0.001          | 63       | -21      | -6       |
|                                 |                                    | 23.50       | 4.66            | <0.001          | 57       | -27      | 18       |
|                                 |                                    | 33.22       | 5.57            | <0.001          | 24       | 15       | 54       |
| Right superior frontal gyrus    | 11                                 | 32.65       | 5.52            | <0.001          | 6        | 36       | 24       |
| Right anterior cingulate cortex | 54                                 | 32.33       | 5.49            | <0.001          | 30       | 54       | 21       |
| Right superior frontal gyrus    | 51                                 | 28.50       | 5.15            | <0.001          | 21       | 63       | 6        |
|                                 |                                    | 27.36       | 5.04            | <0.001          | 9        | 48       | -3       |
| Right medial frontal gyrus      | 37                                 | 26.27       | 4.94            | <0.001          | 3        | 48       | 6        |

Main effect of task (*F*) at *P* < 0.05 FWE corrected.

**Table 3** Significant CEM-related gray matter activations outside our ROIs

| Clusters                      | Cluster level<br>Number of voxels | <i>F</i> | <i>Z</i> -score | <i>P</i> -value | Coordinates |          |          |
|-------------------------------|-----------------------------------|----------|-----------------|-----------------|-------------|----------|----------|
|                               |                                   |          |                 |                 | <i>x</i>    | <i>y</i> | <i>z</i> |
| Left middle temporal gyrus    | 35                                | 19.52    | 4.23            | <0.001          | -54         | -60      | -3       |
| Left lingual gyrus            | 21                                | 17.64    | 4.01            | <0.001          | -18         | -72      | -15      |
| Right middle temporal gyrus   | 5                                 | 14.51    | 3.61            | <0.001          | 36          | -81      | 21       |
| Right superior temporal gyrus | 14                                | 13.77    | 3.51            | <0.001          | 51          | -30      | 15       |
|                               |                                   | 11.44    | 3.17            | <0.001          | 48          | -36      | 21       |
| Right lingual gyrus           | 9                                 | 12.58    | 3.34            | <0.001          | 21          | -72      | -12      |
| Left postcentral gyrus        | 8                                 | 12.55    | 3.34            | <0.001          | -57         | -27      | 18       |

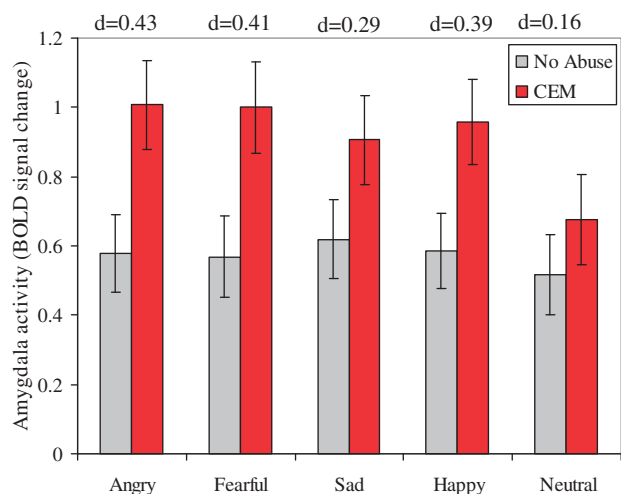
Main effect of CEM vs No Abuse (*F*) whole brain at *P* < 0.001, uncorrected, with spatial extent threshold of five contiguous voxels.

*y* = -6, *z* = -15, cluster size/number of voxels (*K*) = 236, *Z* > 8, *P* < 0.001 and *x* = 18, *y* = -6, *z* = -15, *K* = 263, *Z* > 8, *P* < 0.001; Figure 2 and Table 2. Furthermore, the task was also associated with significant activations in the mPFC, *x* = 6, *y* = 36, *z* = 24, *K* = 50, *Z* = 5.52, *P* < 0.001 and *x* = 9, *y* = 48, *z* = -3, *K* = 37, *Z* = 5.04, *P* < 0.001 (all results are FWE corrected). Other regions that were activated with task (including the right and left fusiform gyrus, the middle occipital gyrus and the superior frontal gyrus) are specified in Table 2. However, facial expressions, (Angry, Fearful, Sad, Happy, Neutral) × CEM (CEM vs No Abuse) whole-brain analysis at *P* < 0.05 FWE corrected, showed no CEM-related activations in any of the task-related regions outside our ROIs (see also Table 3).

**Amygdala activation in response to emotional faces**

We next extracted bilateral amygdala activations for the main effect of task (*F*), and conducted a facial expressions (Angry, Fearful, Sad, Happy, Neutral) × Lateralization (Left amygdala vs right amygdala) RM ANCOVA with CEM (CEM vs No Abuse) as fixed factor. Lateralization was added as fixed factor to investigate a possible effect of lateralization (Maheu *et al.*, 2010). In line with our expectations, individuals reporting CEM showed enhanced amygdala activation compared to the No Abuse group, *F*(1,131) = 5.96, *P* = 0.016, *d* = 0.43, (Figure 3). There was no main effect of facial expressions, *F*(4,524) = 0.354, *P* = 0.83, nor Lateralization, *F*(1,131) = 0.22, *P* = 0.64. Moreover, CEM did not interact with facial expressions, *F*(4,524) = 0.89, *P* = 0.47, Lateralization, *F*(1,131) = 1.25, *P* = 0.26, or facial expressions × Lateralization, *F*(4,524) = 0.89, *P* = 0.47. Finally, age and psychiatric status did not have a main effect on amygdala activation, *F*(1,131) = 1.45, *P* = 0.23 and *F*(1,131) = 2.22, *P* = 0.14. Also when performing a Diagnosis (MDD, AD, CDA, HC) × CEM (No Abuse, CEM) analysis, with Age as covariate, all results remained unchanged, including the main effect of CEM, *F*(1,126) = 5.26, *P* = 0.02. Moreover, again, diagnosis did not have a main effect on amygdala activation, *F*(3,126) = 1.28, *P* = 0.29, nor did diagnosis interact with CEM, *F*(3,126) = 0.22, *P* = 0.89. This absence of a main effect of diagnosis is in line with a recent study in the larger NESDA-MRI sample, where no impact of psychopathology was found on amygdala functioning to emotional and neutral faces (Demenescu *et al.*, 2011).

The CEM group had slightly higher neuroticism and depression severity scores (Table 1). To investigate whether this could potentially explain our findings, we performed two additional RM ANCOVAs. When we added neuroticism as covariate to the analysis, all results



**Fig. 3** Mean (average left and right) and standard errors of amygdala activation in individuals reporting No Abuse vs CEM.  $d$  = Cohen's  $d$  for the difference between amygdala activation within the CEM vs No Abuse group.

remained unchanged (i.e. main effect of CEM,  $F(1,130) = 5.98$ ,  $P = 0.02$ ,  $d = 0.43$ , and neuroticism had no main effect,  $F(1,130) = 0.23$ ,  $P = 0.72$ ), indicating that the findings cannot be explained by the slightly higher neuroticism scores in the CEM group. Also, when we added severity of depression (as measured with the MADRS) as covariate to the analysis, all results remained unchanged [i.e. main effect of CEM,  $F(1,130) = 5.18$ ,  $P = 0.02$ ,  $d = 0.04$ ] and depression severity had no main effect,  $F(1,130) = 1.04$ ,  $P = 0.31$ , indicating that the findings cannot be explained by higher depression levels in the CEM group. In addition, in both the CEM and No Abuse groups, correlation analyses showed no significant relationships between amygdala activations to the emotional and neutral faces and Neuroticism, all  $P$ 's  $> 0.15$ , nor depression, all  $P$ 's  $> 0.29$ .

To exclude the possibility that enhanced amygdala reactivity is driven by a concurrent history of physical and/or sexual abuse in some of the participants ( $n = 23$ ), we next re-ran the RM ANCOVA while excluding these individuals. In this analysis, all results remained unchanged, including the main effect of CEM,  $F(1,108) = 5.05$ ,  $P = 0.03$ ,  $d = 0.39$ .

### mPFC activation in response to emotional faces

A CEM vs No abuse (F) ROI analysis (Figure 1a) revealed no significant CEM-related activations in the ventral or dorsal mPFC, nor in the entire ACC. These results remained unchanged when mPFC volume was added as a covariate (van Harmelen *et al.*, 2010b). Additionally, when we extracted mPFC activations in the mPFC mask that is based on our previous findings (Figure 1b; van Harmelen *et al.*, 2010b), a RM ANCOVA showed that CEM did not have a main effect on activation in this region either,  $F(1,131) = 0.01$ ,  $P = 0.91$ . Thus, individuals reporting CEM did not differ in mPFC activation in response to emotional facial expressions when compared to individuals reporting No Abuse. Also when performing a Diagnosis (MDD, AD, CDA, HC)  $\times$  CEM (No Abuse, CEM) analysis, with age as covariate, all results remained unchanged, including that CEM and diagnosis had no main effect on mPFC activation,  $F(1,126) = 0.001$ ,  $P = 0.98$  and  $F(3,126) = 1.44$ ,  $P = 0.24$ , nor was there a CEM  $\times$  diagnosis interaction,  $F(3,126) = 1.29$ ,  $P = 0.28$ . In addition, no interactions with facial expressions were found.

### Correlation between Amygdala mPFC activations

Following the extraction of Amygdala and mPFC activations (using MARSBAR), we ran correlation analyses to further investigate whether average Amygdala activation for all facial expressions was related to the average mPFC (Figure 1a) activation for all facial expressions, within the No Abuse, or CEM group. However, the test yielded no significant relationship between amygdala and mPFC activations in the No abuse group,  $r = 0.01$ ,  $P = 0.92$ , nor in the CEM group,  $r = 0.01$ ,  $P = 0.92$ . Moreover, a correlational analysis with average amygdala and mPFC activations based on the cluster that we described in van Harmelen *et al.* (2010b) (Figure 1b) also yielded no significant relationships in the No abuse,  $r = 0.06$ ,  $P = 0.59$ , nor the CEM group,  $r = 0.14$ ,  $P = 0.29$ .

### DISCUSSION

This is the first study to show that adults reporting CEM show enhanced amygdala activation in response to emotional facial expressions, independent of psychiatric status, neuroticism, depression severity, and history of concurrent physical or sexual abuse. The amygdala plays a key role in detecting the (emotional or biological) salience of stimuli (Sergerie *et al.*, 2008; Todd and Anderson, 2009; Kim *et al.*, 2011; van Wingen *et al.*, 2011), and in enhancing levels of attention and vigilance toward these stimuli (Davis and Whalen, 2001). Therefore, our results suggest amygdalar hypervigilance toward emotional facial expressions in adults reporting CEM. Moreover, together with similar findings in a small sample of adolescents reporting severe neglect (Maheu *et al.*, 2010), our findings suggest sustained hypervigilance even more than 20 years after the maltreatment took place.

Contrary to our hypothesis, hyper-activation of the amygdala in adults reporting CEM was not restricted to negative facial expressions, but was also found in response to happy and neutral faces, although it should be noted that the effect sizes for the neutral faces are relatively small. Therefore, amygdalar hypervigilance to facial expressions in general, might indicate that individuals with a history of CEM interpret all facial expressions as highly salient. In line with this idea, neglected children are reported to have poor valence discriminatory abilities for different facial emotions (Pollak *et al.*, 2000; Fries and Pollak, 2004; Vorria *et al.*, 2006), and it has been suggested that neglected children may misinterpret all emotional faces as threatening (Pollak *et al.*, 2000). In that respect, happy faces might be interpreted as a mask for more malevolent emotions (Pollak *et al.*, 2000), for example, as being laughed at. Enhanced amygdala activation in response to happy faces could also be indicative of an increased sensitivity toward positive emotional expressions in others (e.g. happy faces might function as safety signal). To disentangle the impact of negative vs positive and neutral faces in individuals reporting CEM, future studies are needed that also assess the subjective ratings of emotional faces besides amygdala activation.

On a neurobiological level, enhanced amygdala responses to all facial expressions may reflect a general noradrenergic sensitization in response to emotional stimuli in individuals reporting CEM. Chronic stress is associated with increased firing of  $p$  neurons in the brain stem, and augmented release of noradrenalin in the brain following subsequent stressors (Bremner *et al.*, 1996; Elzinga and Bremner, 2002). Furthermore, enhanced amygdala activation during stress strengthens emotional memory traces and increases fear conditioning (Strange and Dolan, 2004; Joëls and Baram, 2009; Onur *et al.*, 2009). In accordance, in rats, maternal deprivation is associated with a lasting enhancement of contextual and cued fear conditioning (Oomen *et al.*, 2010) and anxious behavior (Eiland and McEwen, 2010).

Another noteworthy result of this study was that enhanced amygdala reactivity to emotional faces in individuals reporting CEM was

observed independent of psychiatric status and that no main effect of diagnosis was observed. This finding is in contrast with other studies finding amygdala hyper-reactivity in depressed (Sheline *et al.*, 2001; Anand *et al.*, 2005; Fales *et al.*, 2008) and anxious patients (Straube *et al.*, 2004; Bishop, 2007). It should be noted that our patient sample can be characterized as having relatively mild symptoms, due to the fact that we excluded patients using SSRIs. Possibly, this may have led to an underestimation of the true effect of psychopathology. However, in a larger sample of the same cohort, in which medicated patients were also included, we recently reported no effect of psychiatric status on amygdala reactivity to emotional faces (Demenescu *et al.*, 2011; see for similar findings; Lawrence *et al.*, 2004; Gotlib *et al.*, 2005; Lee *et al.*, 2008; Almeida *et al.*, 2009; Norbury *et al.*, 2009, and a meta-analysis showing no amygdala hyper-response in depressed patients; Diekhof *et al.*, 2008). Our findings therefore seem to suggest that enhanced amygdala reactivity to emotional faces does not seem to be directly linked to the development of psychopathology in individuals with CEM. Apparently, additional risk factors, such as genetic make-up in itself, or in interaction with exposure to stressful life events during adulthood, or low social support additionally determine who will subsequently develop a depressive and/or AD (Hariri *et al.*, 2002; Kilpatrick *et al.*, 2007).

We did not find support for abnormal mPFC functioning in individuals reporting CEM, nor did we find a significant relationship between Amygdala and mPFC activity. Thus smaller mPFC volume (van Harmelen *et al.*, 2010b) is not related to abnormal mPFC reactivity to emotional facial expressions in adults reporting CEM. Hence, our findings suggests that amygdala hyper-reactivity to emotional facial expressions in individuals with CEM histories may occur independent of the regulatory influences of the mPFC (Fonzo *et al.*, 2010), at least in this gender labeling task which requires minimal cognitive resources (Reddy *et al.*, 2004). However, abnormal mPFC functioning may be observed in tasks posing greater cognitive demands (see, for example, Shin *et al.*, 2006).

This study is not without limitations. First, although a clinically diagnosed PTSD diagnosis was an exclusion criterion, unidentified current or lifetime PTSD symptoms may still have been present in the current sample, which may have influenced our findings. This is not very likely, however, given that the enhanced amygdala responses in individuals reporting CEM was unrelated to psychiatric status. Second, history of childhood maltreatment was retrospectively assessed. In addition, it is important to acknowledge the inherent subjectivity of self-reported CEM. However, it should be noted that, in the current study, neuroticism did not explain enhanced amygdala activation, and in the overall NESDA sample, current affective state did not moderate the association between CEM (as measured with the NEMESIS interview) and lifetime affective disorder (Spinhoven *et al.*, 2010), indicating that recall of CEM in the current sample was not critically affected by current mood state. Furthermore, a recent study showed that depressed women with emotional neglect histories are less prone to produce false memories on the Deese-Roediger, Mcdermott (DRM; Deese, 1959; Roediger & Mcdermott, 1995) task than depressed women with no emotional neglect and women with any type of maltreatment (Grassi-Oliveira *et al.*, 2011). Finally, our findings are based on a cross-sectional design; therefore, one cannot assume causality. It might be that individuals who have strong amygdala reactions to emotional faces may also have experienced certain behaviors of their parents as more abusive or neglectful. Alternatively, enhanced amygdala reactivity to emotional facial expressions may have been pre-existent and inherited by their parents, whose enhanced amygdala reactivity to emotional faces may have increased their risk to emotionally maltreat their children. Theoretically, longitudinal studies are needed to shed more light on the etiology of our findings, although

from an ethical point of view, this is problematic. However, recently, a prospective study in soldiers showed that combat stress exposure is associated with enhanced amygdala reactivity to emotional faces, indicative of a causal role of stress exposure on amygdala hypervigilance. In addition, it appeared that the subjective appraisal of threat, and not the actual exposure, played a key role in amygdala regulation in the aftermath of severe stress (van Wingen *et al.*, 2011).

Taken together, we found that adults reporting CEM show enhanced amygdala response to emotional facial expressions. These findings may represent a persistent hypervigilance for emotional facial expressions in adults reporting CEM. Potentially, during social emotional encounters, enhanced amygdala activation in individuals with CEM might result in strong memory traces and increased fear conditioning in response to emotionally significant stimuli (in this case emotional facial expressions). This may be an important key in understanding the increased emotional sensitivity and difficulties in inter-personal relationships (Spertus *et al.*, 2003; Teicher *et al.*, 2006; Egeland 2009; Gilbert *et al.*, 2009; van Harmelen *et al.*, 2010a; Horner, in press) that has been reported in these individuals.

## SUPPLEMENTARY DATA

Supplementary Data are available at SCAN online.

## Conflict of Interest

None declared.

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