Altered neural response to rejection-related words in children exposed to maltreatment

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Abstract

Background:

Children exposed to maltreatment show neural sensitivity to facial cues signalling threat. However, little is known about how maltreatment influences the processing of social threat cues more broadly, and whether atypical processing of social threat cues relates to psychiatric risk.

Methods:

Forty-one 10-14 year old children underwent a social rejection-themed emotional Stroop task during functional magnetic resonance imaging: 21 children with a documented history of maltreatment (11 F) and 19 comparison children with no maltreatment history (11 F). Groups were matched on age, pubertal status, gender, IQ, SES, ethnicity and reading ability. Classic colour Stroop stimuli were also administered in the same paradigm to investigate potential differences in general cognitive control.

Results:

Compared with their peers, children who had experienced maltreatment showed reduced activation in the Rejection vs. Neutral condition, across circuitry previously implicated in abuse-related PTSD, including the left anterior insula, extending into left ventrolateral prefrontal cortex/ orbitofrontal cortex; left amygdala; left inferior parietal cortex (STS); and bilateral visual association cortex, encompassing the cuneus and lingual gyrus. No group differences in neural or behavioural responses were found for the classic colour Stroop conditions. Significant negative associations between activity in bilateral cuneus and STS during the rejection-themed Stroop and higher self-reported PTSD symptomatology, including dissociation, were observed in children exposed to maltreatment.

Conclusion:

Our findings indicate a pattern of altered neural response to social rejection cues in maltreated children. Compared to their peers, these children displayed relative hypo-activation to rejection cues in regions previously associated with PTSD, potentially reflecting an avoidant coping response. It is suggested that such atypical processing of social threat may index latent vulnerability to future psychopathology in general and PTSD in particular.

Keywords: Child abuse, Emotion regulation, fMRI, PTSD, Adolescence

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Introduction

Childhood maltreatment, including neglect, is associated with a wide range of maladaptive outcomes for mental and physical health as well as social functioning (Lansford, Dodge, Pettit, Bates, Crozier & Kaplow, 2002). Maltreatment significantly increases risk for psychiatric disorders, including posttraumatic stress disorder (PTSD) and depression (Vachon, Krueger, Rogosch, & Cicchetti, 2015). The theory of latent vulnerability (McCrory & Viding, 2015) provides one framework within which to conceptualise the association between maltreatment and psychopathology. It contends that there are calibrations in biological and neurocognitive systems in response to early risk environments; while adaptive in the short term, these can confer long-term risk for psychiatric disorders following future stressors (McCrory & Viding, 2015). Such changes to neurocognitive systems should be measurable in childhood, allowing the identification of psychiatric risk mechanisms in the absence of overt symptomatology (Hanson, Hariri & Williamson, 2015).

The processing of threat-related cues represents one candidate neurobiological mechanism susceptible to stress-induced alteration (McCrory & Viding, 2015). Maltreatment experience has been associated with heightened perceptual salience of negative stimuli, specifically threatening (i.e. angry) facial expressions (Pollak, Vardi, Bechner, & Curtin, 2005; McCrory et al., 2011). Several studies have demonstrated that maltreated children show an enhanced response to threatening facial expressions at the behavioural (Pollak et al., 2005) and neural levels, with altered functioning reported in the amygdala, anterior insula and prefrontal cortices (e.g. McCrory et al., 2011; van Harmelen et al., 2014). These structures have also been implicated in the psychopathology of affective disorders (Etkin & Wager, 2007) commonly elevated in individuals with maltreatment histories.

Two recent fMRI studies have aimed to assess the processing of more socially complex constructs in maltreated children. Using a Cyberball paradigm, which simulates the experience of social rejection, these studies have demonstrated that maltreatment experience is associated with heightened distress and altered neural activity to social rejection (Puetz et al., 2014; van Harmelen et al., 2014). The experience of social rejection is an established risk factor for psychopathology and poor academic performance in the population at large (Platt, Cohen-Kadosh, & Lau, 2013; Silk et al., 2014; Sebastian, Viding, Williams, & Blakemore, 2010, Masten et al., 2009). Children who have experienced maltreatment are at higher risk for being rejected by their peers from childhood to adolescence (Bolger & Patterson, 2001) and show qualitative differences in interpersonal relationships into adulthood (Wolfe, Scott, Wekerle, & Pittman, 2001). This work is consistent with the finding that adults with childhood histories of maltreatment present with negative cognitive self-schemas and biases (van Harmelen et al., 2010; Zeanah & Zeanah, 1989), which in turn may moderate the effect of social rejection on the development of affective disorders (Shields & Cicchetti, 2001; O'Dougherty Wright, Crawford, & Del Castillo, 2009). One possibility is that maltreatment leads to altered salience of social threat cues, with implications for attentional allocation and emotional and behavioural regulation. This could in turn influence the way in which these individuals interact with others and are perceived by peers.

The current study aimed to investigate neural responses to rejection-themed words in a group of children with documented experiences of maltreatment. Specifically, we explored whether such words would be associated with heightened affective interference on cognitive control processes during an Emotional Stroop (ES) task (see Williams, Mathews & MacLeod, 1996). ES is a modified version of the classic colour-naming Stroop (Stroop, 1935) where interference during colour naming of emotionally-valenced words is thought to indicate attentional biases in response to affective information (see De Ruiter & Brosschot, 1994 for a review). We employed an established version of this paradigm previously used in typical and clinical adolescent and adult populations where the affective information consists of negative self-relevant information, i.e. rejection-themed words (Sebastian et al., 2010; Chechko et al., 2013). While evidence of affective interference at the behavioural level has been mixed (Dalgleish et al., 2003), fMRI studies have been relatively consistent in demonstrating an association between such interference and a network of emotion processing and regulatory regions including the ventromedial and ventrolateral prefrontal cortex (vMPFC/vlPFC; specifically the inferior frontal gyrus (IFG), the anterior cingulate cortex (ACC) the amygdala, the insula, as well as the visual association cortex/cuneus (Sebastian et al., 2010; Chechko et al., 2013). Altered activation of these same areas (patterns of increased and decreased activation, depending on the population and the task) has been implicated in ES paradigms in patients with PTSD (Bremner et al., 2004; Thomaes et al., 2012), depression (Chechko et al., 2013) and anxiety disorders (Dresler et al., 2012). Reduced activation in emotion processing and regulatory areas may reflect a pattern of functional avoidance; such a pattern has been reported for PTSD patients (for whom avoidance is a core feature), during emotional Stroop tasks.

'Hybrid versions' of the task in which a classic colour condition (i.e. non-valenced incongruent colour words such as red written in green ink) is implemented alongside the emotionally-valenced conditions, enables the investigation of group differences in interference that are specific to affective valence as well as those that are primarily related to differences in cognitive control (Chechko et al., 2013; Thomaes et al., 2012; Bremner et al., 2004). The use of a hybrid version is especially important in the present study, as previous studies have demonstrated mixed evidence regarding deficits in executive function (EF) and cognitive control in maltreated samples (e.g. Kirke-Smith, Henry, & Messer, 2014).

Using a hybrid Stroop task comprising both rejection-themed words as well as classic incongruent colour words, we predicted group differences to rejection-themed words in maltreated compared with non-maltreated children in regions previously showing atypical activation during affective interference in PTSD and depression (i.e. vmPFC, vlPFC/IFG, ACC, insula, visual association cortices and amygdala; Bremner et al., 2004; Thomaes et al., 2012; Chechko et al., 2013). We did not make directional predictions in relation to either decreased (possibly reflecting avoidance / more shallow processing) or increased (possibly reflecting hypervigilance) neural activity in this circuit, for two reasons. First, this circuit has been reported to show both atypical increases and decreases in neural activity during affective interference tasks in clinical samples with PTSD and depression, both conditions associated with maltreatment experience. Second, affective interference during a cognitively demanding task such as the Stroop differs from the low cognitive demands of previous studies investigating threat processing in maltreated children and therefore it is difficult to use these prior studies to inform clear directional predictions (McCrory et al., 2011; McCrory et al., 2013).

The amygdala was examined as a region of interest (ROI) given its established involvement in threat processing in general (Phelps & LeDoux, 2005) and in processing rejection-themed words specifically (Sebastian et al., 2010). Given the evidence of altered processing in these regions during affective interference in PTSD and depression, we conducted correlational analyses between symptomatology across these domains and neural response in the maltreated group. Finally, in view of the limited evidence regarding executive processing deficits in children with maltreatment experience, the classic colour Stroop condition was regarded as exploratory.

Methods

<u>Participants</u>

A total of 40 10-14 year-olds, were recruited for this study. Twenty-one children with a documented experience of maltreatment (mean age=12.47 ± 1.66 years; *N*=11 female) were recruited from a London Social Services (SS)

Department. Information on the nature, severity and duration of maltreatment was obtained through independent ratings by the child's social worker (*N*=16) or adoptive parent (*N*=5). An additional 19 Non-maltreated children were recruited from primary and secondary schools, after-school youth clubs in the London area, and via newspaper and Internet advertisement. Exclusion criteria for the Non-maltreated group included any previous contact with SS with regard to the quality of parental care or maltreatment. Participants across groups were comparable in age, pubertal status, sex, handedness, IQ, reading ability, socio-economic status (income, level of education and employment status all *Ps*>.17) and ethnicity (see Table 1).

Consent was obtained from the child's legal guardian. Assent to participate in the study was obtained from all children. All procedures in the study were approved by University College London Research Ethics Committee (0895/002).

Exclusion criteria for all participants included a diagnosis of learning disability, pervasive developmental disorder, neurological abnormalities, standard MRI contra-indications (e.g. ferromagnetic implants) and IQ < 70. All procedures in the study were approved by University College London Research Ethics Committee (0895/002).

PLEASE INSERT TABLE 1 HERE

Measures:

Maltreatment experience: For children referred to SS, maltreatment history, including the estimated severity, onset and duration of maltreatment was provided by the child's social worker or adoptive parent (on the basis of SS records), using an established maltreatment scale (Kaufman, Jones, Stieglitz, Vitulano, & Mannarino, 1994) with an additional rating for intimate partner violence. Severity of each abuse type was rated on a scale from zero (not present) to four (severe). Maltreatment type was rated as follows: neglect *N*=18; emotional abuse *N*=20; sexual abuse *N*=4; physical abuse *N*=2; intimate partner violence *N*=12). See online Appendix S1 for onset, duration and severity by subtype. Additionally, all children completed the Childhood Trauma Questionnaire (CTQ, Bernstein & Fink, 1998; see online Appendix S1).

Psychiatric symptomatology:

The Trauma Symptom Checklist for Children (TSSC; Briere, 1996) was self-rated to assess posttraumatic symptomatology, depression, anxiety, anger, and dissociation symptoms. Average scores in both groups were sub-clinical threshold (clinical range cut-off ≥65; see Table 1). Individuals with T-scores within the clinical range were as follows: *N*=1 depression, *N*=1 anger and *N*=2 dissociation in the MT group; *N*=1 anxiety in the Control group. The Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997) was completed by parents and carers to assess broader aspects of functioning (see online Appendix S1).

Cognitive ability was assessed using the two subscales of the Wechsler Abbreviated Scales of Intelligence (Wechsler, 1999). *Reading ability* was assessed with the word reading subscale of the Wide Range Achievement Test (WRAT 4, Jastak & Wilkinson, 1984) to ensure that interpretation of any differences in Stroop performance was not confounded by differences in reading level.

Experimental task

Participants underwent an emotional Stroop task (ES) comprising three valence categories following the protocol by Sebastian and colleagues (2010): i) Rejection-themed words (e.g. 'loser'; Rejection condition), ii) Inclusion-themed words (e.g. 'admired', Inclusion condition), and iii) Neutral words (e.g. 'cabinet', Neutral condition). Participants indicated with a button press the ink colour of the stimulus words. Additionally, two classic colour Stroop conditions (CS) were implemented in the same paradigm to formally assess cognitive control (i.e. Incongruent colour words condition and Neutral letter strings condition). The task in the present study aims to elicit incidental processing of rejection-themed words while children perform a colour naming task that ensures they are attending to the stimuli, but which is unlikely to elicit marked behavioural differences across groups. Full details of the stimuli characteristics are available in online Appendix S1.

Blocks of each of the five stimulus categories were presented in a permuted design and presented six times over two runs of seven minutes. Within each block, 12 words were each presented for 1500ms followed by an inter-stimulus interval of 500ms. A fixation-cross appeared after every third block for 15 seconds. Order of blocks and the order of the words within each block were pseudo-randomized. Responses were recorded with button boxes for both hands. RTs, missed trials and error rates were recorded. All participants completed a practice session outside the scanner.

fMRI data acquisition

Participants were scanned on a 1.5 Tesla Siemens Avanto MRI scanner (Siemens Medical Systems, Erlangen, Germany) using a 32-channel head coil and whole-brain EPI sequence (parameters: voxel size= 3x3x3mm, slices per volume: 35; slice thickness: 2mm; TR: 2975ms; TE: 50ms; FoV: 192mm; gap between slices: 1mm; flip angle: 90°). A magnetization-prepared rapid gradient-echo sequence (MP-Rage) was used to obtain a high-resolution structural scan (parameters: 176 slices; slice thickness: 1 mm; gap between slices: 0.5mm; TE: 2730ms; TR: 3.57ms; FoV: 256mm; matrix: 256 x 256 mm; voxel size: 1x1x1mm). All children's heads were foam padded, to minimize head motion.

Data analyses

Two participants (*N*=1 Maltreated group; *N*=1 Non-maltreated) were excluded from analyses because error rates were >2.5 SD above the sample mean. Two additional participants (*N*=1 Maltreated group; *N*=1 Non-maltreated) were excluded from the behavioural analyses due to a button-box malfunction but included in fMRI analyses, as their practice files indicated comparable performance. For behavioural data analyses (RT, error and missed trials) please see online Appendix S1. Brain images were analysed using SPM8 (www.fil.ion.ucl.ac.uk/spm/software/spm8), implemented in Matlab 2015a (The MathWorks Inc., 2012b). The first three volumes were discarded to allow for T1 equilibrium effects. Pre-processing: Each participant's scans were realigned within each run and subsequently across both runs to the first image of run one. Realigned images were co-registered with the individual anatomical T1-weighted images and subsequently spatially normalized by resampling to a voxel size of 3x3x3mm to the standard MNI space (Montreal Neurological Institute). An 8mm Gaussian filter was applied to smooth the normalized images and high-pass filtered at 128Hz.

Fixed-effects statistics for each individual were calculated by convolving box-car functions modelling the five conditions (Rejection words; Inclusion words; Neutral words; Incongruent colour words; Neutral letter strings) with a canonical hemodynamic response function (HRF). To reduce movement-related artefacts, we additionally included the six motion parameters as regressors and an additional regressor to model images that were corrupted due to head motion > 1.5mm and were replaced by interpolations of adjacent images (<10% of participant's data for N=9 Non-maltreated and N=8 Maltreated; no difference between groups p= .18). 2nd level group analyses were conducted using a repeated measures mixed-effects ANOVA by entering the individual SPMs containing the parameter estimates of the five conditions as fixed effects and an additional "subject factor" for random effects.

Amygdala ROI-analyses were small volume corrected (SVC) for multiple comparisons at p< .05 using two 8mm radius spheres for left and right amygdala, with co-ordinates based on the protocol by Sebastian et al., 2010. Contrast estimates from the peak voxels of clusters where significant group differences emerged were extracted using the MarsBaR Toolbox (Brett, Anton, Valabregue & Poline, 2002) implemented in SPM8 and subsequently correlated with PTSD, dissociation and depression subscales of the TSCC (Briere, 1996) in SPSS version 21 (IBM Corp. 2012). For completeness, correlational analyses were also performed with the peak contrast estimates and indices of maltreatment (onset, severity and duration of maltreatment). Whole brain analyses were corrected at cluster level *p*= .05, family-wise error (FWE) determined via Monte-Carlo simulations with the AFNI programme 3DClustSim (http://afni.nimh.nih.gov/afni) (voxel-wise *p*< .005, *ke*=75).

Results

Behavioural Results

There were no main effects of group or group x condition (valence or interference) interactions on the ES or CS task, indicating comparable performance across groups (all *Ps*> .511). However, as expected, a significant Stroop interference effect was observed for both groups on the CS task (see online Appendix S1). Online Appendix S1 and Table S1 provide details on behavioural performance across conditions.

fMRI Results

Emotional Stroop (ES): Valence main effects in the Non-maltreated group

Valence main effects were analysed in the Non-Maltreated group in order to ensure our task conditions elicited activation patterns that were comparable to previous studies. As expected, a main effect of valence in the Non-maltreated group emerged, with greater BOLD response to Rejection words vs. Neutral words in a fronto-limbic network, consistent with the pattern seen in typically developing adolescents (Sebastian et al., 2010; see Table S2 in the online Appendix).

Emotional Stroop (ES): Valence X Group Interaction

A significant valence x group interaction (whole brain level: Rejection vs. Neutral word conditions), indicated that the Maltreated group, relative to their peers, showed reduced activation when processing Rejection-themed words in the left inferior parietal cortex (IPC) including the STS, bilateral visual association cortex including cuneus as well as the anterior insula extending into the inferior frontal (IFG) and orbitofrontal gyrus (OFC). The Maltreated group also showed significantly lower neural response in the left amygdala (ROI, *p*= .04, *SVC-corrected*) to Rejection vs. Neutral words. The reverse contrast (Maltreated>Non-maltreated) for Rejection vs. Neutral words, or the comparison of Rejection vs. Inclusion or Inclusion vs. Neutral yielded no significant group x valence interactions (see Table 2).

PLEASE INSERT TABLE 2 HERE

Classic colour Stroop (CS)

No significant between-group differences for congruency (whole brain level: Incongruent colour words vs. Neutral letter string) were found at the whole brain level. Main effects for the CS conditions are presented in Table S3 in the online Appendix S1.

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Isolating the effect of valence by controlling for interference

We wished to isolate the neural activation specific to valence, over and above that elicited by incongruency, by contrasting the Rejection condition (ES) with the Incongruent colour word condition (CS). Main effects are presented in Table S3 in the online Appendix S1. A significant valence X group interaction emerged in a large cluster of the left anterior insula; here the Maltreatment group showed significantly reduced BOLD response to Rejection words relative to Incongruent colour words (see Table 2).

PLEASE INSERT FIGURE 1 HERE

Correlational analyses

In relation to PTSD symptoms, significant negative associations were found with bilateral cuneus activation (left: r_s= -.58, p=.004; right: r_s= .52, p= .017), as well as STS activation (r_s= -.52, p= .015); see Figure 2. Additionally, significant negative associations were found between symptoms of dissociation and bilateral cuneus activation (left: r_s=-0.48, p=0.028; right: r_s=-0.457, p= .037). No significant associations were found in relation to depressive symptoms (*Ps*> .105). In the Non-maltreated group, no significant associations between brain activity and symptoms were found (all *Ps*> .129). No significant associations were found between the neural activation in maltreatment-related regions and maltreatment indices (all *Ps*> .21).

PLEASE INSERT FIGURE 2 HERE

Discussion

In the present study we investigated neural responses to rejection-themed words in a group of children with documented experiences of maltreatment. Compared to non-maltreated children, reduced neural response to social rejection-themed words was observed across a number of brain regions including the left anterior insula, the ventrolateral prefrontal cortex (vlPFC), the amygdala, and the STS. These regions are associated with emotion processing, successful inhibition of emotional responses and socio-affective processing more broadly (Etkin & Wager, 2007; Masten et al., 2009), and have been implicated in previous studies of emotional Stroop interference (Chechko et al., 2013; Sebastian et al., 2010). Our findings suggest that maltreated children are atypical in how they process cues signalling social rejection. In view of the comparable performance across the groups on the classic Stroop task we were able to eliminate the possibility that differences in general cognitive control processes explained our findings. Additionally, reduced neural responses to rejection-themed words in the STS and visual association cortex were found to be associated with PTSD symptomatology in the Maltreated group.

These findings indicate that compared to their peers, children who had experienced maltreatment show reduced neural engagement during the incidental processing of stimuli signalling social rejection despite similar behavioural performance. Specifically, whole-brain analyses revealed less activity when processing Rejection versus Neutral words during ES, in regions previously shown to be positively related to adults' and adolescents' distress during exclusion (e.g. vlPFC and anterior insula; Masten et al., 2009; Masten et al., 2011; Eisenberger, Lieberman, & Williams, 2003), while our ROI analysis indicated reduced engagement of the amygdala. Hypo-activations during ES tasks have been observed in patients with affective- and trauma-related disorders. For example, reduced involvement of the vlPFC, parietal and visual cortices have been reported in both patients with major depressive disorder (MDD; Chechko et al., 2013) and in those with PTSD (Bremner et al., 2004). In addition, altered responses in visual association areas such as the cuneus and lingual gyrus have been observed in patients with PTSD and dissociative symptoms during ES tasks (Bremner et al., 2004) (Shin et al., 1997) and script-driven imagery symptom provocation paradigms (Hendler et al., 2003). It has been suggested that alterations in the higher-order visual association cortices may reflect altered integration of multimodal information and underlie visual and somatosensory symptoms, i.e. relieving the traumatic experience (hyperarousal) or numbing (Lanius, Bluhm, Lanius, & Pain 2006).

In order to isolate neural response specific to valence, we contrasted the Rejection condition (ES) with the Incongruent colour word condition (CS) which also introduced interference, but without the affective element. This revealed reduced response in the left anterior insula in the Maltreated relative to the Non-maltreated group. The insula has been implicated in the processing of aversive emotions such as fear (Etkin & Wager, 2007) and is thought to support the interaction between perceived threat signals and bodily states of arousal, including anticipation of pain (Wiech et al., 2010). Like the amygdala, the anterior insula has been reported to show heightened response to facial cues of threat in maltreated individuals (McCrory et al., 2011; Thomaes et al., 2012).

Our finding of attenuated neural response during incidental processing of rejection-related cues may be interpreted in a number of ways. First, and perhaps most persuasively, it may reflect a pattern of functional avoidance relating to shallower depth of processing in maltreated children during incidental and conscious processing of threat related stimuli. It is notable that when maltreated children experience rejection (during the ‘Cyberball’ social rejection paradigm) they are less able to engage neural regions involved in regulation compared to their non-maltreated peers (Puetz et al., 2014). There are a number of findings from the broader literature, which support the possibility that the pattern of hypo-activation in the current study reflects an avoidant coping style. First, we observed a negative association between PTSD symptomatology and dissociation symptoms and neural response to rejection related words. This suggests that those children who most engage in dissociation strategies show the greatest levels of hypoactivation. Second, similar patterns of hypoactivation during ES tasks are seen in patients with PTSD, who by definition are characterized by avoidance (DSM-5, American Psychiatric Association [APA], 2013). Third, studies of social rejection in other populations have linked deactivation of the anterior insula in particular with maladaptive or avoidant strategies of social engagement, both in adolescents with autism and in adults with an avoidant attachment style (De Wall et al., 2012; Masten et al., 2011). Finally, two previous studies investigating attentional allocation to threat in maltreated children using a dot-probe paradigm have reported a pattern of attentional bias away from threat when the stimulus can be consciously perceived; this has recently been shown to characterise both males and females equally (Pine et al., 2005; Kelly et al., 2015). However, further experimental studies using e.g. eye tracking during the emotional Stroop task are needed to provide direct evidence for the avoidant coping style and shallower processing suggested here. In the context of the theory of latent vulnerability, an attenuated neural response to negative social stimuli may reflect an adaptive mechanism of functional avoidance, that is a neural calibration to an adverse home and social environment that is maladaptive in the longer term.

A second interpretation might contend that reduced neural response to rejection related cues reflects a developmental delay in cortical maturation associated with the maltreatment experience. For example, studies comparing different age groups on the classic and emotional Stroop tasks have reported greater Stroop-related activation in the lateral prefrontal cortex and parieto-occipital cortices with increasing age (Adleman et al., 2002). Considering the cross-sectional design of our study, it is not possible to definitively rule out this possibility. In light of normative behavioural and neural performance on the classic Stroop task in the current study, we consider such a possibility less likely, but longitudinal studies utilising paradigms of social rejection, as well as paradigms that have been designed to specifically interrogate the avoidance strategy hypothesis (e.g. using eye tracking) would arbitrate between these interpretations.

A number of limitations should be noted. First, due to the cross-sectional design, it was not possible to examine the developmental trajectories of altered processing of rejection in this sample. Future studies employing longitudinal designs could examine if altered neural processing of rejection-related material predicts future psychopathology in individuals with histories of childhood maltreatment, consistent with the suggestion that this may represent a marker of latent vulnerability. Second, because of our sample size, we were unable to examine the influence of gender, which we know is associated with differential outcomes for boys and girls exposed to early adversity in general (Bos, Zeanah, Fox, Drury, McLaughlin & Nelson, 2011) and maltreatment in particular (Lansford, Dodge, Pettit, Bates, Crozier & Kaplow, 2002). Thirdly, while we measured symptoms in relation to trauma, anxiety and depression, it is important to note that this did constitute a general diagnostic measure of psychiatric disorder. Finally, it cannot be fully ruled out that differences in reading strategies influenced our result and future studies should consider using eye tracking in fMRI as a complementary measure.

The present study demonstrates altered neural response during incidental processing of rejection-related words in children exposed to maltreatment. In light of the evidence from patients with PTSD and depression, it is conceivable that this neural pattern represents one candidate mechanism indexing latent vulnerability to psychopathology. Longitudinal investigations, however, are needed to establish if such neural calibrations truly index latent vulnerability to subsequent peer problems and mental ill-health, and whether the neurocognitive mechanism underlying rejection sensitivity is amenable to therapeutic manipulation.

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Key points:

- Childhood maltreatment is associated with heightened perceptual salience of threat-related facial stimuli, which may represent one candidate mechanism indexing latent vulnerability to future psychiatric disorder. It is unclear, however, if such sensitivity extends to broader cues signalling social threat.
- Using an emotional Stroop task, we found that maltreated children showed reduced activation to rejection-themed words across circuitry previously implicated in emotion processing and abuse-related PTSD.
- One possibility is that this pattern of neural hypo-activation represents a neural calibration to an adverse home environment consistent with avoidant processing.
- While such a response may be adaptive in the short term, an avoidant response style may be maladaptive in the longer term, increasing the risk for psychiatric disorders following exposure to future stressors.

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Table 1: Demographic and background information for Maltreated and Non-maltreated groups

		Maltreated Group (n=21)	Non-Maltreated Group (n=19)	
Measure		*Mean (SD)*	*Mean (SD)*	*p*
Age (years)		12.47 (1.66)	12.91 (1.32)	0.37
WASI-IQ[1]		105.24 (15.80)	106.21 (12.36)	0.83
Reading score (WRAT[2])		112.95 (20.07)	116.45 (15.02)	0.54
Verbal Fluency		35 (11.54)	36.78 (5.93)	0.54
Pubertal Development (PDS)[3]		2.06 (0.81)	1.84 (0.47)	0.36
		n (%)	*n (%)*	*p*
Gender (% female)		11 (52)	11 (58)	0.73
Ethnicity (% Caucasian)		15 (71)	12 (63)	0.58
SES[4]		2.74 (1.88)	3 (1.28)	0.15
		Mean (SD)	*Mean (SD)*	*p*
CTQ[5] (Total)		36.74 (15.90)	28.29 (4.99)	0.02
TSSC[6]	Anxiety	44.91 (8.12)	42.11 (7.64)	0.27
	Depression	45.10 (6.59)	40.58 (6.50)	0.04
	Anger	45.14 (11.32)	39.63 (5.95)	0.07
	PTSD[7]	43.38 (5.55)	40.79 (6.03)	0.17
	Dissociation	47.24 (9.99)	41.67 (5.39)	0.04

[1]WASI-IQ, 2-subscale IQ derived from the Wechsler Abbreviated Scales of Intelligence (Wechsler, 1999). [2]WRAT, Wide Range Achievement Test (WRAT 4, Jastak & Wilkinson, 1984). [3]Composite score of self-report and parent rating of Puberty Development Scale (Petersen, Crockett, Richards, & Boxer, 1988). [4]SES (Socioeconomic status): Highest level education rated on 6-point scale from 0= no formal qualifications to 5= postgraduate qualification. [5]Childhood Trauma Questionnaire (Bernstein & Fink, 1998). [6]Trauma Symptom Checklist for Children (Briere, 1996). [7]PTSD: Post Traumatic Stress Disorder.

Table 2: Results of whole-brain and region of interest analyses showing group interactions for the Emotional and Classic Stroop conditions

Brain region	R/L	x	y	z	ke	Z
Rejection words-Neutral words						
Non-Maltreated>Maltreated group						
Inferior parietal Cortex (STS)	L	-54	-22	-5	98	4.23
	L	-57	-7	-5		3.25
	L	-42	-34	-2		2.85
Visual Association Cortex	L	-18	-85	13	294	3.69
Cuneus	L	-15	-76	7		3.55
	L	-6	-76	16		3.31
Visual Association Cortex	R	24	-76	13	105	3.56
Cuneus	R	18	-64	10		3.52
	R	15	-73	13		3.28
Anterior Insula	L	-33	-1	-5	113	3.28
Orbitofrontal cortex	L	-33	47	-8		3.23
Thalamus (Pulvinar)	L	-15	5	-5		3.11
Amygdala*	L	-24	-4	-8	17	2.94
Maltreated group>Non-Maltreated		--	--	--	--	

Brain region	R/L	x	y	z	ke	Z
Rejection-Incongruent colour words						
Non-Maltreated>Maltreated group						
Anterior Insula	L	-39	14	-8	198	3.82
	L	-33	23	-5		3.49
	L	-39	2	-8		3.43
Maltreated group>Non-Maltreated		--	--	--	--	

Note. Abbreviations: R/L, Right / Left; ke, cluster extent; * Small Volume Corrected (*p*=.04)

Figure 1.

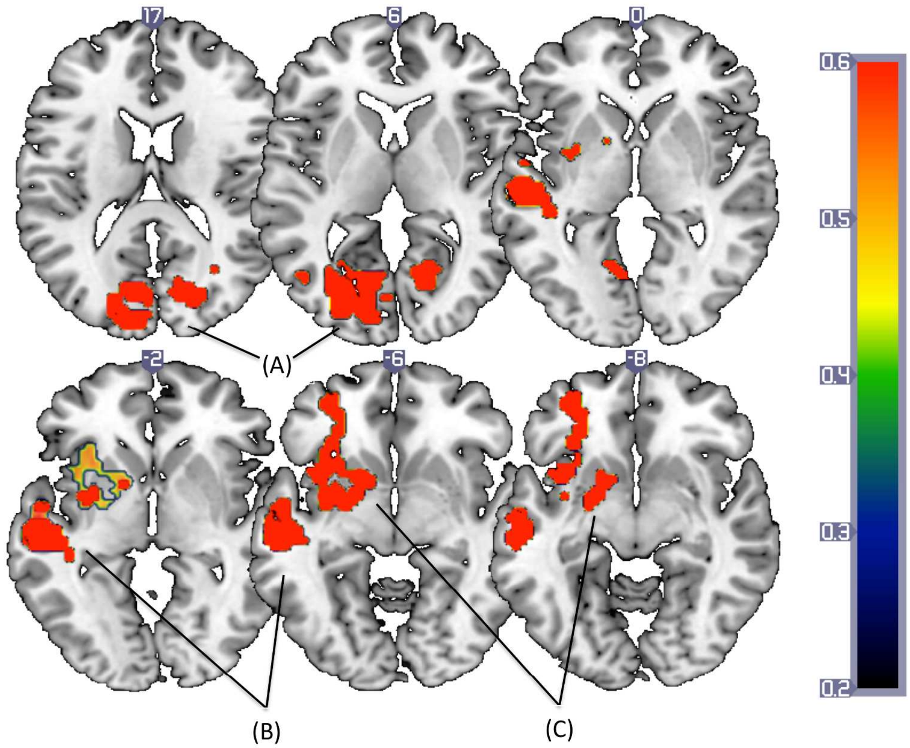

Figure 1. Areas showing attenuated BOLD response in the Maltreated group relative to the Non-Maltreated group in response to the Rejection vs. Neutral words in (A) bilateral visual association cortex (B) left inferior parietal cortex (C) left anterior insula extending into inferior frontal gyrus. Results corrected at *p*= .005, *ke*=74. Slice numbers reference the MNI coordinate system.

Figure 2.

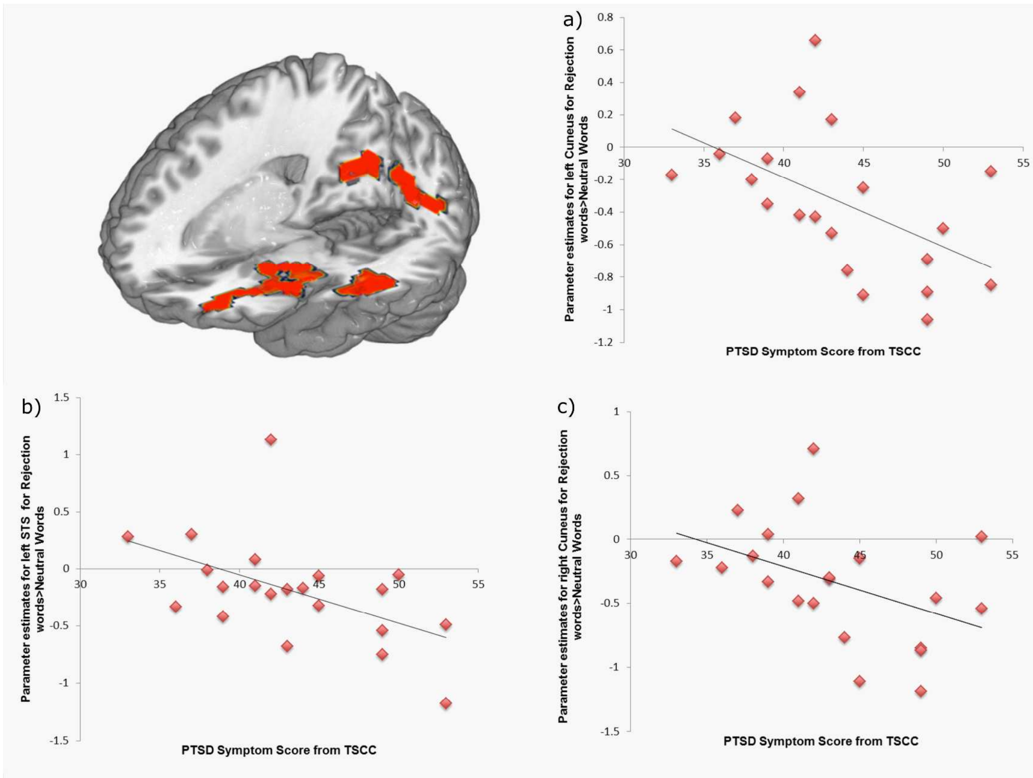

Figure 2. Correlations in the Maltreatment group between PTSD symptoms (TSCC; Briere, 1999) and parameter estimates for the contrast Rejection words>Neutral words (ES) for left and right cuneus and STS.

Online Appendix

Measures

Psychiatric symptomatology

Trauma Symptoms Checklist for Children (TSCC; Briere, 1996)

The Trauma Symptoms Checklist for Children (TSCC; Briere, 1996) was used to assess acute and chronic posttraumatic symptomatology and other symptom clusters. The TSCC is a 44-item self-report measure consisting of five clinical scales (Anger, Depression, Anxiety, Posttraumatic stress and Dissociation). Each item is rated on a four-point scale from *'never'* to *'almost all the time'*. Cronbach α for the scales ranges from 0.84 to 0.88. TSCC T-scores at or above 65 are considered clinically significant.

Strength and Difficulties Checklist (SDQ; Goodman, 1997)

The parent-report version of the SDQ (Goodman, 1997) was used to index current social and emotional functioning as well as levels of hyperactivity symptoms and conduct problems. Please see below for total score and subscale scores for both groups.

	Maltreated Group (n=21)	Non-Maltreated Group (n=19)	
	Mean (SD)	*Mean (SD)*	*p*
Strengths & Difficulties Questionnaire (SDQ)			
Total Difficulties	11.95 (7.34)	5.44 (2.94)	0.00
Emotional Symptoms	3.05 (2.66)	1.39 (1.38)	0.02
Conduct Problems	2.05 (1.83)	0.61 (0.92)	0.01
Hyperactivity Score	4.67 (2.58)	2.5 (1.51)	0.00
Peer Problems	2.19 (2.14)	0.94 (1.26)	0.04
Prosocial	8.14 (2.06)	8.83 (1.58)	0.25

Maltreatment ratings (Self-report)

<u>Childhood Trauma Questionnaire (CTQ, Bernstein & Fink, 1998)</u>

All children were administered the Childhood Trauma Questionnaire (CTQ, Bernstein & Fink, 1998), a child self-report measure assessing emotional and physical neglect, as well as emotional, physical and sexual abuse, yielding separate scores for each domain as well as a composite overall score; see below.

		Maltreated Group (n=21)	**Non-Maltreated Group (n=19)**	
		Mean (SD)	*Mean (SD)*	*p*
Type of maltreatment (CTQ score)				
	Emotional abuse	7.24 (4.22)	5.84 (1.68)	0.19
	Physical abuse	6.14 (4.04)	5.58 (1.50)	0.57
	Sexual abuse	5.00 (0.00)	5.00 (0.00)	/
	Emotional neglect	9.62 (4.91)	6.21 (2.21)	0.01
	Physical neglect	8.05 (3.67)	5.58 (1.35)	0.01

Maltreatment ratings (Social Service & Adoptive Parent report)

		Maltreated Group (n=21)	**Non-Maltreated Group (n=19)**
Measure		*% or Mean (SD)*	
Physical abuse	*n*	2 (10%)	/
	Severity	1.00 (0.00)	
	Onset (years)	1.54 (2.81)	
	Duration (years)	4.00 (1.41)	
Neglect	*n*	18 (81%)	/
	Severity	3.22 (0.94)	
	Onset (years)	1.45 (3.34)	
	Duration (years)	5.95 (4.92)	
Sexual abuse	*n*	4 (20%)	/
	Severity	1.50 (1.00)	
	Onset (years)	0.93 (1.42)	
	Duration (years)	0.25 (0.29)	

Emotional abuse	*n*	20 (95%)	/
	Severity	3.10 (0.64)	
	Onset (years)	2.01 (3.76)	
	Duration (years)	6.06 (4.63)	
Domestic Violence	*n*	12 (57%)	/
	Severity	2.17 (1.19)	
	Onset (years)	3.19 (3.85)	
	Duration (years)	3.47 (3.32)	

Note. Severity of each abuse type (neglect, emotional abuse, sexual abuse, physical abuse, intimate partner violence) was rated on a scale from zero (not present) to four (severe) by the child's social worker or adoptive parent based on SS records.

Stimuli

Stimuli across the ES conditions were matched on frequency (all $p > .50$; Kucera-Francis, 1967), length (all $p > .13$), number of syllables (all $p > .65$) and part of speech ($p > .55$). For all conditions (Rejection, Inclusion, Neutral) normed valence and arousal ratings were taken from the Affective Norms for English Words (Bradley & Lang, 1999). For valence, mean ratings for the rejection, inclusion and neutral words were 1.81, 6.49 and 4.53 respectively (difference between all three conditions: $Ps < .006$). For arousal, mean ratings for the rejection, inclusion and neutral words were 5.60, 4.03 and 3.42 respectively, with both the rejection and inclusion words significantly higher than neutral ($p < .05$) but not differing significantly from each other ($p > .20$).

Classic Stroop Conditions

Two additional, classic colour Stroop conditions (CS) were implemented in the same paradigm to formally assess cognitive control following the procedure by Bremner et al. (2004), Thomaes et al. (2012) and Kikuchi et al. (2010). These consisted of colour words written in incongruent colours (e.g. yellow written in green; Incongruent colour word condition) and coloured XXs

(Neutral letter string condition). Blocks of these two stimulus categories were presented in a permuted design and presented 6 times over two runs of 7 minutes interspersed pseudo-randomly with the three emotional Stroop conditions. Stimuli were projected onto a screen attached to the front of the scanner in font 8pt on a dark grey background, viewed via a mirror mounted on the head coil and presented using EPrime (Version 2; Schneider, Eschman, & Zuccolotto, 2002).

Behavioral Performance

Behavioral data (RT, error and missed trials) for the ES were analysed using a 3 x 2 repeated measures ANOVA with valence (Rejection, Inclusion, Neutral words) as the within-subject factor and group (Maltreated vs. Non-maltreated) as the between-subjects factor. Similarly, a 2 x 2 repeated measures ANOVA was conducted for the CS task, with congruency entered as the within-subject factor (Incongruent colour words, Neutral letter strings) and group (Maltreated vs. Non-maltreated) as the between-subjects factor. On the ES task there were no main effects for valence, group or group x valence interactions for RTs, or missed trials (all *Ps*> .83) (see Table S1 in online Appendix for behavioral data by group). Analyses of error rates revealed a significant main effect for valence [$F(2, 72)=6.90$, $p= .002$, $\eta p^2= .31$; mean error Reject=18.55 ± 1.67; mean error Inclusion=20.66 ± 1.81; mean error Neutral= 22.79 ± 1.84]. On the CS task, the expected significant main effect of congruency was observed for RT [$F(1, 36)=52.81$, $p<.001$, $\eta p^2= .60$; mean RT Neutral letter string=763.78 ± 14.50; mean RT Incongruent words=860.39 ± 14.57], error [$F(1, 36)=30.13$, $p< .001$, $\eta p^2=.46$; mean error Neutral letter string=19.50 ±

1.92; mean error Incongruent words=28.32 ± 2.32] and missed trials [$F(1,36)=21.59$, $p<.001$, $\eta p^2= .38$; mean missed trial Neutral letter string=5.36 ± 1.04; mean missed trial Incongruent words=10.22 ± 1.28], with poorer performance on these indices in the Incongruent condition. There were no main effects of group or group x interference interactions indicating comparable performance across groups (all *Ps*>.511).

Table S1. Behavioral data for the Maltreatment and Non-Maltreatment group for the emotional Stroop conditions and classic colour Stroop conditions.

	Maltreated Group (n=20)	**Non-Maltreated Group (n=18)**
RT (millisecond)	*Mean (SD)*	*Mean (SD)*
Emotional colour Stroop	*791 (69)*	*800 (101)*
Rejection words	793 (72)	804 (105)
Inclusion words	791 (57)	801 (97)
Neutral words	789 (78)	796 (102)
Classic Stroop	811 (84.5)	813 (96)
Incongruent colour words	857 (81)	863 (101)
Neutral letter string	765 (88)	763 (91)
Error (%)	*Mean (SD)*	*Mean (SD)*
Emotional Stroop	20.4 (11.3)	21.0 (10.4)
Rejection words	18.1 (10.6)	19.0 (9.9)
Inclusion words	20.5 (11.9)	20.8 (10.2)
Neutral words	22.4 (11.5)	23.1 (11.1)
Classic colour Stroop	24.8 (15.9)	23.0 (9.0)
Incongruent colour words	29.1 (17.4)	27.5 (9.7)
Neutral letter string	20.5 (14.3)	18.5 (8.4)
Missed Trials (%)	*Mean (SD)*	*Mean (SD)*
Emotional Stroop	5.8 (5.8)	5.2 (5.6)
Rejection words	5.2 (5.1)	5.7 (5.3)
Inclusion words	6.2 (5.8)	4.8 (5.2)
Neutral words	6.1 (6.3)	5.2 (6.4)
Classic colour Stroop	9.1 (9.0)	6.5 (4.1)
Incongruent colour words	6.3 (8.1)	4.4 (3.5)
Neutral letter string	11.9 (9.9)	8.6 (4.6)

Note: n=1 Maltreatment group and n=1 Non-Maltreatment group are not included in the behavioral analyses due to missing data.

fMRI results: Non-Maltreated group

We first analysed the neural activation patterns in the non-maltreated group in order to ensure our task conditions elicited activation patterns that were comparable to previous studies. These analyses indicated that the Emotional Stroop and the Classical Stroop engaged the fronto-limbic network and a left fronto-parietal network respectively, in line with previous studies of adult and pediatric samples using similar tasks (e.g. Sebastian et al., 2010; Chechko et al., 2013, see online appendix 2 (Table S2) for complete results and coordinates). Compared to Neutral stimuli, Negative-Rejection stimuli elicited greater activity in left superior temporal sulcus (STS), the left vlPFC, specifically the inferior frontal gyrus (IFG) extending into the orbitofrontal gyrus as well as the anterior insula extending into the thalamus. Analyses of activation in predicted regions revealed greater activation in the left amygdala at trend level (*ke*=15, *Z*=2.77, *p*=.06 *SVC-corrected*). This set of brain regions replicates a well-established fronto-limbic network known from the adult and pediatric literature (Sebastian et al., 2010; Chechko et al., 2013), suggesting some comparability of results.

Analyses of neural responses during the classic Stroop yielded greater activation in the Stroop-interference condition as compared to control in a set of left-lateralized fronto-parietal regions implicated in working memory and classic Stroop-tasks (Adult sample: Zysset et al., 2001; Pediatric sample: Adleman et al., 2002), i.e. left dorsolateral prefrontal cortex (dlPFC) extending into IFG, left precuneus and intra-parietal sulcus (IPS) as well as left ventrolateral prefrontal cortex (vlPFC; see Table S2).

fMRI results: Between group differences Incongruent colour words-Neutral letter string (CS)

No between group differences were found for the contrast *Incongruent colour words-Neutral letter string (CS) either for Non-Maltreated >Maltreated group or vice versa.* Main effects for this contrast are presented in Table S3.

Table S2. Within-subjects results across groups

Brain region	R/L	x	y	z	ke	t	Z	SVC-corrected
Contrast: Rejection-Neutral								
Non-maltreated group								
Superior Temporal Sulcus (STS)	L	-57	-22	-2	119	4.21	4.11	
	L	-42	-34	-2		3.51	3.45	
Inferior frontal gyrus	L	-33	47	-8	141	3.85	3.77	
Orbitofrontal cortex	L	-48	29	-5		3.03	3	
	L	-42	38	-11		2.79	2.76	
Anterior Insula extenting into Thalamus	L	-27	11	-5	94	3.60	3.54	
	L	-24	-7	-5		3.37	3.32	
	L	-27	2	-5		3.29	3.24	
Amygdala*	L	-24	-4	-8	15	2.80	2.77	0.06
Maltreated group								
	--	--	--	--	--	--	--	

Brain region	R/L	x	y	z	ke	t	Z	SVC-corrected
Contrast: Rejection-Acceptance								
Non-maltreated group	--	--	--	--	--	--	--	
Maltreated group	--	--	--	--	--	--	--	
Contrast: Acceptance-Neutral								
Non-maltreated group	--	--	--	--	--	--	--	
Maltreated group	--	--	--	--	--	--	--	

Brain region	R/L	x	y	z	ke	t	Z	SVC-corrected
Contrast: Incongruent colour words-Neutral letter string (CS)								
Non-maltreated group								
Dorsolateral prefrontal cortex (dlPFC)	L	-51	14	31	491	5.52	5.31	
Inferior frontal gyrus (IFG)	L	-42	20	28		5.42	5.22	
	L	-51	26	19		3.60	3.53	
Intraparietal Sulcus (IPS)	L	-24	-64	43	544	4.77	4.63	
Praecuneus	L	-36	-58	46		4.56	4.44	
	L	-27	-43	43		3.76	3.69	
Ventrolateral Prefrontal cortex (vlPFC)	L	-51	44	-5	82	3.68	3.61	
	L	-33	62	7		3.50	3.44	
	L	-42	53	-2		3.40	3.35	
Praecuneus	L	-3	-61	43	109	3.63	3.56	

	L	-3	-73	49		3.54	3.48
Maltreated group							
Inferior parietal cortex	L	-39	-46	31	2634	7.4	6.93
	L	-33	-52	40		7.35	6.89
	L	-45	-46	40		6.89	6.5
Inferior frontal gyrus (IFG)	L	-39	8	34	1831	6.43	6.11
	L	-42	17	25		6.41	6.09
	L	-48	26	19		5.97	5.71
Inferior frontal gyrus (IFG)	R	48	14	37	413	4.76	4.62
	R	51	29	31		4.14	4.05
	R	42	2	40		3.76	3.68
Ventrolateral Prefrontal cortex (vlPFC)	R	45	50	-2	178	4.57	4.44
	R	39	59	1		4.21	4.11
	R	48	44	-8		4.06	3.97
Middle temporal gyrus (MTG)	L	-54	-46	-5	181	4.23	4.13
	L	-48	-52	-14		4.05	3.96
	L	-42	-76	-8		4	3.91

Note. Abbreviations: R/L, Right / Left; ke, cluster extent; SVC-corrected, Small Volume corrected; CS, Classic colour Stroop.
*Region of Interest Analyses

Table S3. Main Effects of congruency (CS) and Valence (ES)

Brain region	R/L	x	y	z	*ke*	*Z*
Contrast: Incongruent colour words-Neutral letter string (Main effect CS)						
Dorsolateral Prefrontal Cortex (dlPFC)	L	-42	17	28	2589	7.28
	L	-48	26	19		6.14
Ventrolateral Prefrontal Cortex (vlPFC)	L	-51	44	-5		5.82
Precuneus	L	-24	-61	43	2506	7.23
	L	-33	-55	43		6.95
	L	-27	-70	37		6.85
Dorsolateral Prefrontal Cortex (dlPFC)	R	42	56	-2	275	4.54
	R	36	59	10		3.97
Ventrolateral Prefrontal Cortex (vlPFC)	R	33	41	1		3.34
Occipito-Temporal Sulcus	L	-48	-55	-14	202	4.21
	L	-54	-49	-8		4.12
	L	-42	-76	-8		3.99
Contrast: Rejection words-Incongruent colour words (Main effect ES-CS)						
Temporal Pole /Anterior Insula	L	-45	11	-17	2157	5.73
	L	-57	-7	-14		5.63
Posterior Insula	L	-39	-19	10		4.99
Parahippocampal Gyrus	R	21	-34	-17	1447	5.15
Hippocampus / Amygdala	R	24	-16	-17		5.07
Posterior Insula	R	45	-16	10		5.06
Ventromedial Prefrontal cortex (vmPFC)	L	-6	47	-8	455	5.04
Subgenual Anterior Cingulate (sgACC)	L	-3	20	-8		4.5
	R	6	47	-8		4.4
Visual Association Cortex	R	9	-94	-2	76	3.45
	R	21	-73	-5		3.15
	R	12	-85	-2		3.08

Note. Abbreviations: R/L, Right / Left; ke, cluster extent.