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Neural correlates of cognitive and affective processing in maltreated youth with posttraumatic stress symptoms: Does gender matter?

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Abstract

We investigated the relationship of gender to cognitive and affective processing in maltreated youth with posttraumatic stress disorder (PTSD) symptoms using functional magnetic resonance imaging. Maltreated (N=29; n=13 females, n=16 males) and non-maltreated participants (N=45; n=26 females, n=19 males) performed an emotional oddball task that involved detection of targets with fear or scrambled face distractors. Results were moderated by gender. During the executive component of this task, left precuneus/posterior middle cingulate hypoactivation to fear versus calm or scrambled face targets were seen in maltreated versus control males and may represent dysfunction and less resilience in attentional networks. Maltreated males also showed decreased activation in the inferior frontal gyrus compared to control males. No differences were found in females. Posterior cingulate activations positively correlated with PTSD symptoms. While viewing fear faces, maltreated females exhibited decreased activity in dorsomedial prefrontal cortex and cerebellum I–VI; whereas maltreated males exhibited increased activity in left hippocampus, fusiform cortex, right cerebellar crus I, and visual cortex compared to their same gender controls. Gender by maltreatment effects were not attributable to demographic, clinical, or maltreatment parameters. Maltreated girls and boys exhibited distinct patterns of neural activations during executive and affective processing, a new finding in the maltreatment literature.

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Introduction

Child maltreatment is associated with posttraumatic stress disorder (PTSD)(De Bellis, 2001), impairing subthreshold PTSD (Carrion et al., 2002a), and other mental illness later in life (Anda et al., 2006). While there are suggestions that maltreated males may be less resilient to emotional dysregulation and antisocial outcomes compared with maltreated females (Bergen et al., 2004; De Bellis & Keshavan, 2003; Garnefski & Diekstra, 1997; McGloin & Widom, 2001), studies of gender x maltreatment interactions where sufficient numbers of males and females are present are lacking (Maas et al., 2008). Sexual dimorphism is present in the developing human brain (De Bellis et al., 2001b; Lenroot et al., 2007; Neufang et al., 2009;19:464–473) and has been demonstrated in anatomical MRI studies as early as infancy (Gilmore et al., 2007). Furthermore, the presence of testosterone early in fetal life not only determines physical gender but is involved in sexual dimorphism of brain structures and neural connections involved in reproductive and non-gender related networks (e.g., mood, cognition)(McEwen, 2006). Prospective studies show that maltreated boys have poorer outcomes in adolescence (De Bellis & Keshavan, 2003) and adulthood (McGloin & Widom, 2001). McGloin and Widom (2001) prospectively studied resilience defined across a variety of domains (psychiatric, emotional, and behavioral) in a large group of adults with histories of substantiated cases of child abuse and neglect prior to age 11 years and a control group closely matched for age, sex, race, and social class background. In this study, resilience was comprehensively operationalized across eight domains (i.e., employment, homelessness, education, social function, presence of psychiatric disorders and substance abuse, and two measures of antisocial behaviors) and included multiple assessment waves of their data. They found that overall, adults maltreated as youth were less resilient than non-maltreated youth; however, cases of maltreated males were lowest and non-maltreated females highest on their constructed measure of resilience (McGloin & Widom, 2001) suggesting increased vulnerability in maltreated males. In a relatively large cross-sectional anatomical MRI study (De Bellis & Keshavan, 2003), maltreated boys with PTSD showed more evidence of adverse brain development (smaller cerebral volumes and larger lateral ventricular volumes) than maltreated girls with PTSD, suggesting sex differences in brain maturation in traumatized youth even though both boys and girls showed similar psychopathology and trauma histories. A follow-up of a subsample from the original study (De Bellis et al., 1999b) demonstrated that 32% of the maltreated males with PTSD and 5% of the maltreated females with PTSD studied, but none of the controls, developed serious antisocial behaviors within 3 years of initial brain scan, suggesting less resilience in maltreated males (De Bellis & Keshavan, 2003). However, investigations of gender differences on maltreated girls' and boys' developing neural networks are understudied.

The phenotype of PTSD resembles both depression and generalized anxiety disorder, for which two neural networks play key roles (Phillips et al., 2003): an executive network that supports effortful regulation of behavior, attention and emotion (Duncan & Owen, 2000; Yamasaki et al., 2002); and an affective network that processes emotional information and vigilance, including stress and fear responses (Phelps, 2004). The executive network comprises the lateral and dorsomedial prefrontal cortex (PFC), anterior cingulate cortex, and posterior parietal cortex. The affective network comprises ventral medial prefrontal cortex and subcortical regions (e.g., hippocampus and amygdala)(Phelps et al., 2004). Dysfunction in these networks and in their interactions with brain regions involved in social cognition (Gilboa et al., 2004; Mitchell, 2006) are hypothesized to contribute to distress disorders, particularly PTSD (Charney et al., 1993; Lang et al., 2000; LeDoux, 1998; Mayberg, 1997).

The pathophysiology of adult PTSD involves hypoactivation of the executive and hyperactivation of the affective emotional networks (Rauch et al., 2006). In adults, PTSD is associated with medial PFC hypoactivation in response to aversive stimuli (Bremner et al., 1999; Bremner et al., 2005; Bremner et al., 2004; Bremner et al., 2003; Britton et al., 2005; Lanius et al., 2001; Lanius et al., 2003; Lindauer et al., 2004; Shin et al., 1999; Shin et al., 2004a; Shin et al., 2001; Shin et al., 2005). The degree of medial PFC hypoactivation is associated with PTSD severity (Britton, et al., 2005; Hopper et al., 2007; Shin, et al., 2004a). PTSD is associated with amygdala hyperresponsivity to traumatic reminders, fear faces, and during acquisition of conditioned fear responses (Bremner, et al., 2005; Driessen et al., 2004; Francati et al., 2007; Hendler et al., 2003; Liberzon et al., 1999; Pissiota et al., 2002; Protopopescu et al., 2005; Rauch et al., 2000; Shin, et al., 2004a; Shin, et al., 2005).

Limited studies on maltreated youth also suggest dysregulation in executive, affective and social cognition networks (De Bellis & Hooper, 2012; De Bellis et al., 2002). Preliminary studies of neglected children and adolescents showed impaired function in dorsal executive regions (Mueller et al., 2010) and hyperactivation in the amygdala and left anterior hippocampus to fearful and angry faces (Maheu et al., 2010). Previously institutionalized international adoptees demonstrated hyperactivation in affective and social cognition networks (e.g., bilateral amygdala, medial temporal gyrus) to fearful faces but hypoactivation to response cues in executive areas during an emotion-face go/no-go task compared to controls (Tottenham et al., 2011). Youth with PTSD symptoms also exhibited decreased activation in the middle frontal gyrus and increased medial frontal activation in a similar task, suggesting response inhibition dysfunction in traumatized youth (Carrion et al., 2008). However, these neuroimaging studies in maltreated youth lacked sufficient sample size and statistical power to examine group by gender differences.

In this investigation, we used a variant of The Emotional Oddball Task to examine executive and affective processing in maltreated and non-maltreated youth. The sample size was adequate to examine group by gender differences. The Emotional Oddball Task was originally designed as an event-related task, which demonstrated in adults that the executive and affective neural networks are dissociable and can be examined separately in one task (Wang et al., 2008; Wang et al., 2006; Wang et al., 2005). The Emotional Oddball Task contained four types of stimuli: targets, sad faces or photographs, neutral faces or photographs, and phase-scrambled photographs (as standards). Subjects detected infrequent circles (targets) within a continual stream of phase-scrambled images (standards). Sad and neutral images were intermittently presented instead of phase-scrambled photographs as task-irrelevant distracters. Healthy adults activate executive networks to targets and affective neural networks (i.e., the amygdala and ventral prefrontal cortex) to sad images during this task (Wang, et al., 2006; Wang, et al., 2005). Healthy youth also activate executive networks to targets; and affective neural networks to sad images or sad distracters during this task (Wang et al., 2008). Adults with distress disorders show attenuated activation in executive networks (Wang, et al., 2008) and accentuated activity in affective neural networks (Drevets, 2000; Mayberg, 1997; Nitschke et al., 2009). In an exploratory study using the Emotional Oddball Task, we found that the maltreated youth revealed significantly decreased activation in the left middle frontal gyrus and right precentral gyrus to target stimuli and significantly increased activation to sad stimuli in bilateral amygdala, left subgenual cingulate, left inferior frontal gyrus, and right middle temporal cortex compared to non-maltreated participants, suggesting that maltreated youth with distress disorders demonstrated dysfunction of neural networks related to executive and affective processing (De Bellis & Hooper, 2012).

To investigate the impact of the interaction of maltreatment and gender in the executive and affective neural network in youth, we conducted a functional MRI study in maltreated youth with PTSD symptoms compared with non-maltreated controls. Participants performed an emotional oddball task that involved detection of targets presented alongside task-irrelevant fearful face distracters. We hypothesized that maltreated youth compared to controls would show increased activation in the affective emotional network during passive viewing of fearful faces and decreased executive network activation during target detection when presented with task-irrelevant fearful face distracters. Given that gender influences emotional regulation in adults (Koch et al., 2007; McRae et al., 2008; Schienle et al., 2005), a planned investigation examining the relationship of neural correlates in maltreated males and females compared to control males and females was undertaken. We hypothesized that maltreated males would demonstrate greater executive and affective dysregulation than maltreated females. Planned comparisons were undertaken to determine the relationship between functional activation in brain structures involved in affective emotional and executive networks, and PTSD symptoms.

Materials and Methods

Subjects

Thirty-seven maltreated and 57 healthy control youth, the latter with no history of DSM-IV Axis I disorders or Type A traumas, participated. Of these, 8 maltreated and 12 controls were eliminated due to non-correctable motion artifacts or gradient problems within the imaging apparatus, leaving 29 maltreated and 45 non-maltreated participants with usable data included in this study. We recruited more controls than maltreated subjects to increase statistical power, reduce inter-subject variance, and obtain a more normative comparison, given that individual developmental trajectories in adrenarchy and puberty differ during this period (Blakemore et al., 2010; Giedd et al., 2008). The maltreated groups were defined by a positive forensic investigation with child protective services (CPS) that indicated physical, sexual, emotional abuse and/or neglect as defined by State Criteria. Maltreated participants were recruited through Statewide advertisements and recruitment presentations targeted at

CPS agencies. To reduce bias, the study was advertised to CPS in the State of North Carolina on a statewide level and participants who lived more than 75 miles from the Research Program were given overnight accommodations. Controls were recruited from schools and other community settings and had a negative screen on both telephone interview for eligibility and research interview for any history of participant or participant sibling having CPS involvement.

Exclusion criteria were: IQ < 70; chronic medical illness; head injury; neurological disorder; schizophrenia; anorexia nervosa; pervasive developmental disorder; birth weight under 5 lbs.; severe prenatal compromise with NICU stay; alcohol/substance use disorder; and contraindications for safe MRI scan. The local university hospital IRB committee approved the study. Legal guardians gave informed consent and youth assented prior to participation.

Characteristics of the maltreated and control groups are shown in Table-1. The groups were similar in age, race, handedness, and sex. The maltreated group was of lower socioeconomic status (SES) than controls as measured by the Hollingshead Four factor index. Lower SES is an inherent confound and risk factor in child maltreatment (Gilman et al., 2003; Lansford et al., 2006), while higher SES or positive change in parental income reduces pediatric mental disorders (Costello et al., 2010). Despite attempts to control for SES between groups, lower SES children recruited as controls were more likely to meet exclusionary criteria. Two-factor IQ, measured by the Wechsler Intelligence Scale for Children-III and comprising Vocabulary and Block Design (Wechsler, 1991), was lower in maltreated youth versus controls. Lower IQ is a consequence of child maltreatment (De Bellis, et al., 1999b; Perez & Widom, 1994).

Measures

To examine psychiatric symptoms, the Kiddie Schedule for Affective Disorders and Schizophrenia- Present and Lifetime Version (KSADS-PL) (Kaufman et al., 1997) was administered to caregivers and youth. Because multiple sources of information are needed to gather accurate maltreatment history and related symptoms (Kaufman et al., 1994), we also used archival records (e.g., pediatric records, school attendance records, birth records, forensics records) as sources of mental health, birth history, trauma history, and pediatric health. The KSADS-PL was modified to collect data on additional types of adverse life events as previously described (De Bellis et al., 2009). Child maltreatment was defined as witnessing domestic violence (which was State defined as neglect by omission or commission and/or emotional abuse), physical abuse, sexual abuse and/or neglect. Maltreated youth experienced multiple maltreatment types that were chronic in nature. There were no significant differences in maltreatment experiences or number of maltreatment types experienced between maltreated males and females. There were no significant sex differences in PTSD symptoms or psychopathology (Table-2).

PTSD was a common diagnosis in maltreated youth. In our sample, 16 had the disorder while 13 did not meet the diagnostic criteria. As commonly seen in PTSD studies (De Bellis, 2001; De Bellis et al., 2001a), there was significant co-morbidity with other disorders and with impairing subthreshold PTSD (N=8/13)(Carrion, et al., 2002a), making a comparison of maltreated subjects with and without PTSD scientifically inappropriate. Attention deficit hyperactivity disorder (ADHD) Predominantly Inattentive Type co-occurred with 77% of maltreated youth who either met PTSD criteria or had impairing subthreshold PTSD. Eight of the maltreated youth were on stable doses of medications (N=2 stimulant and antidepressant (n=1 female), N=4 stimulants only (n=2 females), N=2 antidepressants only (n=2 females)). If significant brain differences were found between maltreated and non-maltreated groups, we addressed the influence of medications in secondary brain region of interest (ROI) analyses to confirm group differences by excluding all 8 maltreated subjects on medications in these secondary general linear analyses.

Experimental Paradigm

Emotional and executive control was probed using a block design variant of the Emotional Oddball Task (Wang, et al., 2008), consisting of fear, calm, and scrambled face stimuli mixed with target events. There were 15 trials presented sequentially of which two had a target (a cartoon running rabbit) on one of the four sides of the stimulus image. Participants pressed a button when they saw this target. We used randomly selected fearful and calm faces from the NimStim, a valid and reliable set of facial expression stimuli of multiracial individuals (Tottenham et al., 2009), to ensure a gender and racially diverse balance that was similar to our subject demographics. The same set of faces was randomly given to all participants. The block design involved five runs, each lasting 6 minutes. Each run consisted of twelve blocks, or stimulus presentations, where a set of four of each stimulus type was presented in a pseudorandom order to ensure that two of the same stimulus block types were not consecutive. Images of calm expressions with relaxed facial musculature were used for the calm condition because elevated amygdala response to neutral faces was reported in children (Thomas et al., 2001). Since children show heightened amygdala activations to a variety of emotional faces compared with adults (Hoehl et al., 2010), we planned to examine responses to both fearful and calm faces. To increase motivation, subjects could earn additional compensation for responding to targets. Fear target refers to when a target was presented with a fearful face, calm target refers to when a target was presented during a calm face, and scrambled target refers to when a target was presented during a scrambled face. The experimental task is described in further detail in Figure-1.

Image Acquisition

Prior to scanning, subjects underwent mock scanning desensitization and task training. Anatomical and functional images were acquired using a 3.0-Tesla General Electric Signa EXCITE HD scanner (Waukesha, WI) with 40-mT/m gradients and an 8-channel head coil. High-resolution T_1-weighted anatomical images were acquired in the axial plane using spoiled gradient-recalled acquisition with repetition time = 7.5 ms, echo time = 3.0 ms, field of view = 24 cm, flip angle = 12°, matrix = 256 × 256, yielding 1 mm^2 in-plane resolution with 124 contiguous images (1 mm slice thickness) per brain volume. Functional images were collected with echo-planar imaging acquisition sensitive to blood oxygenation-level-dependent (BOLD) contrast with TR = 2000 ms, TE = 28 ms, FOV = 24 cm, flip angle = 90°, matrix = 64 × 64, yielding 4 mm isotropic voxels and 31 contiguous images per brain volume.

Image Analysis

Functional images were analyzed using FMRI Expert Analysis Tool (version 5.98, Analysis Group, FMRIB, Oxford, UK). Image preprocessing included correction for slice acquisition time, motion correction with MCFLIRT (Jenkinson et al., 2002), normalization into standard Montreal Neurological Institute stereotaxic space (MNI, Montreal, Quebec, Canada), and subject to high-pass filtering (pass frequency >1/100Hz). FSL's Brain Extraction Tool (Smith, 2002) was used to exclude non-brain voxels from our analyses.

This emotional oddball paradigm was designed to characterize cognitive processing, emotional processing, and their interactions. The scrambled condition was left unmodeled as a baseline for comparison, as conventional in the FSL analysis package. Statistical analyses were conducted using a general linear model with local autocorrelation (Woolrich et al., 2001). Events were time locked to stimulus onset and included facial stimuli and targets presented with facial stimuli. Targets were orthogonalized from corresponding face blocks. Estimated motion parameters and ventricle regressor were included as nuisance regressors.

The second-level analyses averaged results for each contrast across runs for an individual using a fixed effect model. Third-level analyses collapsed across all subjects that included an additional regressor for between-group comparisons using a random effects model (FLAME 1). Third-level analyses provided the following contrasts: fear versus calm, fear versus scrambled, calm versus scrambled, calm target versus scrambled target, fear target versus calm target, and fear target versus scrambled target. The emotional oddball task was designed to have these types of contrasts in adults to examine affective neural networks with and without executive networks. Executive neural networks were examined with attentional control to targets during the scrambled condition and represents the brain circuits for the dorsal attention-executive system task while faces (calm or emotional) during targets were distractors and measure the influence of emotion (e.g., social cues) on attention. Thus, the contrasts of interest in this study were the following: *fear versus calm* (fear face versus calm face), *fear versus scrambled* (fear face versus stimuli with no social cue) for examination of affective processing; and *fear target versus calm target* (fear face versus social cue) and *fear target versus scrambled target* (fear face versus no social cue) for examination of executive networks during emotional and non-social cue distractions. Because we showed in the original emotional oddball task (on which this task is based) that healthy youth activate dorsal attention-executive system including the anterior middle frontal gyrus, dorsal anterior cingulate, posterior cingulate, insula, and supramarginal gyrus to targets like adults but, unlike adults, youth exhibited strong activation to the emotional distracter images (i.e., sad images) not only in the ventromedial prefrontal cortex, but also in the posterior middle frontal gyrus and in the parietal cortex (Wang, et al., 2008); and because the limited neuroimaging studies in youth show that children show heightened amygdala activations to a variety of types of emotional faces than adults (Hoehl, et al., 2010) including neutral faces (Thomas, et al., 2001), we examined two types of comparison contrasts (calm or scrambled faces) for our contrasts of interest. In the third level analyses, group, gender, and their interactions were examined. All statistical results of whole-brain voxelwise analyses reported in figures of brain images and tables were thresholded using clusters determined by $Z>2.3$ and a corrected cluster significance threshold of $p=0.05$ (Worsley, 2001).

To examine the relationship between brain regions of interest (ROI) and clinical variables, we used mean ROI BOLD activation extracted from baseline (the scrambled condition) from the level 2 analyses to illustrate the activation patterns during each contrast for significant clusters in third level whole-brain analyses. Given the significant difference between maltreated and control youth in SES, IQ, and possible medication effects, these measures were included as covariates in separate ROI analyses using general linear regression models to control for the influences of these parameters. The relationship between these ROI and clinical variables (e.g., total number of PTSD symptoms) were examined with Spearman's rho correlations.

RESULTS

Task Performance

The task performance was measured by the percentage of omission errors and reaction times for target detection in each type of target event. Mixed ANOVA analysis did not show significant effects by group, gender, or interaction of group by gender suggesting similar task performance between groups (Table-3).

Gender x Maltreated Effect in Brain Activation During Fearful Face (Emotional) Processing

The *fear versus calm* contrast examined emotional processes during fearful face presentation while controlling for calm (non- emotional) faces, while the *fear versus scrambled* contrast examined emotional processes during a fearful face controlling for a non-social stimuli. The whole-brain voxelwise analyses revealed no main effects of group or gender in the *fear versus calm* or the *fear versus scrambled* contrasts.

However, the whole-brain voxelwise analyses revealed significant clusters of activations during emotional processing of fear information for the gender x maltreated group interaction analyses in the *fear versus calm* and *fear versus scrambled* contrasts (Table-4). Maltreated females compared to control females exhibited less BOLD signal to the *fear versus calm* contrast in the dorsomedial prefrontal cortex (dmPFC) (Figure-2a). Post-hoc ROI analyses revealed that maltreated females showed less BOLD signal in dmPFC than the control female, control male, and the maltreated male groups ($p<0.05$) (Figure-2b). The maltreated females also showed less BOLD signal than control females in the *fear versus scrambled* contrasts in the right cerebellum I, II, III, IV, and V, and left cerebellum I, II, III, IV, V, and VI (Figure-4a); but more BOLD signal than control females in the left lateral occipital cortex, left middle temporal lobe, and left angular gyrus (Table-4). Post-hoc ROI analyses revealed that maltreated females showed less BOLD signal in right and left cerebellum I–V and left cerebellum VI than the control females and control males ($p<0.05$) (Figure-4c).

Maltreated males compared to control males showed increased BOLD signal to the *fear versus calm* contrast in a cluster in the calcarine cortex that included right lingual gyrus (Figure-2b) and to the *fear versus scrambled* in the right cerebellum (crus I, cerebellum VI, VIIb, VIIIa, vermis VI) (Figure-4a&b), left middle temporal pole, left hippocampus (Figure-3a), paracentral cortex, and right supplementary motor area (Table-4). Post-hoc ROI analyses revealed that maltreated males showed more BOLD signal in calcarine cortex compared to control male, control female, and the maltreated female groups ($p<0.05$) (Figure-2d). In addition, post-hoc ROI analyses revealed increased right cerebellar BOLD signal for maltreated males compared to maltreated females and control males in a large cluster that included the right cerebellum crus I ($p<0.05$)(Table 4, Figure-4b). It should be noted that these areas of cerebellar activation differences to the *fear versus scrambled* contrast between maltreated youth and their same gender controls were different for males and females with little regions of overlap (Figure-4a).

In summary, maltreated females showed hypoactivation in dmPFC to fearful faces compared to control females, while maltreated males showed greater BOLD signal in visual cortex, cerebellum, and hippocampal regions compared to control males in the *fear versus calm contrast*, the contrast that controlled for face presentation; while the variety of gender differences seen in the *fear versus scrambled contrasts* most likely represented emotional processing due to both fearful face presentation and face presentation.

However, we did not find whole-brain voxelwise main effects in the maltreated versus control, gender groups, or group by gender interaction for calm versus scrambled, suggesting that the fearful face was responsible for our overall results. In order to explore these differences between the two emotional processing contrasts, we also undertook two ROI exploratory analyses to examine the relationship of dmPFC and calcarine cortex BOLD activations in the fear versus scrambled contrast. We found a significant difference for control females compared to maltreated females to show increased BOLD signal in the dmPFC for the *fear versus scrambled* contrast ($t_{1,37}=-2.04$, $p<.05$), which was consistent with the findings in the *fear versus calm* contrast. We found a trend for maltreated males compared to control males to show increased BOLD signal in the calcarine cortex, for the *fear versus scrambled* contrast ($t_{1,33}=1.8$, $p<.09$). These findings were consistence with the significant gender x group findings seen in the *fear versus calm* contrast and further suggest that the fearful face was responsible for our results.

Group, Gender, and Group x Gender Effects in BOLD Signal During Executive Control Processing (Target Detection) with Fear Distraction

The *fear targets versus calm targets* contrast examined executive control processing during emotional distractors (fearful face versus calm (non-emotional) face distractors). The whole-brain voxelwise analyses revealed no main effects of group or gender in the *fear targets versus calm targets* contrast. However the whole-brain voxelwise analyses revealed significant clusters of activations during executive control processing (target detection) with fear distraction for the gender x maltreated group interaction analyses in the *fear targets versus calm targets* contrast (Table-5). Maltreated males showed decreased activations in the *fear targets versus calm targets* contrast in left posterior cingulate cortex (PCC) (Figure-5a). Post-hoc ROI analyses revealed that maltreated males showed less BOLD signal in left PCC compared with control male, control female, and maltreated female groups ($p<0.05$) (Figure-5b). Greater PTSD symptoms were also correlated significantly with increased BOLD signal to *fear targets versus calm targets* in the PCC (Spearman's rho

=0.37, $p<0.05$) (Figure-5c). This relationship was similar in maltreated boys (Spearman's rho =0.50, $p<0.05$) and suggestive in maltreated girls (Spearman's rho =0.52, $p<0.07$).

The *fear targets versus scrambled targets* contrast examined executive control processing during emotional distractors (fearful faces versus non-social stimuli distractors). The whole-brain voxelwise analyses revealed a main effect of group and a main effect of gender in the *fear targets versus scrambled targets* contrast. There was a significant group difference in response to *fear targets versus scrambled targets,* with controls showing greater BOLD signal in left precuneus, left middle cingulate, and right supplementary areas than maltreated subjects (Figure-6a, Table-5). Post-hoc ROI analyses revealed that maltreated males showed less BOLD signal in left precuneus cortex (PC) compared with control males and maltreated females ($p<.05$) (Figure 6b), but not compared with the maltreated females. Although there was a whole-brain voxelwise main group effect for controls to show greater PC activations than the maltreated groups, this finding was influenced by the lower PC activations in maltreated males. There was a main whole-brain voxelwise gender effect on the *fear targets versus scrambled targets* contrast in that all females showed significantly greater BOLD signal activation in bilateral lingual gyrus, left fusiform gyrus, and right cerebellum I, II, III, IV and V, than all males (Figures-6c &7a). The post-hoc ROI analyses revealed that control females showed greater BOLD signal in left precentral/postcentral gyrus compared with control and maltreated males; while maltreated females showed greater BOLD signal in left precentral/postcentral gyrus compared with maltreated males ($p<.05$) (Figure-6d). This was the only finding where gender showed a clear difference in response to executive control processing (target detection) during fear distraction that was not influenced by maltreatment status or maltreatment x gender interactions. Post-hoc ROI analyses of the lingual gyrus revealed that whole-brain voxelwise gender effects were mainly influenced by the lower BOLD signal seen in maltreated males compared to control males and females ($p<.05$), but not compared with the maltreated females (Figures-7a & 7b). Post-hoc ROI analyses of the temporal gyrus/fusiform cortex also revealed that the main gender findings were mainly carried by the lower BOLD signal seen in maltreated males compared to control males and females ($p<.05$); but not compared with the maltreated females (data not shown in figures).

In addition to the main effects of group and gender, there was a significant whole-brain voxelwise main effect of maltreatment x gender interaction in response to *fear targets versus scrambled targets* contrast. A maltreatment x gender interaction effect showed that maltreated males exhibited less activation to *fear targets versus scrambled targets* in the left PC (Figure-6b) and left inferior frontal gyrus (also known as the ventrolateral prefrontal cortex, vlPFC, Figure-7d) than control males. Post-hoc ROI analyses revealed that maltreated males showed less BOLD signal in left PC than control male and females, but not the maltreated females (Figure-6b) and that maltreated males showed less BOLD signal in left PCC than control male and females ($p<.05$); but not the maltreated females (data not shown in figures). Post-hoc ROI analyses revealed that maltreated males showed less BOLD signal in left vlPFC than control male, control female, and maltreated female groups ($p<.05$) (Figure-7d).

We did not find main effects in the maltreated versus control, gender groups, or group by gender interaction for calm target versus scrambled target, which suggests that the fearful face was responsible for our results. The findings of greater left PC and PCC activations in control males compared with maltreated males were consistence in the *fear target versus calm targets* and *fear target versus scrambled targets contrasts* suggesting that the fearful face distraction to targets were responsible for our results.

The influence of SES and FS IQ on findings

In the overall sample, IQ and SES were significantly correlated (Spearman's rho =.34, p<.003). Therefore, we controlled for SES and FSIQ separately in the above ROI analyses as seen in Tables-4&5. These analyses remained significant or suggestive except for one finding in the *fear target versus scrambled target contrast* for control males to show greater BOLD response compared with maltreated males (interaction effect of control males versus maltreated males in left precentral and postcentral gyrus cluster, Table-4). Among maltreated youth, PTSD symptoms were not significantly related to IQ (Spearman's rho =.17, p=.38) or SES (Spearman's rho =−.16, p=.40). Excluding maltreated participants on medications did not influence results except for that same *fear target versus scrambled target contrast* (interaction effect of control males versus maltreated males in left precentral and postcentral gyrus cluster, Table-5). Unless otherwise reported, we did not find any other significant correlations between brain regions of interests reported between groups; and age, SES, IQ, or PTSD symptoms.

Discussion

Although maltreated boys and girls had similar maltreatment experiences, number of PTSD symptoms, types of Axis I mental health disorders, psychopathology, and performance on the emotional oddball task, maltreated youth significantly demonstrated gender differences during affective regulation and executive attentional control during fear distracters. During the affective processing of fearful faces controlling for calm faces, maltreated females compared to control females exhibited decreased activation in the dmPFC; while maltreated males compared to control males exhibited increased activation in the visual cortex and right lingual gyrus. When investigating executive attentional processing of oddball targets with the task irrelevant emotional distraction of fearful faces controlling for calm faces, maltreated males compared to control males exhibited decreased activation in left middle and posterior cingulate cortex and the PC. Furthermore, greater PTSD symptoms were positively and significantly correlated with increased BOLD signal to fear targets versus calm targets in the PCC. This relationship remained significant in maltreated boys and was suggestive in maltreated girls. The PCC is involved in visual attention and is consistently activated during the processing of emotional stimuli and emotional memories (Maddock, 1999). The PC is a complex structure that is associated with multiple functions including the posterior default mode network or resting state network (Eichele et al., 2008; Fransson, 2005, 2006; Raichle et al., 2001), and integration of tasks that include visual-spatial imagery, episodic memory retrieval, and social cognition (Cavanna & Trimble, 2006). These functions that were needed to perform this task. Only maltreated males compared to control males demonstrated differences in executive attentional processing of oddball targets with the task irrelevant distraction of *fear faces versus calm faces*. Less PC activation may mean that additional deactivation of the resting state network was needed to focus more attention on the task in maltreated male youth to integrate information and to maintain the same level of attention to the task for similar performance to the non-maltreated youth. No differences were found in maltreated female youth, suggesting that maltreated females exhibited differences in brain regions including executive regions (e.g., dmPFC) only during the processing of affective stimuli or emotion, but not during the executive component of the task. These findings suggest that maltreated male youth are more vulnerable to the influence of emotion during executive functions compared to maltreated females; while maltreated females youth may be more resilience to the influence of emotion during executive functions compared to maltreated males.

Maltreated females compared to control females exhibited decreased activation in the dmPFC during the affective processing of fearful faces versus calm faces. The dmPFC is implicated in emotion appraisal, emotion expression, and explicit threat evaluation (Etkin et al., 2011). Decreased activation in the dmPFC in maltreated females during passive viewing of fearful faces is consistent with previous findings in both male and female adults with PTSD (Bremner, et al., 1999; Bremner, et al., 2005; Bremner, et al., 2004; Britton, et al., 2005; Shin, et al., 1999; Shin et al., 2004b; Shin, et al., 2001; Shin, et al., 2005). Previous findings in adult PTSD demonstrated decreased medial prefrontal cortex activation in response to aversive stimuli including fearful faces (Francati, et al., 2007; Lanius, et al., 2001; Lanius, et al., 2003; Lindauer, et al., 2004; Shin, et al., 2004a). Increased dmPFC activation was observed post-treatment in adults (Felmingham et al., 2007). Thus, dmPFC hypoactivation in female youth may identify those individuals at risk for developing chronic PTSD or depression from child maltreatment. Although we did not see decreased activation in the dmPFC in maltreated females in the whole-brain voxelwise analyses for the fear versus scrambled contrast compared to control females, ROI exploratory analyses of the dmPFC showed that the maltreated females had decreased BOLD signal in the dmPFC in this contrast compared to control females, which was consist with the findings in the *fear versus calm* contrast and suggested that fearful face response was responsible for this finding. During the affective processing in the fear versus scrambled contrast, maltreated females compared to control females exhibited increased activation compared to control females in the left middle temporal cortex and angular gyrus. These regions are involved in face processing and social cognition, suggesting greater neural resources are needed for emotional and face processing in maltreated females than for non-maltreated females.

We observed gender differences in maltreated male and female youth during the affective processing of *fear versus scrambled faces*, a contrast that reflected both response to viewing a fearful face and a face; maltreated females compared to control females exhibited decreased activation in the right cerebellum I–V, and increased activation compared to control females in the left middle temporal cortex and angular gyrus. However, maltreated males compared to control males exhibited a pattern of increased activation in multiple brain regions, including the occipital cortex and fusiform gyrus, brain regions which also showed activations in the *fear versus calm contrast;* additionally, maltreated males demonstrated increased activations in the hippocampus, parahippocampus, left middle temporal lobe, paracentral gyrus, and right cerebellum crus I compared with control males.

Our results demonstrated gender differences during examination of executive attentional control with task irrelevant fear distracters versus scrambled faces, a task examining executive processing during emotional distractors (fear faces versus non-social stimuli distractors). Maltreated females compared to control females did not demonstrate differences in executive attentional processing of oddball targets with the task irrelevant distraction of fear faces or scrambled faces. However, maltreated males compared to control males exhibited decreased activations in multiple brain regions including in the PC and the PCC as was seen in the *fear target versus calm target* contrast. Maltreated males compared to control males additionally exhibited decreased activations during the *fear target versus scrambled target* contrast in multiple brain regions (left inferior frontal gyrus and vlPFC, bilateral precuneus, and left inferior parietal lobe). These results represent decreased brain activation to both fear faces and faces in maltreated male youth in ROI involved in visual-spatial attention and emotional regulation. The vlPFC is associated with inhibition of emotional distraction (Dolcos et al., 2011). Previous studies (Bishop et al., 2007) found that left vlPFC activation to threat-related distracters is negatively correlated with anxiety. Hypoactivation in PCC to fear target versus calm target and vlPFC hypoactivations to fear target versus scrambled target suggests dysfunction in the executive functions of attentional control and inhibition of emotional distraction in maltreated males compared with control males. Indeed, our ROI analyses of the inferior frontal gyrus during the *fear target versus scrambled target* contrast and the PCC during the *fear target versus calm targe*t contrast suggested that maltreated male youth show altered executive attentional processing during emotional and non-emotional (scrambled face) distraction compared to maltreated female and both male and female non-maltreated control youth.

In contrast, maltreated males compared to control males exhibited increased activation in the visual cortex (calcarine) and right lingual gyrus during the affective processing in the fear versus calm contrast and exhibited a pattern of increased activation in multiple brain regions (i.e., hippocampus, parahippocampus, left middle temporal lobe, paracentral gyrus, right cerebellum crus I) including the occipital cortex and fusiform gyrus as also seen in the fear versus calm contrast, during the affective processing of fear versus scrambled contrast. Maltreated males may be dedicating significant functional neural resources to processing affective and face stimuli as indicated by increased visual cortex and the extended limbic system activations. The hippocampus is sensitive to stress. In early stages of stress, enlarged hippocampal volume or increased activation is seen, whereas long-term chronic stress results in hippocampal atrophy (Kitayama et al., 2005; Teicher et al., 2012; Tottenham & Sheridan, 2010; Tupler & De Bellis, 2006). Smaller hippocampi are seen in adults but not children with PTSD (Karl et al., 2006). Increased left hippocampal and parahippocampal gyrus activations were seen in adults with complex PTSD, a chronic form of PTSD that can stem from child abuse, during preferential recall of negative words (Thomaes et al., 2009). Increased amygdala and left hippocampal activation to angry faces were seen in youth with PTSD symptoms, where smaller N did not permit examination of gender differences (Garrett et al., 2012). Consistently, we found increased hippocampal activation during processing fearful faces in maltreated males with PTSD symptoms. Maltreated youth did not exhibit amygdala hyperactivation in response to fearful faces. Some PTSD investigations have also failed to find exaggerated amygdala responses (Bremner, et al., 1999; Bremner, et al., 2003;

Britton, et al., 2005; Lanius, et al., 2001; Shin, et al., 1999) including a study that used fearful face stimuli in both block and event-related designs (Schäfer et al., 2005).

In the cerebellum, gender differences in maltreated youth were notable during affective processing of fearful faces versus scrambled faces, a contrast that reflected both response to viewing a fearful face and a face. It should be noted that these regions of cerebellar activations differences to the *fear versus scrambled* contrast between maltreated youth and their same gender controls were not only in the opposite direction but also seen in different regions for males and females with little regions of overlap. This represents a new finding in the youth trauma literature. Maltreated males showed increased activation in right cerebellum Crus I, right cerebellum VI, VIIb, VIIIa, vermis VI, Vermis Villa, whereas maltreated females exhibited decreased activation to their same gender controls in the right and left cerebellum I–V and left cerebellum VI in response to fear versus scramble contrasts. Thus, during both fear and face processing, maltreated females demonstrated decreased activation in cerebellar areas involved referred to as primary sensorimotor cerebellar zones (V, VI) (O'Reilly et al., 2010) and other cerebellar areas thought to be involved in higher order cognitive cerebellar regions (Schmahmann et al., 2009). In maltreated females, decreased cerebellar activation was seen in higher order cognitive regions with corresponding decreased prefrontal activation in dmPFC compared with control females to fearful faces. Maltreated males showed extensive increases in activations in the right cerebellum. The right cerebellum is implicated in executive functioning, language, and working memory (Habas et al., 2009; Stoodley & Schmahmann, 2009). The Crus I is involved in identifying emotional tone and cognitive function (Stoodley & Schmahmann, 2010). In maltreated males, increased cerebellar activation was also seen in the vermis, an area of the extended limbic system. Thus, in maltreated males greater activations were seen in cerebellar and cortical regions involved in emotional function, executive function, language, visual spatial function, and working memory than control males to fearful faces. These findings suggest gender differences in cerebellar-cortical activations to fear in maltreated youth. Results remained significant when controlling for SES and IQ effects. These findings are consistent with animal studies showing that stress is associated with cerebellar damage (Liu et al., 1996) and human studies showing smaller cerebellums in youth with PTSD (De Bellis & Kuchibhatla, 2006) and previously institutionalized children (Bauer et al., 2009). The human cerebellum is the most sexually dimorphic structure in the brain (Tiemeier et al., 2010). Gender differences and gender specific responses to trauma and their relationship to the cerebellum are an area of study that requires further exploration.

We saw one main group difference between the maltreated and control groups during the executive attentional processing of oddball targets with the task irrelevant distraction of *fear versus scrambled* contrast. Maltreated youth showed less activation in a cluster that included mainly the left precuneus, but also middle cingulum, left paracentral cortex and the right supplementary motor area. However, upon examination of the ROI for these findings, post-hoc ROI analyses revealed that maltreated males showed less BOLD signal in left precuneus compared with control males and maltreated females, but not compared with the maltreated females, suggesting the main group finding was influenced by these gender differences.

In this *fear target versus scrambled target* contrast, we saw one main gender difference. Females demonstrated increased activations in lingual gyrus, left fusiform, and left precentral cortex as well as in right cerebellum I–V. The post-hoc ROI analyses of the findings in the lingual gyrus and temporal gyrus/fusiform cortex revealed that whole-brain voxelwise main gender effects were mainly influenced by the lower BOLD signal seen in maltreated males compared to control males and females, but not compared with the maltreated females. The only contrast (*fear target versus scrambled target*) that indicated a clear gender effect that was not influenced by maltreatment status or maltreatment x gender interactions was the finding that the control females showed greater BOLD signal in left precentral/postcentral gyrus compared with control and maltreated males; while maltreated females showed greater BOLD signal in left precentral/postcentral gyrus compared with maltreated males. Thus, this study demonstrated gender differences during affective regulation and executive attentional control during fear distracters in maltreated youth.

To the best of our knowledge, this is the first functional imaging study of brain activation in traumatized youth that has shown gender differences during cognitive and affective information processing. Gonadal hormones influence brain development in a sexually dimorphic fashion in animals. This occurs during critical periods prenatally and in infancy when testosterone is converted to estradiol by the enzyme aromatase and then organizes neural steroid receptors (Clark et al., 1988). Brain development and function in youth is accomplished through increases in cell number, dendritic elaboration and axonal sprouting, and apoptosis and synaptic pruning. These processes are known to be influenced by both androgens (MacLusky et al., 2006) and estrogens (Galea et al., 2006). In studies of youth undergoing puberty, male youth compared to female youth show larger grey matter volume in the amygdala and smaller striatal and hippocampal volumes; while parietal grey matter including precuneus and superior parietal gyrus, are decreased with increasing levels of circulating testosterone (Neufang, et al., 2009). Although sex differences in brain development is understudied in youth, in adults, brain structures which contain high levels of sex steroid receptors include the superior frontal and frontal medial cortex, anterior and posterior cingulate, angular gyrus, parietal cortex, postcentral gyrus, superior calcarine sulcus, basal ganglion, amygdala, and hippocampus (Goldstein et al., 2001). In this study, we demonstrated group x gender interactions in many of these steroid sensitive brain regions using the Emotional Oddball Task in maltreated youth. In another study from our group, anatomical brain differences were seen in boys and girls with maltreatment-related PTSD compared with healthy non-maltreated controls (De Bellis & Keshavan, 2003); significant group x gender interactions demonstrated smaller cerebral volumes and corpus callosum regions 1 (rostrum) and 6 (isthmus) and greater lateral ventricular volume increases in maltreated males with PTSD compared with maltreated females with PTSD, despite that fact that maltreated boys and girls had similar trauma experiences, mental health histories, and scores on a variety of measures of psychopathology. Estradiol promotes the formation of synapses and is protective against neuronal cell death throughout the lifespan (Wise et al., 2001). Estrogens may be protective against damage induced by glucocorticoids (McEwen, 2002), which are elevated in maltreated youth with impairing PTSD symptoms (Carrion et al., 2002b; De Bellis et al., 1999a). Furthermore this protection is mediated through the estrogen receptor-alpha, which can be de-silenced via epigenetic processes, and returned to a more plastic and protective developmental state in females (Wilson et al., 2011). Thus, it is plausible that traumatized youth can show similar levels of traumatic experiences and psychopathology, but marked differences in their brain development and function. Although the area of gender differences in traumatized adults is understudied, similar to a study in healthy adults (Koch et al., 2007), we found that all female youth in our study showed greater activation in temporal and occipital regions compared with all male youth in response to negative emotion (See Table-5). In fact, Koch et al., 2007 concluded that the neural interplay between emotion and cognition for the same task performance relies on differential processing mechanisms in healthy men and women. Given our data, these gender differences are seen early in youth and may also be influenced by trauma history.

This study has several strengths. We recruited the healthiest youth involved in child protective services, which was not an easy task as physical problems (Hussey et al., 2006; Leslie et al., 2005) and prenatal substance exposure (Besinger et al., 1999 ; Kelleher et al., 1994) are over-represented in maltreated youth. Our inclusion/exclusion procedures were major strengths of our study. Our sample size was sufficient for a MRI study of gender differences in youth involved with child protective services, where small sample sizes predominate. There were no gender differences between the maltreated males and females in any of the maltreatment and mental health variables that we could measure by interview or other objective archival records that could influence our fMRI data. This study has several limitations. Despite efforts to recruit demographically-matched controls, the maltreated youth differed from the control group in IQ and SES, both of which may contribute to psychosocial adjustment independently from maltreatment (Masten et al., 1990; McLoyd, 1998). This limitation is inherent in child maltreatment studies (De Bellis, 2001). We used statistical methods to control for these confounds. Higher IQ participants demonstrate a linear relationship with neural efficiency compared with lower IQ participants (Neubauer & Fink, 2009). Thus, IQ group differences we believe were appropriately addressed in general linear models of statistical analyses. We were also not able to examine age of maltreatment in our analyses because maltreated youth had multiple episodes and types of maltreatment experiences. Our data agree with other studies which show that most maltreated children involved in child protective services suffered from several types of abuse and neglect (Kaufman, et al., 1994; Levy et al., 1995; McGee et al., 1995; Widom, 1989). Thus determining the age of maltreatment is not a simple construct and was not feasible in our study. Our study employed a cross-sectional design which limits inferences regarding causality regarding the relationships between maltreatment, PTSD symptoms, and neural activations.

The gender moderation effect reflects a new finding in child maltreatment and PTSD pediatric imaging literature and is important given different outcomes in maltreated males and females. Whereas females are more likely to develop PTSD and depression following trauma (Saul et al., 2008), prospective studies show that maltreated boys have more antisocial outcomes in adolescence (De Bellis & Keshavan, 2003) and less resilience in adulthood (McGloin & Widom, 2001). Maltreated males exhibited a pattern of increased visual cortex, cerebellum, left temporal pole, and hippocampal activation to fearful faces but decreased activation in left vlPFC, and PCC, to target detection during fearful face distraction, indicating that maltreated males may be dedicating significant functional neural resources to processing affective stimuli in lieu of cognitive processes. The pattern of findings in maltreated males suggests executive attentional dysfunction secondary to emotional distraction, which may lead to impulsive decision-making during states of high emotion. Gender differences in traumatized children is an unexplored area. Further work is needed to determine whether this pattern of disrupted functional activation mediates the link between maltreatment in males and poor long-term outcomes including elevated rates of antisocial behavior (De Bellis & Keshavan, 2003; McGloin & Widom, 2001).

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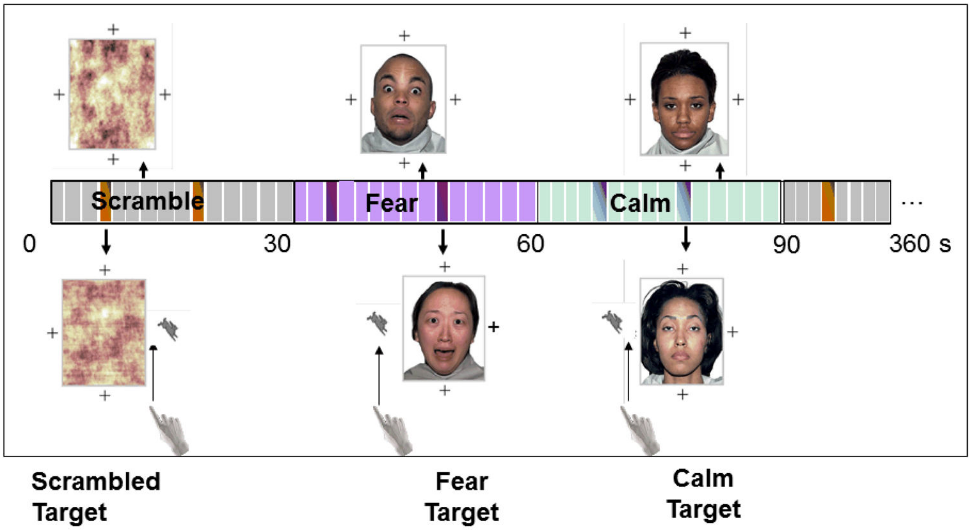

Figure 1. Illustration of the fMRI task

The experimental task was described to participants as the "Catch the Rabbit Game" and is described in detail here. The task was a block design consisting of fearful, calm, and scrambled face stimuli mixed with target events surrounding each image. We used fearful faces from the NimStim, a valid and reliable set of facial expression stimuli of multiracial individuals (Tottenham, et al., 2009), to ensure a gender and racially diverse balance that was similar to our sample demographics. Each block contained fearful faces, calm faces, or control stimuli. For control images, photographs of faces were Fourier transformed, phase-scrambled, and then inverse-Fourier transformed, resulting in images that were matched with the faces on average spatial frequency and luminance, but that had no recognizable content. Images of calm expressions with relaxed facial musculature were used for the calm condition rather than neutral faces. The block design involved five runs, with each run consisting of twelve blocks, or stimulus presentations. For each 30 second stimulus presentation, four crosshairs were displayed on all four sides of the stimulus image (Fear, Calm, or Scrambled). There were 15 trials presented sequentially, of which two had a target (a running cartoon rabbit) on one side of the stimulus image. For example, for two trials during each stimulus presentation, one of the crosshairs displayed with the stimulus image was randomly replaced by a running cartoon rabbit (the target). The participants' task was to press a button as soon as they saw this target. To increase motivation, subjects could earn additional compensation for responding to targets. Each picture image was presented for 1500 ms and was followed by a single crosshair during a 500 ms interstimulus interval. Scrambled target refers to when a target was presented during a scrambled face. Fear target refers to when a target was presented with a fearful face and calm target refers to when a target was presented during a calm face. There were 12 blocks with 4 of each stimulus type which were presented in a pseudorandom order to ensure that two of the same stimulus block types were not consecutive.

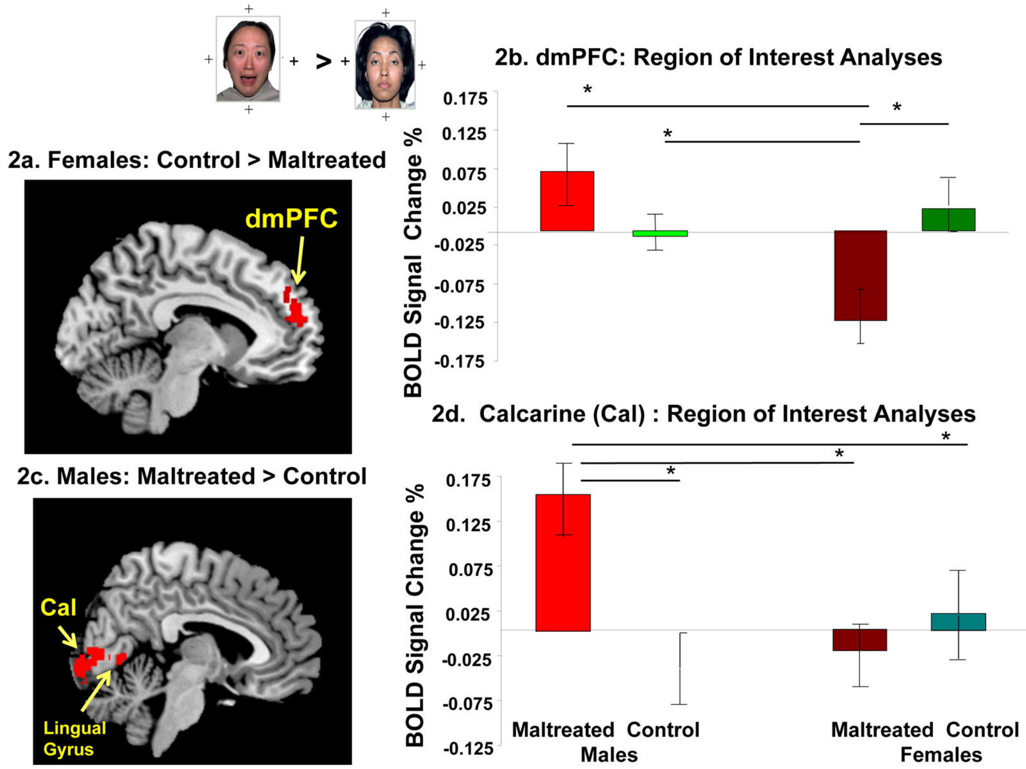

Figure 2. Gender x group effect on percent BOLD signal in response to the *fear versus calm* contrast in the dorsomedial prefrontal cortex (dmPFC) and calcarine region

This contrast examined emotional processes during fearful face presentation while controlling for calm (no emotional) faces. **Figure-2a:** The brain image illustrates the whole-brain analysis demonstrating significantly decreased percent BOLD signal change in the dmPFC in maltreated females than control females (red label in brain images). **Figure-2b:** The Region of Interest (ROI) analysis (bar graph) revealed that maltreated females showed significantly decreased percent BOLD signal when examining the individual subject's dmPFC activations extracted from the *fear versus calm* contrast from the scrambled baseline than the control males, maltreated males, and control females. **Figure-2c:** The brain image illustrates the whole-brain analysis showing significantly increased percent BOLD signal in maltreated males in a cluster that was composed of mainly the bilateral calcarine regions, but also the left lingual gyrus, compared with control males (red label in brain images). **Figure-2d:** Post-hoc ROI analyses revealed that the maltreated males showed significantly increased percent BOLD signal in the calcarine than control males, maltreated females, and control females. The bar graphs show the ROI analysis in the dmPFC and calcarine regions respectively confirming the whole-brain analysis. Post-hoc analyses (i.e., "*") indicates significant ROI differences between gender groups (Dunnett's Method, $p<.05$) (Figures-2b&d).

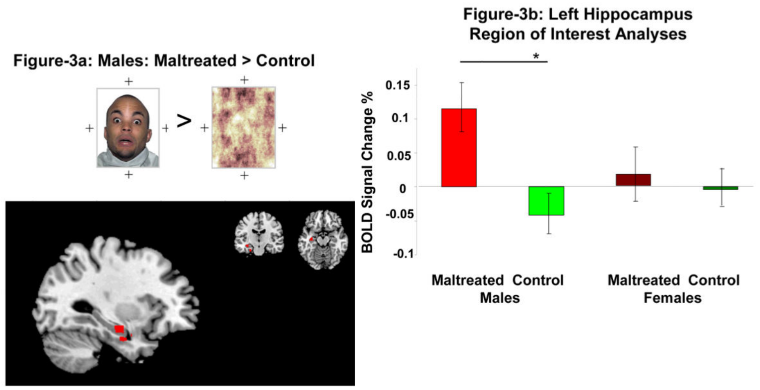

Figure 3. Gender x group effect on percent BOLD signal in response to Fear versus Scrambled in the Left Hippocampus

The *fear versus scrambled* contrast examined emotional processes during a fearful face controlling for a non-social stimuli. **Figure-3a:** The brain image illustrates the whole-brain analysis showing greater BOLD signal change in maltreated males compared with control males in response to a fear face. **Figure-3b**: The ROI analysis bar graph showed greater percent BOLD signal in maltreated male groups in the left hippocampus to *Fear versus Scramble* compared with control males. Females did not show differences in the hippocampus. The bar graphs show the ROI analysis in the left hippocampus confirming the whole-brain analysis. Post-hoc analyses (i.e., "*") indicates significant ROI differences between gender groups (Dunnett's Method, p<.05)

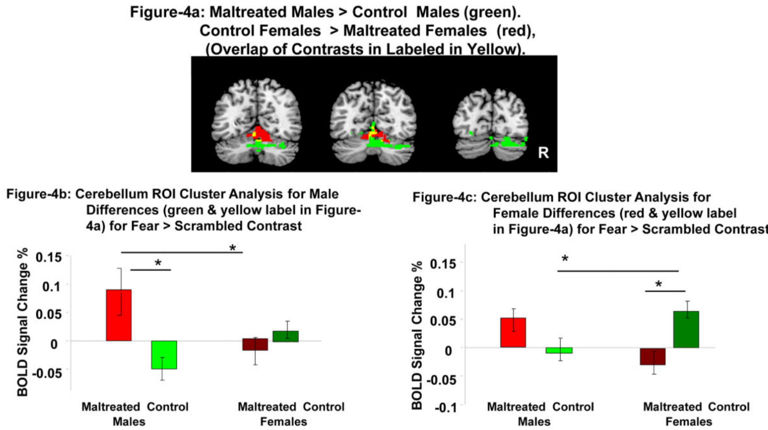

Figure 4. Gender x group effect on percent BOLD signal in Response to *Fear versus Scrambled* in the Cerebellum

Figure-4a: The brain image illustrates the whole-brain analysis demonstrating greater percent BOLD signal in the cerebellum for maltreated males showing increased BOLD signal compared with control males (labeled in green and yellow), and maltreated females showing decreased BOLD signal compared with control females (labeled in red and yellow) in response to a fear face. The overlap of these two clusters is showed in yellow. **Figure-4b:** The ROI analysis (bar graph) showed greater percent BOLD signal change in the cerebellum for the maltreated males compared with the control males and maltreated females to the *Fear versus Scramble* contrast for the ROI in the cerebellum from this significant cluster that involved the differences in the two male groups (i.e., crus I, cerebellum VI, VIIb, VIIIa, vermis VI). **Figure-4c:** Whole-brain analysis demonstrated that control females had increased cerebellar percent BOLD signal in response to a fear face compared with maltreated females. The bar graphs show the ROI analysis for the *Fear versus Scramble* contrast for the ROI in the cerebellum from this significant cluster that involved the differences in the two female groups (i.e., right and left cerebellum I–V and left cerebellum VI); and showed that control females demonstrated greater activations to fear faces than maltreated females and control males. Post-hoc analyses (i.e., "*") indicates significant ROI differences between gender groups (Dunnett's Method, p<. 05) (Figures-4b&d). Note the brain regions of cerebellar activations for males and females were different and showed little areas of overlap (i.e., yellow label in Figure-4a).

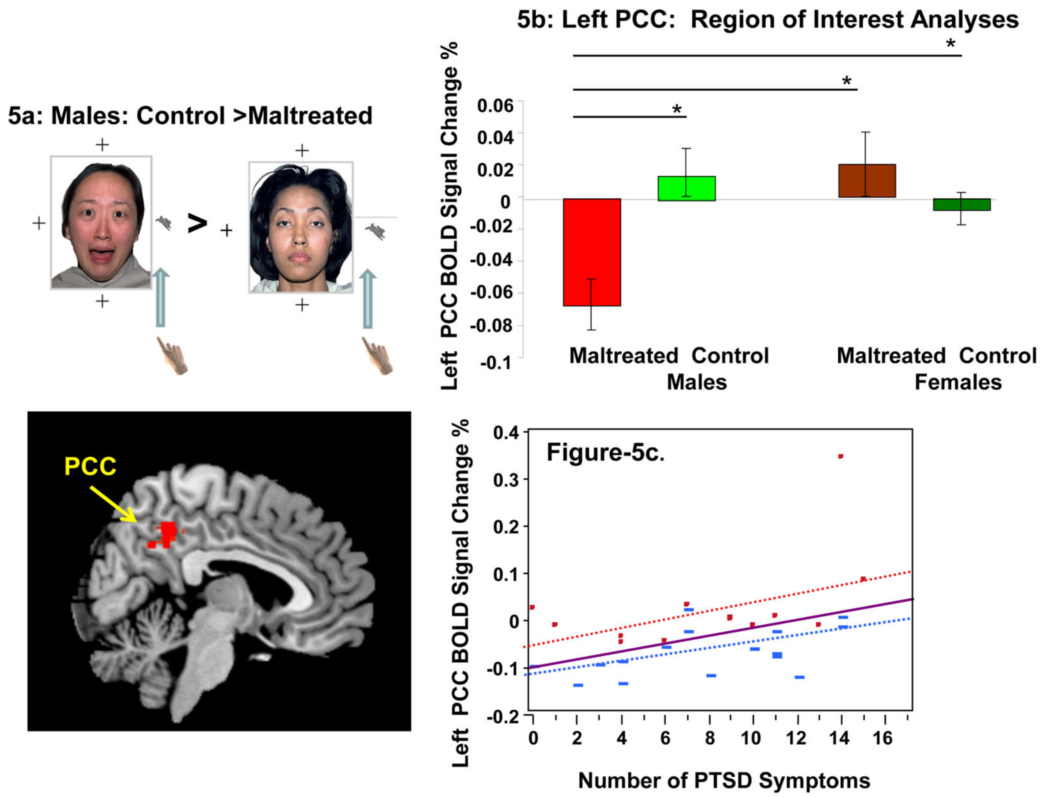

Figure 5.

This contrast examined executive control processing during emotional distractors (fearful faces versus calm (no emotional) faces as distractors). **Figure-5a:** Gender x group effect on percent BOLD signal in response to *fear target versus calm target* in the posterior cingulate cortex (PCC).The brain image illustrates the whole-brain analysis demonstrating decreased activation in maltreated males compared with control males in the PCC. **Figure-5b:** The bar graph illustrates decreased PCC ROI activations in the maltreated males compared with maltreated females, and control males and females confirming the whole-brain analysis. Post-hoc analyses (i.e., "*") indicates significant ROI differences between gender groups (Dunnett's Method, p<.05). **Figure-5c:** Greater PTSD symptoms in maltreated youth were significantly and positively correlated with increased BOLD signal activation to *fear target versus calm target* in the PCC (Spearman's rho =0.37, p<0.05). This relationship was similar in maltreated boys (blue squares, dotted line, Spearman's rho =0.50, p<0.05) and suggestive in girls (red circles, red crossed line, Spearman's rho =0.52, p<0.07).

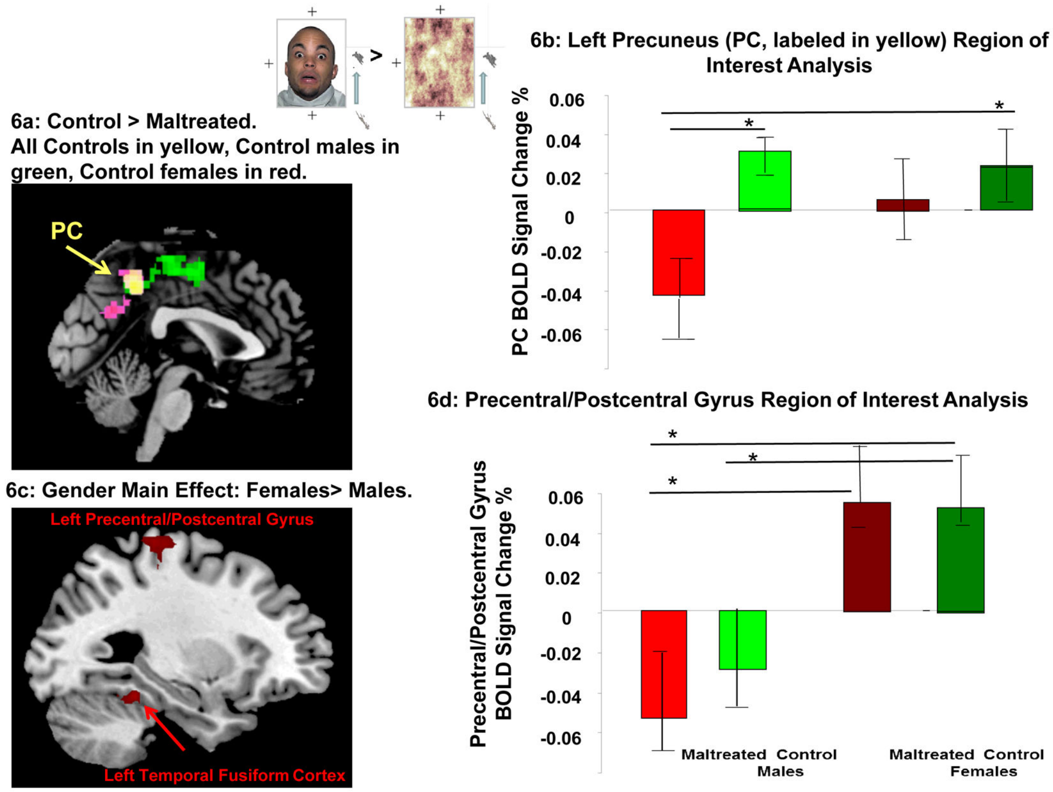

Figure 6.

Figure 6a: The *fear target versus scrambled target* contrast examined executive control processing during emotional distractors (fearful faces versus non-social stimuli distractors). Figure 6a: Main Group effect on percent BOLD signal in response to *fear target versus scrambled target* in the precuneus (PC). The brain image illustrates the whole-brain analysis demonstrating decreased percent BOLD signal change in the maltreated group compared to the control youth; the voxels in yellow indicate the main effect of group (controls greater than maltreated in left precuneus (PC)). **Figure-6b:** The ROI analysis bar graph showed decreased percent BOLD signal in maltreated males in the PC to *fear target versus scrambled target* compared with the control males and control females;. but not compared with the maltreated females. Although there was a whole-brain voxelwise main group effect for controls to show greater PC activations than the maltreated groups, this finding was influenced by the lower PC activations in maltreated males. **Figure-6c:** Main whole-brain voxelwise gender effect on the *fear targets versus scrambled targets* contrast in that all females showed significantly greater BOLD signal activation in left precentral/postcentral gyrus, left temporal fusiform cortex, and right cerebellum I, II, III, IV and V (data not showed), than all males. **Figure-6d:** The post-hoc ROI analyses revealed that control females showed greater BOLD signal in left precentral/postcentral gyrus compared with control and maltreated males; while maltreated females showed greater BOLD signal in left precentral/postcentral gyrus compared with maltreated males. Post-hoc analyses (i.e., "*") indicates significant ROI differences between gender groups (Dunnett's Method, p<.05).

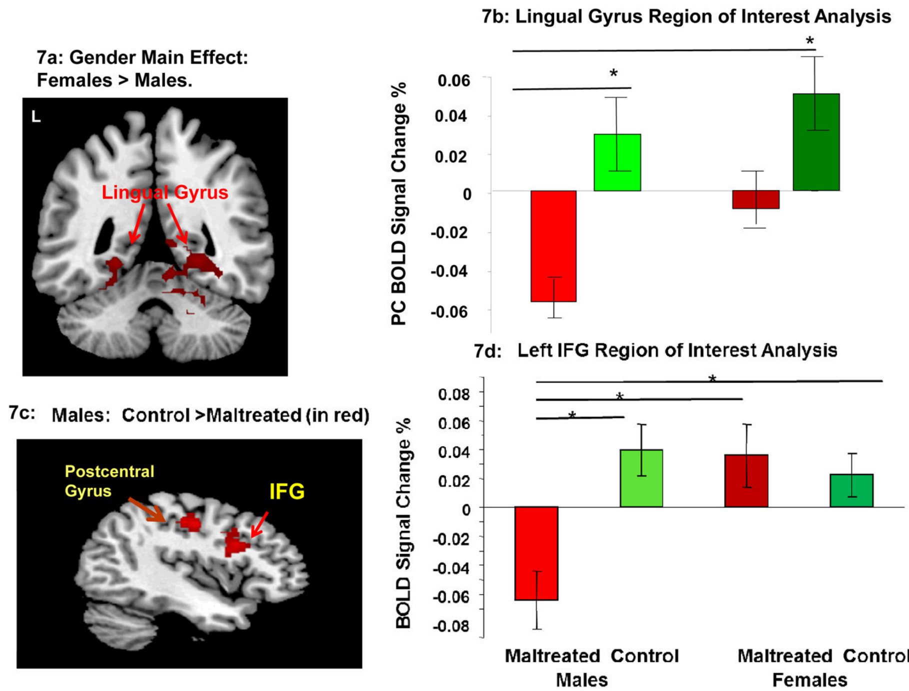

Figure 7.

Figure-7a: Main whole-brain voxelwise gender effect on the *fear targets versus scrambled targets* contrast in that all females showed significantly greater BOLD signal activation in lingual gyrus than all males. **Figure-7b:** The ROI analysis bar graph showed decreased percent BOLD signal in maltreated males in the lingual gyrus to *fear target versus scrambled target* compared with the control males and control females;. but not compared with the maltreated females, suggesting that the main gender findings were mainly carried by the lower BOLD signal seen in maltreated males compared to control males and females. **Figure-7c:** Gender x Group effect on a BOLD signal in response to *fear target versus scrambled target* in the left inferior frontal gyrus (IFG). The brain image illustrates the whole-brain analysis demonstrating decreased percent BOLD signal change in the maltreated males compared with the control males for IFG and postcentral gyrus. **Figure-7d:** The graph illustrates decreased percent BOLD signal in maltreated males compared with maltreated and control female groups, and control males in the IFG (also called the vlPFC). The bar graphs show the ROI analysis confirming the whole-brain analysis. Post-hoc analyses (i.e., “*”) indicates significant ROI differences between gender groups (Dunnett’s Method, p<.05).

Table 1

Demographic and Clinical Characteristics of the Study Participants

	Healthy Control Subjects Mean (SD)			Maltreated Pediatric Subjects Mean (SD)					
	Control N=45	**Control Females N=26**	**Control Males N=19**	**Maltreated N=29**	**Maltreated Females N=13**	**Maltreated Males N=16**	**Group**	**Gender**	**Group x Gender**
Age (years) (Age range)	12.0 (2.5) (8–16.8)	13.0 (2.6) (8.1–16.8)	12.6 (2.5) (8.3–16.8)	12.8 (2.5) (8–16.6)	12.6 (2.2) (9–16.2)	11.5 (2.8) (8–16.6)	$F_{1,70}$ =1.56 p=0.22	$F_{1,70}$ =1.48 p=0.23	$F_{1,70}$ =0.26 p=0.61
SES	44.2 (10.6)	40.5(11.6)	49.2 (6.6)	35.9 (15.0)	35.8(14.7)	36. (13.66)	$F_{1,70}$ =10.64 p=0.002	$F_{1,70}$ =2.63 p=0.11	$F_{1,70}$ =2.42 p= 0.124
FSIQ	109.5(16.1)	107.4(17)	112.3 (15)	94.9 (13.8)	91.5 (12)	97.6 (15)	$F_{1,70}$ =10.50 p<0.0001	$F_{1,70}$ =2.22 p=0.14	$F_{1,70}$ =0.02 p=0.878
Race (Caus/AA/other)	26/14/5	15/9/2	11/5/3	13/14/2	3/8/2	10/6/0	X^2=3.7 P=0.45	X^2=2.4 P=0.67	X^2=12.8 P=0.38
Handed-ness Right/Left	43/2	25/1	18/1	27/2	11/2	16/0	FET P=0.64	X^2=.84 P=0.34	X^2=3.6 P=0.31
CBCLtotal T-score	39.2 (9.2)	39.6 (8.9)	38.6 (9.9)	61.6 (10.4)	61.8 (11.5)	61.5 (9.8)	$F_{1,70}$ =90.7 p<0.0001	$F_{1,70}$ =0.07 p=0.80	$F_{1,70}$ =0.02 p=0.87
CBCL inter T-score	44.3 (8.1)	43.8(8.2)	44.9 (8.1)	59.4 (9.5)	58.6 (9.8)	60.0 (9.5)	$F_{1,70}$ =50.68 p<0.0001	$F_{1,70}$ =0.35 p=0.558	$F_{1,70}$ =0.01 p=0.944
CBCLexter T-score	39.2 (8.0)	39.9(6.7)	40.7 (9.6)	61.4 (12.5)	63.2 (13.5)	59.9 (11.8)	$F_{1,70}$ =77.57 p<0.001	$F_{1,70}$ =0.24 p=0.626	$F_{1,70}$ =0.71 p=0.402

SES=social economic status; FSIQ = Full Scale IQ estimated from 2-factors;

FET= Fisher's Exact Test

Caus= Causician; AA = African American; Other = Multi-racial;

CBCL=child behavior checklist; CBCL inter T-Score =CBCL internalizing T-score; CBCL exter T-Score =CBCL externalizing T-score;

Note there were no statistical differences in sex distribution between the Healthy Control and Maltreated Groups (X^2=1.19, p= .28)

Table 2

Maltreatment, PTSD Symptoms, and Clinical Characteristics of Male and Female Maltreated Youth

Variable (SD)	Maltreated Males (N=16)	Maltreated Females (N=13)	Statistic	p
History of Maltreatment Types				
Witnessing Intimate Partner Violence (Yes/No)	13/3	10/3	FET	0.56
Physical Abuse (Yes/No)	16/0	13/0		NS
Sexual Abuse (Yes/No)	2/14	3/10	FET	0.89
Neglect Failure to Supervise (Yes/No)	14/2	11/2	FET	0.62
Failure to Provide (Yes/No)	9/7	10/3	FET	0.94
Mean Number of Maltreatment Types (SD)	3.4±0.9	3.6±1.0	$F_{1,27}$=.45	.51
PTSD Symptoms and Co-morbidity at time of MRI scan				
Total PTSD symptoms	7.8±4.3	7.9±4.8	$F_{1,27}$=0.01	0.91
PTSD Cluster B symptoms	2.3±1.4	2.4±1.8	$F_{1,27}$=0.014	0.90
PTSD Cluster C symptoms	2.9±2.1	2.8±2.3	$F_{1,27}$=0.001	0.97
PTSD Cluster D symptoms	2.6±1.3	2.7±1.8	$F_{1,27}$=0.05	0.82
PTSD (Yes/No)	10/6	6/7	X^2=0.78	0.38
Major Depression (Yes/No)	7/9	6/7	X^2=0.23	0.88
Dysthmia (Yes/No)	3/13	3/10	FET	0.77
Oppositional Defiant Disorder (Yes/No)	9/7	6/7	X^2=0.29	0.59
ADHD-Combined Type (Yes/No)	6/10	5/8	X^2=0.003	0.96
ADHD-Predominantly Inattentive Type (Yes/No)	8/8	5/8	X^2=0.39	0.53
ADHD-Predominantly Hyperactive-Impulsive Type (Yes/No)	1/15	0/13	FET	0.55
Total Number of Axis I disorders	2.2±1.1	2.1±1.2	$F_{1,27}$=0.004	0.95

FET= Fisher's Exact Test; ADHD = Attention-Deficit/Hyperactivity Disorder

Table 3

Task Performance Characteristics of the Study Participants

	Healthy Control Subjects Mean (SD)			Maltreated Pediatric Subjects Mean (SD)			Statistics		
	Control N=45	**Females N=26**	**Males N=19**	**Maltreated N=29**	**Females N=13**	**Males N=16**	**Group**	**Gender**	**Group x Gender**
RT fear target (ms)	641.6(99.67)	638.5(110.5)	645.8 (85.4)	655 (98.2)	658.4 (88.9)	653.9 (88.0)	$F_{1,70}$=0.34 p=0.564	$F_{1,70}$ =0.00 p=0.954	$F_{1,70}$ =0.04 p=0.808
RT calm target (ms)	634.5(97.8)	624.8(103.2)	647.9 (91.0)	661.7 (109.4)	662.8 (94.5)	660.8 (123.3)	$F_{1,70}$=1.05 p=0.309	$F_{1,70}$ =0.18 p=0.671	$F_{1,70}$ =0.25 p=0.616
RT scrambled target (ms)	632.3(102.7)	624.1(111.1)	643.5 (91.7)	651.2(100.9)	647.9 (86.2)	653.9 (108.0)	$F_{1,70}$ =0.48 p=0.493	$F_{1,70}$ =0.26 p=0.613	$F_{1,70}$ =0.07 p=0.786
OE of fear target (%)	1.1(3.1)	0.8(2.2)	1.5(4.0)	1.45(3.1)	1.1 (3.3)	1.7 (3.1)	$F_{1,70}$=0.12 p=0.73	$F_{1,70}$=0.73 p=0.394	$F_{1,70}$=0.00 p=0.981
OE of calm target (%)	0.97(2.7)	0.8(2.2)	1.1 (3.4)	1.6(3.1)	1.1 (3.3)	2.0 (2.9)	$F_{1,70}$=0.66 p=0.420	$F_{1,70}$=0.68 P=0.414	$F_{1,70}$ =0.21 P=0.649
OE of scrambled target (%)	0.84(2.9)	0.7(2.7)	1.0(3.4)	1.2(2.5)	1.3(3.1)	2.0(3.1)	$F_{1,70}$=0.09 p=0.764	$F_{1,70}$=2.78 p=0.10	$F_{1,70}$=1.38 P=0.244

RT= reaction time in milliseconds(ms); OE=Omission Error in percentage (%);

Fear target = Target detection while viewing Fearful faces; calm target = Target detection while viewing neutral or “calm” faces;

Scrambled target = Target detection while viewing scrambled faces.

Table 4

Whole Brain Analyses: Interaction Effect in Activation to Fear versus Calm and Fear vs. Scramble Pictures.

	Regions	Brodmann Area	Cluster size	Peak Z value	X_{MNI}	Y_{MNI}	Z_{MNI}	ROI Analysis			
								SES adjusted		FSIQ adjusted	
								F	p	F	p
Interaction Effect Fear vs. Calm											
Control females > Maltreated females	Left Dorsal Medial Prefrontal Cortex/ Paracingulate Gyrus	BA9	1276	3.69	−4	50	18	12.05 (4.5	.001 .04)^{A}	11.97 (6.1	.001 <0.02)^{A}
	Right Dorsal Medial Prefrontal Cortex			3.44	10	56	14				
Maltreated males > Control males	Right Calcarine/Occipital Lobe		1085	5.28	10	−94	−6	4.67 (6.6	.04 .015)^{A}	4.96 (6.9	.03 .01)^{A}
	Right Lingual Gyrus/Fusiform Gyrus	BA18		3.83	24	−90	−14				
	Right Intracalcarine /Lingual Gyrus/ Supracalcarine Cortex	BA18		3.51	4	−82	2				
	Left Intracalcarine Cortex/Lingual Gyrus			3.58	−6	−86	−2				
Fear vs. Scramble											
Control females > Maltreated females	Right Cerebellum V		759	4.57	8	−60	−12	20.57 (8.9	<.0001 .006)^{A}	9.99 (2.5	.003 .12)^{A}
	Right Cerebellum I, II, III, IV, & V			3.98	4	−56	−16				
	Left Cerebellum VI			3.05	−12	−70	−18				
	Left Cerebellum I, II, III, IV, & V			4.22	−2	−58	−10				
Maltreated females > Control females	Left Lateral Occipital Cortex, Middle Temporal Lobe/ Angular Gyrus	BA39	482	4.26	52	−74	18	19.47 (13.8	<.0001 .0008)^{A}	16.60 (9.5	.0003 .004)^{A}
	Left Lateral Occipital Cortex/Left Angular Gyrus			3.5	−46	−64	52				
Maltreated males > Control males	Right Cerebellum Crus I		2150	5.22	24	−76	−28	6.74 (2.36	.01 .025)^{A}	8.84 (2.47	.0056 .02)^{A}
	Right Cerebellum Crus I	BA18		4.31	30	−92	−22				
	Right Cerebellum VI, VIIb, VIIIa, Vermis VI			4.14	8	−66	−28				
	Right Vermis VI, VIIb, Vermis Villa			4.16	1	−64	−28				
	Right Vermis VI	BA18		4.13	4	−92	−16				
	Occipital Fusiform Gyrus//Lingual Gyrus			4.16	0	−64	−28				

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Regions	Brodmann Area	Cluster size	Peak Z value	X_{MNI}	Y_{MNI}	Z_{MNI}	ROI Analysis			
							SES adjusted		FSIQ adjusted	
							F	p	F	p
Left Middle Temporal Pole/ Temporal Fusiform Cortex (anterior and posterior divisions)		502	4.45	−38	12	−32	6.56 (4.85	.015 <.04)[A]	5.77 (4.26	.02 <0.05)[A]
Left Middle Temporal Lobe	BA21		3.66	−54	−6	−22				
Left Parahippocampus	BA35		3.52	−24	−14	−30				
Left Hippocampus			3.35	−34	−14	−16				
Left Precentral and Postcentral Gyrus	BA6	452	4.08	−2	−32	66	3.25 (2.66	.08 .11)[A]	4.08 (4.25	.05 <0.05)[A]
Left Precentral and Postcentral Gyrus/Precuneous Cortex			4.02	0	−40	68				
Right Supplementary Motor Cortex	BA6		2.5	6	−18	66				

[A] Under ROI adjusted analyses in parentheses throughout are further analyses controlling for medication status by excluding maltreated subjects on medications in the general linear models.

Regions were labeled in MNI coordinates with the FSL Atlases: Harvard-Oxford Cortical Structural Atlas, Harvard-Oxford Subcortical Structural Atlas, Cerebellar Atlas in MNI 152 space after normalization with FNIRT, and Talairach Daemon Labels for Brodmann areas.

Table 5

Whole Brain Analyses: Main Effect or Interaction Effect of the ANOVA Analysis in Activation to Targets.

	Regions	Brodmann Area	Cluster size	Peak Z value	X_{MNI}	Y_{MNI}	Z_{MNI}	ROI Analysis			
								SES adjusted		FSIQ adjusted	
								F	p	F	p
Fear target vs calm target											
Interaction Effect											
Control males > Maltreated males	Left Precentral Gyrus/Left Middle Cingulum/ Posterior Cingulate Cortex	BA31	418	3.61	−16	−28	42	8.82 (7.60	.0056 <0.01)^{B}	9.45 (8.34	.004 .007)^{B}
	Right and Left Precuneus Cortex	BA7		2.66	2	−60	34				
Fear target vs scrambled target											
Main Effect											
Control>Maltreated	Left Precuneus Cortex/Cingulate Gyrus	BA31	1030	3.94	−6	−46	46	6.43 (9.43	.01 .004)^{B}	6.86 (8.62	.01 <0.005)^{B}
	Left Precuneus/ Cortex/Cingulate Gyrus Posterior Division			3.81	0	−48	44				
	Left Precuneus Cortex/Cingulate /Middle Cingulum/Postcentral Gyrus			3.42	−12	−42	48				
	Left Precentral Gyrus/Paracentral Cortex	BA6		3.38	−4	−26	62				
	Right Supplementary Motor Cortex/Precentral Gyrus	BA6		3.34	2	−10	54				
Gender Effect											
Females >Males	Left Lingual Gyrus		1602	3.67	−22	−50	−4	5.35 (2.93	.02 .09)^{B}	5.02 (2.79	.03 .10)^{B}
	Right Lingual Gyrus	BA18		3.65	14	−70	−4				
	Left Temporal Fusiform Cortex, posterior division/Temporal Occipital Fusiform Cortex/ Parahippocampal Gyrus	BA37		3.56	−28	−40	−18				
	Right cerebellum I, II, III, IV, and V			3.39	14	−44	−22				
	Left Precentral Gyrus/ Postcentral Gyrus	BA4	540	3.55	−34	−20	68	15.69 (10.8	.0002 <.002)^{B}	16.38 (11.4	.0001 .001)^{B}
	Left Postcentral Gyrus			3.12	−34	−32	64				

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	Regions	Brodmann Area	Cluster size	Peak Z value	X_{MNI}	Y_{MNI}	Z_{MNI}	ROI Analysis			
								SES adjusted		FSIQ adjusted	
								F	p	F	p
	Left Postcentral & Precentral Gyrus	BA3		3.1	−34	−28	64				
Interaction Effect											
Control males > Maltreated males	Left Precuneus/ Posterior Cingulate		739	3.64	0	−48	44	10.36 (14.5	.003 .0007)[B]	7.92 (9.37	.008 <0.005)[B]
	Left Precuneus Cortex	BA7		3.3	−6	−48	54				
	Right Precuneus Cortex/ Posterior Cingulate Gyrus	BA7		3.55	6	−44	48				
	Left Precentral and Postcentral Gyrus	BA4	483	3.68	−44	−14	44	.07 (0.01	.80 .99)[B]	.01 (.33	.92 .57)[B]
	Left Inferior Parietal/ Left Anterior Supramarginal Gyrus	BA40		3.12	−62	−32	46				
	Left Precentral/ Middle Frontal Gyrus	BA4		2.87	−40	−12	54				
	Left Inferior Frontal Gyrus, Pars Opercularis (ventral lateral prefrontal cortex, vlPFC), Left Middle Frontal Gyrus		473	3.52	−46	12	28	17.14 (18.8	.0002 .0002)[B]	7.55 (8.01	.01 .008)[B]
	Left Precentral Gyrus/Left Middle Frontal Gyrus /Left Inferior Frontal Gyrus	BA9		3.28	−50	8	36				
	Left Middle Frontal Gyrus /Left Inferior Frontal Gyrus Pars Opercularis, Pars Triangularis			3.27	−38	18	26				
	Left Precentral Gyrus			2.76	−40	−2	30				
	Left Precentral Gyrus			2.69	−36	−2	26				

[B] Under ROI adjusted analyses in parentheses throughout are further analyses controlling for medication status by excluding all maltreated subjects on medications in the general linear models.

Regions were labeled in MNI coordinates with the FSL Atlases: Harvard-Oxford Cortical Structural Atlas, Harvard-Oxford Subcortical Structural Atlas, Cerebellar Atlas in MNI 152 space after normalization with FNIRT, and Talairach Daemon Labels for Brodmann areas.