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Chapter 7: Enhanced mPFC reactivity to social rejection in young adult patients and controls reporting childhood emotional maltreatment

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Under Review

Abstract

Children who have experienced chronic parental rejection and exclusion during childhood, as is the case in childhood emotional maltreatment (CEM), may become especially sensitive to social exclusion. This study investigated the neural and emotional responses to social exclusion in individuals reporting CEM using the Cyberball task. Using functional magnetic resonance imaging (fMRI), we investigated brain responses and self-reported distress to social exclusion in 46 young adults (mean age=19.2, SD=2.16) reporting low to extreme CEM. Consistent with prior studies, social exclusion was associated with activity in the ventral medial prefrontal cortex (mPFC) and posterior cingulate cortex. In addition, severity of a history of CEM was positively associated with increased dorsal mPFC responsivity to social exclusion. The dorsal mPFC plays a crucial role in self- and other-referential processing, suggesting that the more individuals have been rejected and maltreated in childhood, the more self- and other-processing is elicited by social exclusion in adulthood. Negative self-referential thinking, in itself, enhances cognitive vulnerability for the development of psychiatric disorders. Therefore, our findings may underlie the emotional and behavioural difficulties that have been reported in adults reporting CEM.

INTRODUCTION

Chronic parental rejection (active and/or passive) can be considered a core aspect of Childhood Emotional Maltreatment (CEM; emotional abuse and/or emotional neglect) (APSAC, 1995). For instance, during episodes of CEM, children may be ignored, isolated, or siblings may be favored. CEM has severe and persistent adverse effects on behavior and emotion in adulthood (Hart & Rubia, 2012), and CEM is a potent predictor of depressive and anxiety disorders in later life (Iffland, Sansen, Catani, & Neuner, 2012; Spinhoven et al., 2010). Social rejection, ranging from active isolation to passively ignoring a person, may enhance sensitivity towards future rejection (DeWall & Bushman, 2011). Along these lines, individuals reporting CEM may be especially sensitive to (perceived) social rejection. Individuals high in rejection sensitivity have a tendency to expect, perceive, and overreact to social rejection, and show enhanced distress and related neural responses to social rejection in the lab (DeWall & Bushman, 2011). Furthermore, rejection sensitivity (both behaviourally and in terms of brain responses) is positively related to the development and maintenance of depression, social anxiety, and borderline personality disorder symptoms (Masten et al., 2011; Rosenbach & Renneberg, 2011). Therefore, enhanced distress and neural responses to (perceived) social rejection may be one of the mechanisms through which a history of CEM may predispose individuals to the development of depressive and anxiety disorders in later life. However, the subjective and neural responses to social rejection in individuals reporting CEM are currently unknown.

Social rejection in the lab has been examined most frequently with the Cyberball task (Williams, Cheung, & Choi, 2000; Williams & Jarvis, 2006). During an fMRI compatible variation of the Cyberball task, participants play two games of virtual toss with two other players (computer controlled confederates). In the first (inclusion) game, participants are thrown the ball an equal number of throws as compared to the other players. However, in the second (rejection/exclusion) game they may receive the ball once or twice in the beginning of the game, but thereafter never receive it again. Social exclusion during the Cyberball task induces a cascade of negative emotions, including anxiety, depression, reduced sense of belonging and meaningful existence, and a reduced sense of control, and lowered self-esteem (Boyes & French, 2009; DeWall & Bushman, 2011; Moor et al., 2012; Themanson, Khatcherian, Ball, & Rosen, In Press; Zadro, Williams, & Richardson, 2004).

Neuroimaging studies have revealed a set of brain regions that are typically activated during social exclusion in the Cyberball task, primarily in cortical midline structures; the anterior cingulate cortex (ACC)/ medial prefrontal cortex (mPFC), and Insula (Cacioppo et al., 2013; Eisenberger, 2012). The ACC and mPFC are vital for expectancy-violation, error-detection, the processing of cognitive conflict, and self- and other referential processing (Etkin, Egner, & Kalisch, 2011; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004; Somerville, Heatherton, & Kelley, 2006). In line, a recent meta-analysis suggested that activation in these regions during social exclusion might be related to enhanced social uncertainty, social distress, and social rumination (Cacioppo et al., 2013). Activation in the dorsal ACC/mPFC and Insula have been related to self-reported distress during exclusion in the Cyberball game, however, not all studies found dorsal ACC/mPFC responsivity to social exclusion (Cacioppo et al., 2013; Eisenberger, 2012; Masten, Eisenberger, Pfeifer, & Dapretto, 2010; Yoshimura et al., 2009), or only found it in the first trials of the exclusion game (Moor et al., 2012). Furthermore, studies investigating adolescents and children found ventral ACC/mPFC responses to distress during social exclusion (Bolling et al., 2011; Masten et al., 2009; Moor et al., 2012; Sebastian et al., 2011). Increased dorsal ACC/ mPFC to exclusion may be dependent on individual differences. As dorsal mPFC activity is especially pronounced in individuals sensitive to interpersonal rejection (Burklund, Eisenberger, & Lieberman, 2007; Eisenberger, Way, Taylor, Welch, & Lieberman, 2007), anxiously attached (DeWall et al., 2012), and/or having low self-esteem (Onoda et al., 2010; Somerville, Kelley, & Heatherton, 2010). Therefore, dorsal ACC/mPFC responsivity to social rejection may also be evident in individuals with CEM. However, CEM related brain functioning during social exclusion has not yet been examined.

We examined the impact of a history of CEM on brain functioning and emotional distress to social exclusion. We compared young adult patients reporting a moderate to extreme history of CEM (N=26) with healthy controls (N=20) reporting low to moderate CEM. We examined whole brain responses while specifying the mPFC, ACC and Insula as regions of interest (ROIs) because of their important role in social exclusion (Cacioppo et al., 2013; Eisenberger, 2012). We hypothesized that individuals reporting a history of CEM would show enhanced brain responses and emotional distress to social exclusion. Therefore, we hypothesized that the severity of CEM would show a dose-response relationship with self-reported distress and brain responsivity.

METHODS

SAMPLE

We included a total of 26 out- and inpatients reporting moderate to extreme CEM ('CEM group') who were in treatment at a center for youth specialized mental health care in the Hague, the Netherlands (mean age=18.31 years, SD=1.23; 6 males) and 20 healthy controls reporting low to moderate CEM (mean age=18.85, SD=1.95; 6 males). The CEM and control groups were matched in terms of age ($F(1,44)=1.38$, $P=.25$), gender ($X^2(1)=.28$, $P=.74$), and IQ ($F(1,44)=2.76$, $P=.10$) (see Table 1). In the CEM group, 11 patients reported regular use of anti-depressant and anti-anxiogenic medication (n=8 used SSRI's, n=1 used the tricyclic antidepressant (TCA) = amitrypteline, and n=3 used benzodiazepam).

Table 1. Demographics for the Control and CEM groups.

	Controls (n=20)		CEM (n=26)				
	Mean	SD	Mean	SD	X^2	F	P
Gender M/F	6/14		6/20		.281		0.74
IQ	111.5	9.54	107.0	8.76		2.76	0.10
Age	18.85	1.90	18.31	1.23		1.38	0.25
Emotional Abuse	5.2	0.89	11.81	4.20		47.70	0.00
Emotional Neglect	6.85	1.76	17.65	3.60		151.81	0.00
Physical Abuse	5.00	0.00	6.38	2.65		5.41	0.03
Physical Neglect	4.05	0.22	6.77	3.90		9.64	0.00
Sexual Abuse	5.45	1.00	9.15	2.66		34.75	0.00

Patients in the CEM group were excluded when they had a comorbid pervasive developmental disorder or psychosis (as measured with the SCID-I; Spitzer, Williams, Gibbon, & First, 1990). In addition, current substance abuse was also set as an exclusion criterion. Current substance abuse was measured through random urine samples that are mandatory for individuals admitted at the center.

Fifteen participants from the control group had participated earlier in a study on developmental differences in neural responses during social exclusion (Gunther Moor et al., 2012). Twenty-six participants who were >15 years of age at the time of scanning in the Gunther Moor et al. study, and who had indicated that they could be approached for future research were contacted. Twenty-one participants agreed to participate and completed the Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998). Five participants were excluded based on CTQ scores indicating a history of childhood abuse; two reported moderate to severe physical abuse (both scored 12), two reported severe emotional neglect (both scored 19), and one reported borderline moderate/severe emotional neglect (14). To further obtain a good match with the CEM group, five control participants were recruited from the general public through a recruitment website, and through adevertisements. All control participants included in this study indicated no history of psychiatric disorder, were not taking any psychotropic drugs and had scores of low-moderate emotional abuse (<12), emotional neglect (<14), and physical neglect (<10), and no physical abuse (<6), and sexual abuse (<6), on the CTC according to the American cut offs (Bernstein & Fink, 1998).

Finally, exclusion criteria for all participants were left-handedness, or general contra-indications for MRI, such as metal implants, heart arrhythmia, and claustrophobia, difficulty understanding the Dutch language, or a IQ < 80 (all participants completed the WAIS, or if <18 years the WISC intelligence subscales similarities and block design; Wechsler, 1991, 1997). All participants provided written informed consent, and the Leiden University Medical Center Medical Ethics committee approved this study.

ASSESSMENT OF PSYCHOPATHOLOGY

In all patients with a history of CEM, DSM-IV axis 1 (psychiatric disorders) and DSM-IV axis II disorders (personality disorders) were assesed using the Structured Clinical Interview for DSM Disorders (SCID-I & SCID-II; First & Gibbon, 1997; Spitzer et al., 1990). All patients in the CEM group had at least one axis I disorder (18 participants had multiple axis I disorders), and 19 participants had a concurrent axis II personality disorder (see Table 2 for all axis I and II diagnoses). Control participants over the age of 18 at the time of scanning reported no history of neurological or psychiatric disorders.

Table 2. Clinical characteristcs of the CEM group.

SCID I	Depression	Alcohol abuse	Social phobia	Obsession	Generalized Anxiety	PTSD	
# current	16		10	2	1	10	
# Lifetime	9	3	4	1		3	
Total	24	3	14	3	1	13	
SCID II	Avoidant	Dependent	Obsessive	Depressive	Passive Agressive	Paranoid	Borderline
	11	2	3	10	1	5	7

Note. Scid II data for 2 participants was missing

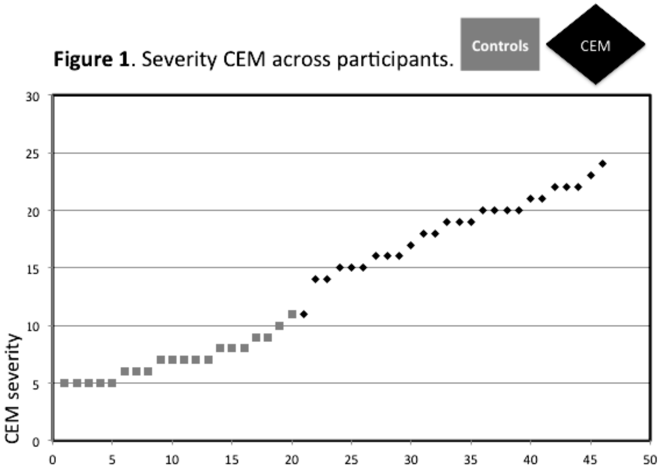
Control participants who were under the age of 18 at the time of scanning were screened for psychiatric disorders using the Child Behavioural Checklist (CBCL; Achenbach, 1991) that was filled in by their parents. Control participants were only included in this study if they scored in the normal range of the CBCL. Control participants over the age of 18 at the time of scanning were screened for DSM-IV axis II personality disorders with the Dutch Questionnaire for Personality Characteristics (Vragenlijst voor Kenmerken van de Persoonlijkheid (VKP); Duijsens, Eurelings-Bontekoe, & Diekstra, 1996). Because the VKP is known to be overly inclusive (Duijsens, Eurelings-Bontekoe, & Diekstra, 1996), controls with a score that indicated a 'probable' personality disorder on the VKP (n=8) were also assessed with a SCID-II interview by a trained clinical psychologist (K.H.). All controls that were followed up with the SCID-II were free from personality disorder diagnoses.

CHILDHOOD EMOTIONAL MALTREATMENT

History of childhood emotional maltreatment was assessed using the Dutch version of the Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998). In the Dutch version of CTQ (Arntz & Wessel, 1996), a total of 24 items are scored on a 5-point scale, ranging from 1=never true to 5=very often true. The CTQ retrospectively assessed five subtypes of childhood abuse: emotional abuse, sexual abuse, physical abuse, emotional neglect and physical neglect. The CTQ is a sensitive and reliable screening questionnaire with Cronbach's alpha for the CTQ subscales varying between .63-.91 (Thombs, Bernstein, Lobbestael, & Arntz, 2009).

In line with the American Professional Society on the Abuse of Children (APSAC, 1995) and our previous studies on CEM (Van Harmelen, Elzinga, Kievit, & Spinhoven, 2011; Van Harmelen et al., 2010), emotional maltreatment in childhood was defined as a history of emotional neglect and/or emotional abuse before the age of 16 years. For the entire sample, overall CEM score (i.e. severity) was defined as the highest score on the emotional abuse or emotional neglect subscale of the CTQ (e.g., if emotional abuse score was 19, and emotional neglect score was 14, overall CEM score was 19). In our study, Cronbach's alpha for the emotional abuse subscale was .88, for the emotional neglect subscale .94, and for the combined emotional abuse and neglect subscales .83. The CEM group reported significantly higher levels of childhood abuse compared to controls on all subscales of the CTQ (all F's>5.41, P's<.03) see Table 1. Self-reported CEM ranged from low to extreme CEM across participants (see Figure 1). In the control group self-reported severity of CEM ranged from low to moderate, whereas in the CEM group severity of CEM ranged from moderate to extreme (Bernstein & Fink, 1998).

Figure 1. Severity CEM across participants.



THE CYBERBALL GAME

In the Cyberball game (Williams et al., 2000; Williams & Jarvis, 2006) participants played a game of virtual toss with two other players (computer controlled confederates), depicted using animated avatars. Participants were led to believe that the other players (one female, one male) played the game online on the Internet. Fictitious names of the players (common Dutch names, counterbalanced between participants) were displayed on the screen just above their avatars (i.e. in the left and right hand corners of the screen). The participant's self was displayed on the screen as an animated hand, with the participant's name displayed just below the hand. In the Cyberball game, participants first played the inclusion game, followed by the exclusion game. During inclusion, participants threw the ball one-third of the total amount of throws (thus, achieving an equal number of throws as compared to the other players). During social exclusion, they received the ball once in the beginning of the game, but thereafter never received it again. Immediately after inclusion, and after exclusion, participants filled in two questionnaires that assessed their distress during the game (see below for specifics on the questionnaires). All instructions, and questionnaires were presented on the screen, and all instructions were read out loud (through the intercom) by the experimenter. Finally, and before starting the Cyberball game, participants were questioned whether they understood the instructions of the game.

Both Cyberball games consisted of a total of 30 ball tosses, and each game was administered in a separate run that lasted circa 5 minutes. The duration of each ball toss was fixed to 2 seconds. We added a random jitter interval (100-4000 ms.) in order to account for the reaction time of a real player. To further increase credibility of the Cyberball game, both games started with a loading screen that notified that 'the computer is trying to connect with the other players'.

DISTRESS: NEED SATISFACTION AND MOOD RATINGS

To assess distress after inclusion, exclusion, and after scanning (just before the debriefing; 'post scanning'), all participants completed the Need Threat Scale (Van Beest & Williams, 2006), and a mood questionnaire (Sebastian, Viding, Williams, & Blakemore, 2010). The need threat questionnaire consists of eight items that measure self-esteem, belonging, meaningful existence, and control (each was measured with two questions). The mood questionnaire consisted of eight items that (two of each) measured feeling good/bad, relaxed/tense, happy/sad, and friendly/unfriendly. All items on the questionnaires were rated from 1 ('not at all') to 5 ('very much'), and a high score on both questionnaires indicates good mood, or high needs threat[XI].

After inclusion and exclusion, participants were instructed to describe their mood and need threat feelings during the inclusion and exclusion game. At post-scanning, participants were instructed to assess their current mood and need threat feelings.

FMRI DATA ACQUISITION

Upon arrival to the lab, we first familiarized the participants with the scanning environment and sounds, using a mock scanner, and recorded scanner sounds. Actual scanning was performed on a 3.0 Tesla Philips fMRI scanner in the Leiden University Medical Center. To restrict head motion, we inserted foam cushions between the coil and the head. Functional data were acquired using T2*-weighted Echo-Planar Images (EPI) (TR = 2.2 s, TE = 30 ms, slice-matrix = 80 × 80, slice- thickness = 2.75 mm, slice gaP= 0.28 mm,

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[XI] *To enhance the readability of this paper, we inverted the need threat scores (in the original scale a high need threat score indicated low need threat), which explains the negative need threat scores in Figures 2 and S2* field of view= 220). The two first volumes were discarded to allow for equilibration of T1 saturation effects. After the functional run, high-resolution T2-weighted images and high- resolution T1-weighted anatomical images were obtained.

FMRI DATA ANALYSIS

Data were analyzed using Statistical Parametric Mapping (SPM8; Wellcome Department of Cognitive Neurology, London), version 8, and MATLAB 12.b. Images were corrected for differences in timing of slice acquisition, followed by rigid body motion correction. Preprocessing further included normalization to reorientation of the functional images to the anterior commissure and spatial smoothing with an 8-mm full-width half-maximum Gaussian kernel. The normalization algorithm used a 12-parameter affine transformation together with a nonlinear transformation involving cosine basic functions, and resampled the volumes to 3 mm cubic voxels. Movement parameters never exceeded 1 voxel (<3 mm) in any direction for any subject or scan. Preprocessing of the fMRI time series data used a series of events convolved with a canonical hemodynamic response function (HRF) model. In line with Gunther Moor et al., (2012), BOLD responses were distinguished for events on which participants received (inclusion), or did not receive the ball (exclusion). We divided the inclusion game in three conditions; '*receiving/ not receiving/ playing the ball*', and during the exclusion game, the first two trials where participants received and played the ball once were not analyzed, and all other throws were set as 'not receiving the ball'.

First level models were assessed using general linear model, with modeled events, and a basic set of cosine functions (to high pass filter the data) as covariates. The least-squares parameter estimates of height of the best-fitting canonical HRF for each condition were used in pair-wise contrasts. For all participants, contrasts between conditions were computed by performing one-tailed t-tests, treating participants as a random effect. To examine the effect of social exclusion and inclusion, for all analyses, we compared brain responses using the t contrast: *'exclusion out-inclusion to'*. This contrast has previously been used by Gunther Moor et al (2012), where it was associated with activations in regions commonly associated with Cyberball (i.e. Insula, the ACC, and mPFC). This analysis was also performed as a t-sample t-test to examine differences between the CEM group and the control group.

Next, individual differences were added as predictors in regression analyses. First, we examined whether activation in the contrast *'exclusion out-inclusion to'* was associated with the self-report measurements, using whole brain regression analyses with mood, or need threat scores2 after exclusion (i.e. a higher score indicates a better mood, or high needs threat) as regressors of interest.

In order to examine whether the severity of CEM (see Figure 1) was related to activation in the contrast *'exclusion out-inclusion to'*, we performed whole brain multiple regression analyses with CEM score as regressor of interest, and physical abuse, physical neglect, and sexual abuse scores as regressors of no interest [XII]. Activations related to other types of maltreatment (e.g. sexual/ physical abuse) during exclusion were examined with a similar whole brain multiple regression analysis, while specifying a specific type of abuse as regressor of interest, and CEM and the other types of abuse as regressors of no interest.

For these analyses, brain activations were first examined at whole brain level with a threshold of P<.005 uncorrected, with a spatial extend K>25 voxels because this threshold and cluster extend have been suggested to provide a good balance between type 1 and type 2 errors (Lieberman & Cunningham, 2009). Because of their presumed role during social exclusion, we then set the entire ACC, mPFC and Insula as Regions of interest (ROIs) (see also Eisenberger, 2012; Meyer et al., 2012). If peak voxel activations fell within these predetermined ROIs, to further protect against Type 1 errors, we also report whether these activations were significant after small volume correction (P_{SVC}) for the spatial extend of the activated region (family wise error at the cluster level). For this SVC we used the automatic anatomical labeling (AAL) toolbox within the Wakeforest-pickatlas toolbox (Maldjian, Laurienti, Kraft, & Burdette, 2003). Brain activations where peak voxel activations fell outside our predetermined ROIs were examined at P<.05 FWE corrected at the whole brain level. All brain coordinates are reported in MNI atlas space. For illustration purposes, we extracted cluster activations (for the main effect of task) using the Marsbar region of interest toolbox (Brett, Valabregue, & Poline, 2002).

BEHAVIORAL ANALYSES

Behavioral responses for the mood and need threat scales were analyzed using Group (CEM, Controls) by measurement moment (Inclusion, Exclusion, Post Scanning) Repeated Measures Analyses of Variances (ANOVAs) in IBM SPSS statistics 19. In addition, the relationship between severity of CEM across participants, and distress (mood and need threat scores) after inclusion, exclusion, and post scanning was assessed using correlational analyses. All analyses were Bonferroni corrected for multiple testing, and significance was set at P<.05 two-sided.

[XII] We were unable to add diagnosis (yes/no) as regressor of interest in this model, as we only had SCID II data for n=7 controls, and no SCID II data was available for all controls. When we calculated a binary presence vs. absence variable while setting all controls at 0, there was a very high correlation between CEM score and this binary variable (r=.90). Therefore, we choose to examine the impact of Axis I and Axis II diagnosis separately within the CEM group (see Supplement), while focussing on those disorders that are known to impact responses to social exclusion (Current Depression, and Borderline Personality Disorder).

RESULTS

IMPACT OF SOCIAL EXCLUSION ON SELF-REPORTED MOOD AND NEED THREAT.

A Group (CEM, Controls) by measurement moment (Inclusion, Exclusion, Post Scanning) rmANOVA on mood revealed a main effect of measurement moment on mood score ($F(2,86)=67.47$, $P<.001$), and post-hoc t-tests showed that for both groups mood scores significantly decreased from inclusion to exclusion (t's> 5.58, Ps<.001), and significantly increased from exclusion to post scanning (t's<-4.53, Ps<.001). In addition, there was a main effect of group ($F(1,43)=6.19$, $P=.02$), and there was a significant mood×group interaction ($F(2,86)=9.52$, $P<.001$). Figure 2 shows that after inclusion, the CEM group reported significantly lower mood scores when compared to controls ($F(1,43)=6.83$, $P=.012$), however after exclusion, this difference disappeared ($F(1,43)=.09$, $P=.77$). At post scanning, the CEM group again reported lower mood feelings compared to controls ($F(1,43)=15.54$, P=<.001).

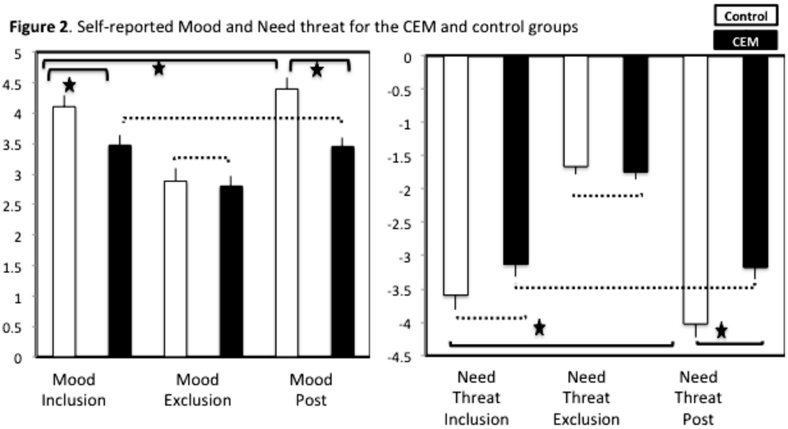
A Group (CEM, Controls) by measurement moment (Inclusion, Exclusion, Post Scanning) rmANOVA on need threat revealed a main effect of measurement moment on need threat scores ($F(2,88)=162.80$, $P<.001$), and post-hoc t-tests indicated that need threat scores significantly increased from inclusion to exclusion in both groups (t's>9.08, Ps<.001), and significantly decreased from exclusion to post scanning (t's>-7.80, Ps<.001), suggesting that exclusion in the Cyberball task significantly increased threat related feelings across participants. There was a marginal main effect of group ($F(1,44)=3.80$, $P=.06$), and a significant need threat×group interaction ($F(2,88)=8.33$, $P<.001$). Post-hoc tests showed that after inclusion, the CEM group reported similar need threat when compared to controls ($F(1,44)=2.62$, $P=.11$), which remained after exclusion ($F(1,44)=.24$, $P=.62$).

However, at post scanning, the CEM group reported increased need threat feelings when compared to controls ($F(1,44)=9.72$, P=<.005), see Figure 2.

RELATIONSHIP BETWEEN SEVERITY OF CEM AND SELF-REPORTED DISTRESS (MOOD AND NEED THREAT)

Across participants, correlation analyses revealed that the severity of the CEM score was negatively related to mood ($r=-.45$, $P<.001$) and positively with feelings of need threat ($r=.29$, $P<.05$) after inclusion. However, after exclusion, no relationships with CEM score and mood, nor need threat were found (*r*'s<-.02, P's>.29). Finally, post scanning, CEM score was again significantly negatively related to mood ($r=-.49$, $P<.001$) and positively with need threat scores ($r=.58$, $P<.001$).

Figure 2. Self-reported Mood and Need threat for the CEM and control groups



Note. Significant differences are indicated with an asterisk, whereas dotted lines depict non-significant differences. A high score on the mood scale indicates high mood, whereas a low score on the need threat scale indicates low need threat.

FMRI ANALYSES

MAIN EFFECT OF EXCLUSION>INCLUSION

Across participants, the contrast *'exclusion out-inclusion to'* resulted in activations in the posterior ACC (x=0, y=-36, z=36, K=61, Z=3.43, P<.001, P_{SVC}=.09), and the ventral mPFC (x=-3, y=57, z=-12, K=44, Z=3.51, P<.001), see Figure 3. The activation in posterior ACC marginally survived SVC, but the ventral mPFC area did not survive SVC. All brain regions that were active at the reported threshold (P<.005, K>25) are presented in Table 3. An independent (CEM vs. Controls,) t-test in the same and the reversed contrast revealed no significant group differences.

IMPACT OF CEM SEVERITY ON BRAIN ACTIVATIONS DURING EXCLUSION ACROSS PARTICIPANTS

A whole brain regression analysis across all participants indicated that in the contrast 'exclusion out-inclusion to' the severity of CEM score had a positive association with dorsal mPFC activation (x=-3, y=48, z=33, K=80, Z=3.53, P<.001, P_{SVC} <.05, see Figure 3). Interestingly, both within the control and CEM groups, dorsal mPFC activity in the same cluster was related to CEM severity (see Table S1, Figure S1). There were no significant negative brain activations (see Table 3), nor any brain activations related to physical abuse, physical neglect, nor sexual abuse for the contrast '*exclusion out-inclusion to'*.

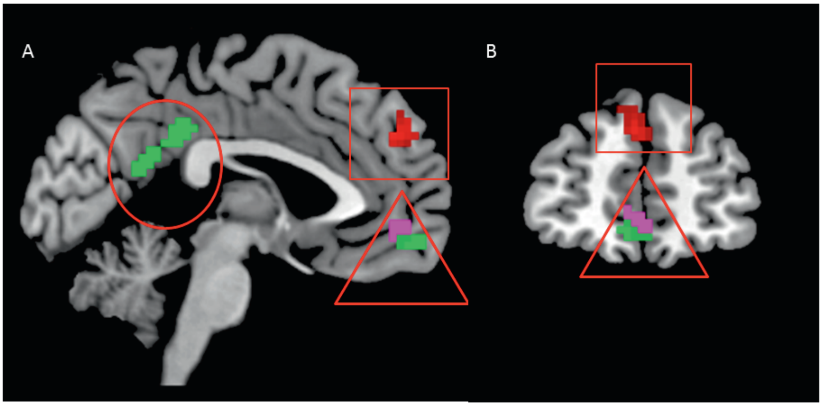
BRAIN ACTIVATIONS RELATED TO DISTRESS ACROSS PARTICIPANTS

A whole brain regression analysis indicated that need threat scores after exclusion were related to activation in the ventral mPFC contrast 'exclusion out-inclusion to' (x=-3, y=51, z=-6, K=31, P<.001), however, this did not survive SVC (P_{SVC}=1) (Figure 3). The reversed contrast did not result in any significant differences in brain activation. Additionally, self-reported mood scores after exclusion were not associated with significant brain activations (positively, nor negatively) in the contrast '*exclusion out-inclusion to*'.

Correlational analyses between distress and dorsal mPFC activation

Correlational analyses between activations in the dorsal mPFC cluster (x=-3, y=48, z=33), and self-reported Need Threat revealed a marginal positive relationships after inclusion (r=.26, P=.08), but not after exclusion, nor post measurement (r's<.17, P's>.25). Similar correlational analyses revealed that the dorsal mPFC activation was not related to self-reported mood at any of the measurement moments (r's<-.23, Ps>.14).

Figure 3. Brain responses to social exclusion ('*exclusion to-inclusion out*') at x=-3 (A), y=51(B)



Note. The green blobs depict the posterior cingulate (circle), and ventral mPFC cluster (triangle) that were related to social exclusion ('*exclusion to-inclusion out'*) across participants.
The violet blob (triangle) depicts the ventral mPFC that was activated in response to need threat at exclusion across participants. The red blob depicts the dorsal mPFC cluster that was related to CEM across participants.

Table 3. Activations for the ' *Exclusion out - Inclusion to* ' contrast at P<.005, K>25.

			K	P FWE	T	Z	P	x,y,z	ROI P SVC
Main effect across participants		Ventral mPFC	44	0.93	3.79	3.51	0.000	-3 57 -12	1.00
				1.00	3.15	2.98	0.001	6 57 -9	
				1.00	2.97	2.82	0.002	-9 45 -9	
		Posterior ACC	61	0.97	3.69	3.43	0.000	0 -36 36	0.09
				0.99	3.52	3.29	0.000	-6 -54 18	
		Inferior frontal gyrus	36	0.98	3.61	3.37	0.000	-42 27 15	
				1.00	3.31	3.11	0.001	-57 24 15	
				1.00	2.98	2.83	0.002	-54 27 6	
Mood exclusion	positive relationship	ns							
	negative relationship	Frontal inferior Opperculum	35	1.00	3.31	3.11	0.001	54 9 27	
Need treat exclusion	positive relationship	ventral mPFC	31	0.92	3.81	3.53	0.000	-3 51 -6	ns
	negative relationship	ns							
CEM vs Controls	CEM> Controls	Superior frontal gyrus	51	0.78	4.04	3.71	0.000	-24 24 51	
				1.00	2.84	2.70	0.003	-36 15 51	
		Angular gyrus	64	0.99	3.53	3.29	0.000	-51 -69 27	
				1.00	3.09	2.93	0.002	-42 -69 36	
				1.00	2.87	2.74	0.003	-33 -78 42	
	Controls> CEM	ns							
CEM severity	Negative	Superior Frontal Gyrus	56	0.71	4.15	3.77	0.000	-18 30 51	
		Dorsal mPFC	80	0.92	3.85	3.53	0.000	-3 48 33	0.05
				0.98	3.62	3.35	0.000	-12 48 42	
				1.00	2.97	2.81	0.002	6 60 30	

DISCUSSION

We examined whether individuals reporting CEM showed enhanced neural responses and emotional distress to social exclusion. We found a dose-response relationship between the severity of CEM and dorsal mPFC responsivity to social exclusion across participants, both in individuals reporting CEM and healthy Controls. Contrary to our expectations, we did not find differences in neural responses to social exclusion when comparing patients reporting moderate to extreme CEM with Controls reporting low to moderate CEM.

Across participants, we found that social exclusion was associated with increases in posterior ACC and ventral mPFC. Although the ventral mPFC response was not significant after small volume correction, ventral mPFC/ACC responsivity to exclusion is reported by numerous studies in adolescents and children (Bolling et al., 2011; Masten et al., 2009; Gunther Moor et al., 2012; Sebastian et al., 2012). Interestingly, the ventral mPFC and posterior ACC have been implicated in a model for self-referential processing (Van der Meer, Costafreda, Aleman, & David, 2010); the posterior ACC is involved in the integration of autobiographical memory with emotional information about the self (Van der Meer et al., 2010). Whereas, the ventral mPFC is assumed to play a role in the more affective components of self-referential processing, through emotional appraisal of self-relevant information and the coupling of emotional and cognitive processing during self-referential processing (Van der Meer et al., 2010). In line with the more affective role of the ventral mPFC, we found that increases in self-reported needs threat after social exclusion (i.e. reduced self-esteem, sense of belonging, meaningful existence, and control) were positively related to ventral mPFC responsivity, albeit at sub-threshold level. Taken together, our findings of posterior ACC and ventral mPFC response during social exclusion suggest that social exclusion led to negative self- and other referential processing in our sample.

Social exclusion was related to decreases in mood, and increases in needs threat in our sample, which is in line with the idea of enhanced negative self-referential processing related to social exclusion in our participants. The CEM group reported lower mood after inclusion, and at post measurement, yet after exclusion there was no significant difference between the CEM and Control group. In line, the severity of a history of CEM was negatively related to mood after inclusion; however this relationship disappeared after exclusion. These findings may be due to a floor effect in self-reported mood scores, i.e. participants could only rate their distress on a 1-5 scale, and the CEM group already reported lower mood at inclusion, leaving them little space for further reductions. The CEM group also reported higher needs threat at post-measurement, whereas the need threat scores were not significantly different from the control group during in- or exclusion, even though both groups reported an increase in need threat after exclusion. Apparently, need threat feelings were restored at post measurement in the control group, whereas in the CEM group need threat remained relatively high. These findings suggest that, at least for needs threat, the control group seems to recover quicker in the aftermath of social exclusion compared individuals with CEM. Indeed, the severity of CEM was positively related to needs threat after inclusion and at post-measurement. Perhaps, the CEM group is characterized by persistent negative self- and other- referential processing which was present at post-measurement level, and after inclusion. This is in line with findings of our research group that CEM is associated with more negative self-cognitions (Van Harmelen et al., 2010), and more frequent self and other referential processing (i.e. more intrusions of autobiographical interpersonal memories)(Van Harmelen et al., 2011).

We found that the severity of CEM was positively related to dorsal mPFC responsivity to social exclusion. CEM related dorsal mPFC responsivity may reflect a further increase in negative self-and other-referential processing in these individuals, since the mPFC is pivotal in self-referential processing (Blair et al., 2012; Grimm et al., 2009; Lemogne et al., 2009; Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012; Moran, Macrae, Heatherton, Wyland, & Kelley, 2006; van der Meer et al., 2010; Yoshimura et al., 2009). And a recent meta-analysis suggested that dorsal mPFC responsivity to social exclusion is related to enhanced social uncertainty, social distress, and social rumination (Cacioppo et al., 2013)

Dorsal mPFC in the self-referential processing model (Van der Meer et al., 2010) has been suggested to be important for the evaluation and decision making of self-and other referential information (the evaluation whether information is relevant to the self). Therefore, our findings suggest that severity of CEM may be associated with a further increase in negative self- and other referential thinking during social exclusion. Perhaps individuals reporting CEM perceive social exclusion as especially relevant to themselves. Moreover, negative self- referential processing enhances (negative) bias and recall, resulting in more frequent, and more intense negative experiences, which in its turn enhances negative self-referential cognitions (Beck, 2008). This is consistent with the slower recovery in the CEM group, and with our previous findings of more negative and more frequent self and other referential processing in CEM (Van Harmelen et al., 2011; Van Harmelen et al., 2010).

The finding of CEM related dorsal mPFC activity is of interest since animal studies utilizing paradigms that closely resemble CEM (e.g. maternal isolation/ separation or isolation rearing) show that the mPFC is particularly affected by early life emotional stress (Arnsten, 2009; Czéh et al., 2007; Lupien, McEwen, Gunnar, & Heim, 2009; McEwen, Eiland, Hunter, & Miller, 2012; Sánchez, Ladd, & Plotsky, 2001; Sanchez et al., 2007). In line, patients and healthy controls reporting CEM show a reduction in dorsal mPFC volume (Dannlowski et al., 2012; Tomoda et al., 2011; Van Harmelen, Van Tol, et al., 2010), and dorsal mPFC hypoactivity during higher order cognitive processing (Van Harmelen et al., under review). Therefore, our findings that individuals reporting CEM show enhanced dorsal mPFC responsivity during interpersonally stressful situations, suggest altered regulation/fluctuations of dorsal mPFC activity in individuals reporting CEM. Perhaps these findings resemble attenuation (mPFC hypoactivity) or increases (mPFC hyperactivity) in negative self- and other-referential processing in these individuals. Future studies should examine this.

Dorsal mPFC responsivity to social stress has been found to be predictive of current, and future depressive symptoms in healthy young adolescents aged 12-14 years old (Masten et al., 2011). However, in our study we did not find that the CEM related dorsal mPFC responsivity was more prominent in our patient sample, nor was it related to a diagnosis of current depression. Across participants, mPFC responsivity was not related to self-reported mood or needs threat (although mPFC responsivity was only related to needs threat in the CEM group). Thus, our findings of CEM related enhanced mPFC responsivity in individuals with CEM may not be related to current (psychiatric) distress. Rather, these findings are more in line with the idea that increased negative self-and other referential thinking (dorsal mPFC) constitutes a vulnerability or sensitivity factor, that may underlie the emotional and behavioral vulnerabilities that have been reported in these individuals (Egeland, 2009; Gilbert et al., 2009). And, only in interaction with other risk factors such as exposure to more recent adverse events, genetic make-up, or low social support, will this vulnerability eventually lead to psychopathology in later life (Ellis, Boyce, Belsky, Bakermans-Kranenburg, & Van Ijzendoorn, 2011).

The main effects of brain activations related to social exclusion in our sample were relatively weak. This may be related to the fact that we used the contrast *'exclusion out-inclusion to'* in order to calculate brain activations for social exclusion. The CEM group already reported lower mood at inclusion, and we found no reduction in self-reported needs threat, nor mood in the CEM group when compared to Controls after social exclusion. This suggests that social exclusion in our sample predominantly seemed to cause distress in the control group. In addition, because the CEM group already reported relatively low mood after inclusion, the social exclusion appeared to have a relatively little further impact on self-reported distress within the CEM group. In other words, even though the CEM group may be highly sensitive to social exclusion, they may also be chronically stressed. In that sense, additional social stress may therefore not further increase brain activations related to distress during social exclusion in these individuals. Therefore, including the CEM group when examining overall brain responses related to social exclusion ('*exclusion out- inclusion to'*) in our sample may have led to a reduction in those brain responses. This may also have blurred the overall brain responses to social exclusion.

Finally, contrary to our expectations, we found no group effects on brain activations to social exclusion when comparing the CEM group with healthy Controls. This may be explained by the fact that the CEM group reported moderate to extreme CEM, and the healthy Controls reported low to moderate CEM. Whereas, we found that the severity of CEM showed a positive association with dorsal mPFC responsivity. Therefore, low-moderate CEM in the control group may have reduced our chances of finding group differences, at least in dorsal mPFC responsivity. Moreover, the CEM and Control groups did not show subjective differences in self-reported distress during exclusion, which may have further reduced our chances of finding group differences in brain functioning.

There are some limitations that need to be addressed. First of all, we could not disentangle the effect of current depression from that of history of CEM in our analyses due to high multicollinearity, although current Axis I depressive diagnosis was not related to activations in the dorsal mPFC. And the findings of CEM related dorsal mPFC responses to exclusion were found across participants, and were even apparent in the Control group, suggesting that an Axis I depressive diagnosis might not confound our findings. However, to better disentangle the impact of CEM from the impact of depressive diagnosis on brain functioning during social exclusion, future studies examining patients with depression with and without CEM, and controls with and without a history of CEM are needed.

Second, in our study we assessed CEM retrospectively, and we have to stress the relative subjectivity of self-reported CEM. Furthermore, self-reported CEM may be subject to biased recall. Although, CEM is more likely to be under-reported than over-reported (Hardt & Rutter, 2004). And it should be noted that the test-retest reliability of the CTQ subscales for emotional abuse and emotional neglect have been found satisfactory across different ranges of samples (i.e. college students, psychiatric patients, and convenience samples) (Tonmyr, Draca, Crain, & Macmillan, 2011). Furthermore, in a large sample of patients and controls, it was found that retrospective recall of CEM was not affected by current mood state (Spinhoven et al., 2010).

CONCLUSION

Taken together, we show that severity of CEM is positively related to dorsal mPFC responsivity to social exclusion in both patients with psychiatric disorders and healthy controls. The dorsal mPFC is vital for self and other-referential processing (Etkin, Prater, Hoeft, Menon, & Schatzberg, 2010; van der Meer et al., 2010). Together with findings of more negative and more frequent self-referential processing in CEM (Van Harmelen et al., 2011; Van Harmelen et al., 2010) and slower recovery in terms of need threat after the social exclusion task, our findings suggest increased dorsal mPFC activity during social exclusion may be related to more negative self- and other-reflective thinking in individuals reporting CEM. Increased negative self-and other referential thinking (dorsal mPFC) enhances vulnerability to the development of psychiatric disorders (Beck, 2008). Therefore, our findings may be important in understanding the emotional and behavioral problems that has been reported in these individuals in adulthood (Egeland, 2009; Gilbert et al., 2009)

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Supplement

Post-hoc analyses within the Control and CEM groups

We also performed post-hoc analyses in order to test whether CEM related brain activations were present separately within the CEM group and control groups using a whole brain simple regression analysis with CEM score as regressor per group.

In addition, in the CEM group, 25 out of 26 patients had a current or history of Axis 1 diagnosis of depression (i.e. 16 patients had a DSM-IV axis 1 current depression diagnosis, see Table 2). Therefore, we examined the impact of presence vs. absence of current depression in a separate regression analysis. Using a similar simple regression analyses we also examined the impact of the presence vs. absence of borderline personality disorder, given the fact that rejection sensitivity has been related to borderline personality symptoms (Rosenbach & Renneberg, 2011). Finally, we also examined the impact of medication use on brain functioning during exclusion within the CEM group using a whole brain regression analysis.

All post-hoc regression analyses examined whole brain activations at P<.005, K>25. Because of their presumed role during social exclusion, we then set the entire ACC, mPFC and Insula as Regions of interest (ROIs) (see also Eisenberger, 2012; Meyer et al., 2012). Brain activations where peak voxel activations fell outside our predetermined ROIs were examined at P<.05, FWE corrected at the whole brain level. All brain coordinates are reported in MNI atlas space. The results of these analyses are summarized in Table S1.

CEM related brain activations to exclusion within the groups

In the control group, CEM score was positively associated in the contrast *'exclusion out-inclusion to'* with activations in the right mPFC (x=21, y=48, z=27, K=346, Z=4.02, P<.001, and left dorsal mPFC (x=-6, y=54, z=39, K=34, Z=3.36, P<.001). Figure S1 shows that this was the same region where we found CEM related activations across participants. Finally, CEM score was also associated with Insula activation in the controls (x=39, y=6, z=-15, K=27, Z=3.26, P<.001). There were no other significant brain activations (see Table S1).

Within the CEM group, CEM score was positively associated in the contrast *'exclusion out-inclusion to'* with activation in dorsal mPFC (x=-9, y=54, z=39, K=28, Z=3.98, P<.001). This is the same region that was also significantly related to CEM score across participants (see Figure S1). There were no other significant brain activations (Table S1).

Brain activations related to current depression, borderline personality or medication use

A whole brain regression analysis showed that the presence (n=16) vs. absence (n=10) of a current diagnosis of depression in the CEM group was not associated with any brain activations in the contrast *'exclusion out-inclusion to'*.

A similar whole brain regression analysis revealed that medication use (yes, no) was not associated with significant brain activations in the contrast *'exclusion out-inclusion to'*.

Moreover, a whole brain regression analysis showed that the presence (n=7) vs. absence (n=17) of Borderline personality disorder was associated with activations in the mPFC and caudate in the contrast *'exclusion out-inclusion to'* (see Table S1). However, the very small number of individuals with a BPD diagnosis severely hampers the interpretation of this finding. Moreover, this region did not overlap with the mPFC cluster that was related to CEM, and hence cannot explain these findings (Figure S2).

Table S1. Activations for the ' Exclusion out - Inclusion to' contrast at P<.005, K>25 for the Post-hoc analyses.

						peak		
			K	P FWE	T	Z	*P*	x,y,z
Control group	CEM score	Dorsal mPFC	346	0.64	5.21	4.02	<.001	21 48 27
				0.85	4.81	3.81	<.001	12 63 21
				0.87	4.76	3.78	<.001	6 63 27
		Inferior parietal gyrus	43	0.73	5.05	3.94	<.001	39 -48 42
		Middle temporal gyrus	42	0.95	4.55	3.66	<.001	54 -21 -15
		Inferior frontal gyrus triangu	27	0.99	4.19	3.46	<.001	36 24 24
				1.00	3.50	3.01	0.001	45 21 27
		Temporal middle gyrus	37	1.00	4.14	3.42	<.001	-66 -45 -6
				1.00	3.49	3.01	0.001	-60 -36 -12
		Dorsal mPFC	42	1.00	4.13	3.42	<.001	-6 54 39
				1.00	4.00	3.34	<.001	-12 45 45
				1.00	3.89	3.27	0.001	-9 51 30
		Temporal mid Rechts	57	1.00	4.03	3.36	<.001	51 -45 -6
				1.00	3.48	3.01	0.001	63 -39 -6
		Insula	27	1.00	3.88	3.26	0.001	39 6 -15
		Caudate	33	1.00	3.55	3.05	0.001	-9 15 6
				1.00	3.47	2.99	0.001	3 15 9
CEM group	CEM score	Dorsal mPFC	28	0.52	4.80	3.98	<.001	-9 54 39
	SSRI	Post Central gyrus	30	0.988	3.85	3.36	<.001	-21 -30 60
	Current Depression	ns						
	Borderline	mPFC	128	0.765	4.56	3.79	<.001	-12 48 3
				0.858	4.4	3.68	<.001	-12 57 -3
				0.998	3.72	3.24	0.001	9 51 0
		Caudate	28	0.959	4.12	3.51	<.001	-15 3 15
				0.965	4.09	3.49	<.001	-12 12 12

RELATIONSHIP DORSAL MPFC AND SELF-REPORTED DISTRESS WITHIN THE GROUPS

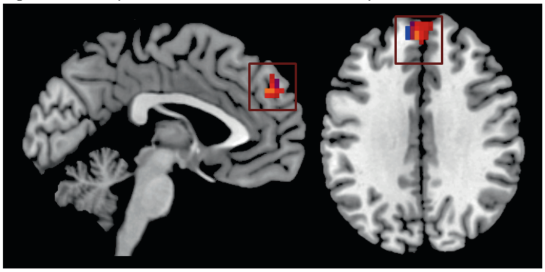
Within the Control group, there was no significant relationship between this dorsal mPFC activation and self-reported need threat after inclusion, exclusion, or post measurement (*r*'s<.21, P's>.38). Similarly, there was no relationship between dorsal mPFC and self-reported mood after inclusion, and exclusion (*r*'s<.23, P's>.34), however, there was a significant relationship between mood at post-measurement and dorsal mPFC responsivity (*r*=.44, P=.06).

Interestingly, within the CEM group, there was a marginal significant relationship between dorsal mPFC activation and need threat after exclusion (*r*=.34 P=.09, see Figure S3), but not after inclusion or at post measurement (*r*’s<.21 P’s>.31). Furthermore, dorsal mPFC activity was not associated with mood after inclusion, exclusion, or at post measurement (*r*’s<-.19, P’s>.35).

Relationship CEM severity and self-reported distress (mood and need threat)

Within the CEM group, CEM score was (marginally) negatively related to mood at all measurement moments (*r*’s>-.37, P’s<.06), and positively related to needs threat after exclusion (*r*=.53, P<.005), but not after inclusion and at post measurement (*r*’s<.33, P’s>.10). No relationships with CEM score and mood or needs threat were found in the control group (all *r*’s<.37, all P’s>.12).

Figure S1. Overlap in MPFC activations for CEM severity.



Note. Figure S1 depicts dorsal mPFC responsivity related to CEM severity across participants (Red), controls (Blue), and patients (yellow). Blurred colours indicate overlap between the regions.

Figure S2. MPFC activations for CEM (circle) and Borderline personality (square).

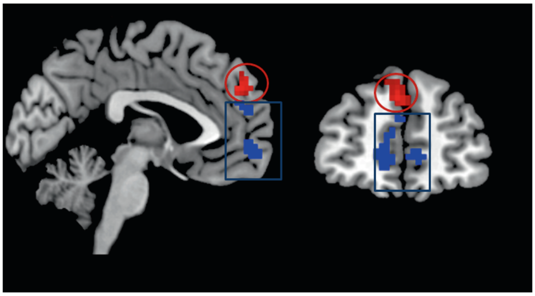


Figure S3. Relationship mPFC and Needs Threat **CEM**