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Sex differences in socioemotional functioning, attentional bias, and gray matter volume in maltreated children: A multilevel investigation

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Abstract

While maltreatment is known to impact social and emotional functioning, threat processing, and neural structure, the potentially dimorphic influence of sex on these outcomes remains relatively understudied. We investigated sex differences across these domains in a large community sample of children aged 10 to 14 years ($n = 122$) comprising 62 children with verified maltreatment experience and 60 well-matched nonmaltreated peers. The maltreated group relative to the nonmaltreated comparison group exhibited poorer social and emotional functioning (more peer problems and heightened emotional reactivity). Cognitively, they displayed a pattern of attentional avoidance of threat in a visual dot-probe task. Similar patterns were observed in males and females in these domains. Reduced gray matter volume was found to characterize the maltreated group in the medial orbitofrontal cortex, bilateral middle temporal lobes, and bilateral supramarginal gyrus; sex differences were observed only in the supramarginal gyrus. In addition, a disordinal interaction between maltreatment exposure and sex was found in the postcentral gyrus. Finally, attentional avoidance to threat mediated the relationship between maltreatment and emotional reactivity, and medial orbitofrontal cortex gray matter volume mediated the relationship between maltreatment and peer functioning. Similar mediation patterns were observed across sexes. This study highlights the utility of combining multiple levels of analysis when studying the "latent vulnerability" engendered by childhood maltreatment and yields tentative findings regarding a neural basis of sex differences in long-term outcomes for maltreated children.

Childhood maltreatment is a robust and substantiated risk factor for a wide range of psychiatric disorders (Gilbert et al., 2009) including depression, anxiety, and posttraumatic stress disorder (Anda et al., 2006; De Bellis, 2001; Scott, Smith, & Ellis, 2010). It is notable that if psychiatric disorders do emerge following childhood maltreatment, they are likely to be particularly severe, develop earlier (Hovens et al., 2010), and show an attenuated response to standard treatment (Hovens et al., 2012; Nanni, Uher, & Danese, 2012) compared to psychiatric disorder as it presents in those with no history of abuse. Sex appears to impact both the nature and the severity of psychiatric outcome following maltreatment. It has been shown that maltreatment-related psychiatric disorders are associated with a greater preponderance of internalizing symptomatology in females but greater preponderance of externalizing symptomatology in males (Bos et al., 2011; Keyes et al., 2012). There is also some evidence from prospective studies that maltreatment has a more detrimental impact on males (De Bellis & Keshavan, 2003; McGloin & Widom, 2001) although at least one study has reported that females are more affected (Thompson, Kingree, & Desai, 2004). In light of these findings, the relative dearth of studies systematically investigating maltreatment-related sex differences in social, cognitive, and neurobiological is surprising, because investigation here may help shed light on the sex-dependent differences observed in relation to psychiatric outcome.

Latent Vulnerability and Multilevel Approaches

The theory of latent vulnerability has recently been proposed to provide a framework for understanding the link between maltreatment and psychiatric disorder (McCrory & Viding, 2015). According to this theory, childhood maltreatment results in alterations at multiple levels of biological and neurocognitive functioning, reflecting calibration in response to early risk environments. While such changes may have short-term benefits, they can serve to embed heightened vulnerability to psychiatric disorder that may manifest following exposure to future stressors. It is suggested that the identification of makers of latent vulnerability that are predictive of future disorder, particularly in neurocognitive systems implicated in socioemotional and cognitive functioning, can inform a preventative psychiatry strategy that aims to offset risk trajectories before disorders emerge. However, under-

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standing the mechanisms that underpin latent vulnerability requires a multilevel approach that links biological, cognitive, and behavioral outcomes in ways that transcend diagnostic categories (Cicchetti & Blender, 2006; Cicchetti & Curtis, 2007; Cicchetti & Dawson, 2002).

The Impact of Maltreatment on Social and Emotional Functioning

Maltreatment experience has been associated with aspects of social and emotional functioning that may increase vulnerability or resilience to later psychiatric disorder. For example, social and peer functioning impairments that characterize many maltreated individuals (Bolger & Patterson, 2001; Bolger, Patterson, & Kupersmidt, 1998; Kim & Cicchetti, 2010; Rogosch, Cicchetti, & Aber, 1995) may compromise the degree to which successful peer relationships can buffer the impact of early life stress (Evans, Steel, & DiLillo, 2013; McLewin & Muller, 2006; Pepin & Banyard, 2006). At the psychological level, personal attributes such as a child's emotional reactivity, sense of mastery, and sense of relatedness have been linked to an increased risk of negative behavioral outcomes and trauma symptomatology in maltreated individuals (Kim & Cicchetti, 2003; McLaughlin et al., 2010; Toth & Cicchetti, 1996). In line with the finding that maltreated female adolescents are more resilient than their maltreated male peers (DuMont, Widom, & Czaja, 2007), we expected that the maltreated females, compared to the maltreated males, may show higher levels of mastery and social relatedness, and lower emotional reactivity. It is important to establish whether the social and emotional functioning following maltreatment is similar for boys and girls, or whether maltreatment exerts sex-specific effects across these domains in ways that could account for the observed pattern of sex-dependent differences in psychiatric outcome.

The Impact of Maltreatment on Cognitive Processes: Threat Processing

At the cognitive level, there is now a substantive body of research pointing to altered processing of threat cues in maltreated children, in particular a pattern of threat vigilance at the psychological and neural levels (Pine et al., 2005; Pollak, Cicchetti, Klorman, & Brumaghim, 1997; Pollak, Klorman, Thatcher, & Cicchetti, 2001; Pollak & Sinha, 2002; Pollak & Tolley-Schell, 2003; Shackman, Shackman, & Pollak, 2007). For example, maltreated children assimilate and remember pictures of angry facial expressions and cues related to aggression better than their nonmaltreated peers, even when those cues are task irrelevant (Rieder & Cicchetti, 1989), display faster reaction times when labeling fearful facial expressions (Pollak & Sinha, 2002), and show heightened amygdala reactivity to threat cues, even when these are presented outside of conscious awareness (McCrory et al., 2011, 2013). Differences in processing threat-related cues appear present by 15 months of age in infants exposed to a maltreating home environment (Curtis & Cicchetti, 2013).

However, there is also preliminary evidence that children who have experienced maltreatment can also show attentional *avoidance* of threat cues (Pine et al., 2005; but see also Romens & Pollak, 2012, for a different pattern of findings). In a study of attention allocation to threat in maltreated children using a dot-probe paradigm, Pine et al. (2005) reported an attentional bias away from threat. While the finding of attentional avoidance in Pine et al.'s (2005) study may at first appear at odds with the general literature on threat vigilance in maltreatment research, it is consistent with an increasing recognition in the adult clinical literature that both threat avoidance and threat vigilance may be associated with psychiatric risk (Bar-Haim et al., 2010). One possibility is that such avoidance may represent a strategy to attenuate the impact of threat cues (Wald et al., 2013) in those individuals who have difficulty in regulating their emotional responses. It is not that such a pattern is inherently problematic, but rather it becomes maladaptive when attentional allocation to threat fails to align with environmental demands (Bar-Haim et al., 2010). In several longitudinal studies of civilians and soldiers, it has now been demonstrated that a pattern of threat avoidance during stress or imminent-stress exposure predicts future posttraumatic stress disorder (PTSD) symptomatology (Wald et al., 2011, 2013). Over time, a pattern of sustained avoidance may serve to inhibit successful emotional processing of environmental threat, and as a result, threat-related cues may maintain their anxiety-provoking properties (Rachman, 2004). In other words, greater emotional reactivity may prompt an avoidant response, which over time may serve to further compromise processing and regulation of subsequent threat cues. If this is the case for maltreated children, one would expect that a pattern of threat avoidance may be associated with underlying difficulties in emotional reactivity and regulation, at least for some of these children.

Sex Differences in Attentional Biases

Although children exposed to maltreatment presenting with PTSD show an attentional bias away from threat (Pine et al., 2005), it is not known if such a bias is present in the absence of concurrent psychiatric disorder, nor if boys and girls show comparable patterns. Studies of attentional bias to negative stimuli in healthy individuals (Pfabigan, Lamplmayr-Kragl, Pintzinger, Sailer, & Tran, 2014) and in those with depression (Peckham, McHugh, & Otto, 2010) appear to find no effect of sex, but it remains to be established whether the strength of any attentional bias would be similar in girls and boys who have been exposed to maltreatment.

The Impact of Maltreatment on Cortical Structure: Gray Matter Volume (GMV)

On a neural level, maltreatment has been shown to be significantly associated with differences in GMV in a number of brain regions. A recent meta-analysis that combined 12 studies of adults and children reported an extensive pattern of reduced GMV in maltreated individuals in several areas, including the orbitofrontal cortex, superior temporal gyrus extending to the amygdala, insula, and parahippocampal and middle temporal gyri (Lim, Radua, & Rubia, 2014). However, it is necessary to be cautious in assuming specificity of all these GMV differences to maltreatment experience in children, given that this meta-analysis combined studies of children and adults, the majority of which comprised participants presenting with comorbid psychiatric disorders. Two studies of community samples of children referred to social services (rather than clinic referred) have reported reduced GMV in a subset of these regions, specifically the orbitofrontal cortex (OFC) and left middle temporal gyrus (De Brito et al., 2013; Hanson et al., 2010), with no volumetric differences observed in the hippocampus or amygdala in either study. This highlights the importance of taking the developmental stage of the sample into account and carefully controlling those factors that may contribute to individual differences in GMV over and above maltreatment experience.

We know little about the functional significance of maltreatment-related GMV differences, and whether they represent true markers of latent vulnerability predictive of future psychiatric disorder (McCrory & Viding, 2015). One important contribution has been a study by Hanson et al. (2010) of 31 community-referred children using tensor-based morphometry. It was found that reduced OFC volume was associated with poorer social functioning across a number of domains, suggesting that reduced OFC GMV following maltreatment may impair the ability to respond to and regulate emotional and social processes (Hanson et al., 2010). However, this study was unfortunately limited by a focus on children who had experienced physical abuse, making it difficult to generalize about the significance of reduced OFC GMV in children who have experienced different forms of abuse. In addition, the analysis did not formally test for a mediation effect of OFC GMV on the relation between childhood trauma and social functioning.

Sex Differences and the Impact of Maltreatment on GMV

As in the cognitive domain, there remains a relative paucity of studies investigating the potential interaction between maltreatment and sex in relation to brain structure. This is a pertinent issue given that males have been reported to possess greater GMV than females in the amygdala, thalamus, and putamen and in cortical surface structures known to show reduced volume following maltreatment experience, including the middle temporal gyrus and right occipital gyrus (Chen, Sachdev, Wen, & Anstey, 2007; Koolschijn & Crone, 2013; Peper et al., 2009). To date there have been few studies that have investigated sex differences in GMV in maltreated children (De Bellis & Keshavan, 2003; De Bellis et al., 1999; De Bellis & Kuchibhatla, 2006; Edmiston et al., 2011). In one set of important early studies De Bellis and colleagues have shown that maltreated boys with PTSD show smaller cerebral volumes and larger lateral ventricular volumes compared to maltreated girls with PTSD (De Bellis & Keshavan, 2003; De Bellis et al., 1999), suggesting that maltreatment experience has a more pronounced impact on brain structure in boys than in girls. However, it is not clear in these studies which GMV differences are driven by maltreatment experience and which by the influence of the PTSD. To our knowledge, there has been one correlational study exploring sex differences and the impact of maltreatment on regional GMV in a single group of children exposed to adversity (Edmiston et al., 2011). Unfortunately, socioeconomic status (SES) and IQ, factors known to covary with maltreatment experience, were not accounted for in the analysis, making it difficult to be confident that any of the observed sex differences were attributable to maltreatment exposure.

The Present Study

The present study sought to investigate how sex influences the impact of documented childhood maltreatment across multiple levels of analysis. In one of the largest brain imaging studies of maltreated children published to date, we set out to investigate sex differences across cognitive and neural levels as well as possible mechanisms that may influence putative latent vulnerability. Specifically, we aimed to understand the significance of any maltreatment-related differences in GMV or attentional bias in terms of behavioral outcomes that could serve to increase risk of future symptomatology. By recruiting a community-referred (rather than clinic-referred) sample, we reduced the likelihood that any observed differences were driven by psychiatric disorder rather than maltreatment experience.

The first of our three aims was to investigate the impact of maltreatment on aspects of social and emotional functioning relevant to psychiatric vulnerability and explore possible sex differences. It was predicted that both boys and girls exposed to maltreatment, relative to their nonmaltreated peers, would show similar impairments in social functioning, as measured by the peer problems scale of the Strengths and Difficulties Questionnaire (SDQ). We also predicted poorer performance in maltreated versus nonmaltreated children in emotional reactivity, mastery, and social relatedness (as measured by the Resiliency Scales for Children and Adolescents [RSCA]). The RSCA measures aspects of emotional and social functioning thought to be associated with resilience. We predicted that the maltreated females, compared to the maltreated males, may show higher levels of mastery and social relatedness, and lower emotional reactivity, in line with one previous study (DuMont et al., 2007).

Our second aim was to investigate the impact of maltreatment on attentional threat bias using a dot-probe task. On the basis of previous findings using a dot-probe paradigm with an identical emotional stimulus duration of 500 ms, we predicted a pattern of threat avoidance in children who had experienced maltreatment (Pine et al., 2005) and also explored sex differences in task performance. We also hypothesized that greater attentional threat avoidance would be observed in those individuals reporting greater emotional reactivity, and finally examined whether attentional avoidance mediates the relationship between maltreatment experience and emotional reactivity.

Our third aim was to investigate the impact of maltreatment on GMV and explore possible sex differences. We wished to delineate those regions associated with maltreatment at both the whole-brain level and in five regions of interest consistent with the existing literature, including the amygdala, hippocampus, prefrontal cortex, temporal lobe, and cerebellum (De Brito et al., 2013; Lim et al., 2014). Based on this prior literature, we expected to observe reduced GMV in both the OFC and bilateral middle temporal gyrus (De Brito et al., 2013; Hanson et al., 2010; Lim et al., 2014). We did not predict atypical GMV in either the amygdala or the hippocampus in line with previous studies of maltreated children (McCrory, De Brito, & Viding, 2010) but nevertheless wished to test the possibility that these prior null findings may have been due to a lack of power. Following Hanson et al. (2010), we predicted that reductions in GMV in the OFC would negatively correlate with peer problems (as measured by the SDQ in our study) and that GMV in the OFC would partially mediate the relationship between maltreatment and peer problems across the sexes. Given the robustness of findings of atypical mOFC GMV in mixed samples of maltreated males and females (Lim et al., 2014), and the similarities between sexes in the pathways from maltreatment to peer rejection (Bolger & Patterson, 2001), we predicted that the mOFC GMV would be associated with peer problems and that the mOFC GMV would at least partially mediate the relationship between maltreatment and peer problems.

Method

Participants

A total of 122 children aged 10–14 years were recruited from London and the Southeast as part of two related studies investigating the neural correlates of childhood maltreatment. Children with documented experiences of maltreatment (physical, sexual, emotional abuse, or neglect; total $n = 62$) were recruited from Social Services (SS) departments in London ($n = 52$) and affiliated adoption agencies ($n = 10$). An additional $n = 60$ comparison children who had no documented history of maltreatment were recruited from primary and secondary schools, as well as after-school youth clubs in the London area, and via newspaper and Internet advertisement. Exclusion criteria for the comparison group included any previous contact with SS with regard to the quality of care or maltreatment of the child. Participants in the maltreated and comparison groups were matched on age, pubertal status, sex, handedness, cognitive ability, socioeconomic status, and ethnicity (see Table 1).

Assent to participate in the study was obtained for all children. For children living with their biological or adoptive parents, consent was obtained from at least one parent. Where there was shared parental responsibility with SS, consent was obtained from the biological parent of the child (if contactable), and SS. Exclusion criteria for all participants included a diagnosis of learning disability, pervasive developmental disorder, neurological abnormalities, standard magnetic resonance imaging (MRI) contraindications (e.g., ferromagnetic implants or braces) and cognitive ability (Wechsler Abbreviated Scale of Intelligence score < 70). All procedures in the study were approved by University College London Research Ethics Committee (0895/002). A subset of participants included in the present study ($n = 38$; maltreated $= 18$, nonmaltreated $= 20$) had been included in a previous study examining the impact of maltreatment on GMV (De Brito et al., 2013). However, the same MRI scanner was used and an identical magnetization prepared rapid gradient echo sequence employed for all participants.

Measures

Sociodemographic and psychiatric symptomatology variables.

Maltreatment history. The SS case files for the maltreated group were independently rated on the child-maltreatment rating by Kaufman, Jones, Stieglitz, Vitulano, and Mannarino (1994). The 5-point scale was rated from 0 = *no abuse present* to 4 = *evidence of severe abuse* by the child's social worker or the adoptive parent based on information provided by social services. The maltreated group children were characterized primarily by neglect ($n = 51$, $M = 3.24$, $SD = 1.12$) and emotional abuse ($n = 58$, $M = 2.93$, $SD = 0.92$) and to a lesser extent by physical ($n = 12$, $M = 1.92$, $SD = 1.16$) and sexual ($n = 8$, $M = 2.29$, $SD = 1.38$) abuse. Only 6 participants experienced just one form of maltreatment (9.7%), while 25 participants experienced two forms of maltreatment (40.3%), with the remaining 31 participants experiencing three or more forms of maltreatment (50%). Twenty-seven cases were double-rated by a senior social work professional; there was 70.37% agreement in relation to the presence of neglect, 88.88% agreement in relation to physical abuse, 92.59% agreement in relation to sexual abuse, and 96.30% agreement in relation to emotional abuse.

Cognitive ability. Participants were administered the vocabulary and matrix reasoning subtests of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) in order to provide an estimated full scale intelligence quotient.

SES. Current SES was assessed using information collected from the parent or caregiver, including highest level of education, household income, and current occupation. Highest level education was rated on a 6-point scale from 0 = *no formal qualifications* to 5 = *postgraduate qualification*. Household income was rated on an 8-point scale from 1 = *£0–£10,000* to 8 = *£60,000–£70,000+*. Current occupa-

Table 1. *Demographic characteristics and questionnaire data for the maltreated and nonmaltreated groups*

Sociodemographic Measures	Control ($n = 60$)		MT ($n = 62$)		*p*
Tanner stage					.61
Pre/early pubertal (%)	15 (25)		22 (35)		
Midpubertal (%)	23 (38)		24 (39)		
Late/postpubertal (%)	22 (37)		16 (26)		
Sex, males (%)	25 (42)		33 (53)		.20
Ethnicity, Caucasian (%)	31 (52)		39 (63)		.21
Handedness, right handed (%)	53 (88)		46 (74)		.37
	Mean	*SD*	Mean	*SD*	
Age (years)	12.68	1.14	12.24	1.52	.07
WASI, two-scale subset[a]	108.88	10.49	104.81	13.23	.06
Puberty development scale	2.22	0.66	2.04	0.71	.15
SES composite score	3.15	0.87	2.89	1.08	.22
Psychiatric Symptomatology					
TSCC					
Anxiety	45.26	11.17	45.72	15.95	.87
Depression	44.19	9.94	44.08	14.55	.97
Anger	41.84	9.07	43.80	13.35	.42
Posttraumatic stress	43.02	8.30	45.60	14.48	.31
Dissociation	43.28	11.46	45.88	13.92	.33
Dissociation, overt	45.28	9.52	45.78	13.68	.84
Dissociation, fantasy	44.33	11.28	46.90	14.63	.35
SDQ					
Emotional symptoms	2.38	2.05	3.22	2.65	.06
Conduct problems	1.32	1.42	2.70	2.05	.00[b]
Hyperactivity/inattention	2.68	1.99	4.23	2.65	.00[b]
Peer problems	1.22	1.27	2.03	1.90	.01[b]
Total difficulties	7.46	5.05	11.48	7.42	.01
Social and emotional functioning					
Peer problems, SDQ	1.22	1.27	2.03	1.90	.01[b]
Mastery, RSCA	51.86	11.06	46.93	9.65	.02[b]
Relatedness, RSCA	51.29	13.64	49.67	10.59	.50
Reactivity, RSCA	44.06	13.07	53.00	11.45	.00[b]

Note: All *p* values were derived from *t* tests with the exception of sex, ethnicity, handedness, and Tanner stage comparisons, which used chi-square tests. WASI, Wechsler Abbreviated Scale of Intelligence; SES, socioeconomic status; TSCC, Trauma Symptom Checklist for Children; SDQ, Strengths and Difficulties Questionnaire; RSCA, Resiliency Scale for Children and Adolescents.
[a]No participant scored below 70 or above 130 on the WASI.
[b]Survived false discovery rate correction ($q < 0.05$).

tion of the primary care giver was classified by a single researcher using the National Statistics Socio-economic Classification's Standard Occupation Classification 2000 manual (Office for National Statistics, 2005) on a four-class scale from 1 = *managerial and professional occupation* to 3 = *routine and manual occupation*, with 4 coding for participants who had never worked or were long-term unemployed. The measure of occupation was reverse coded, and a composite score was derived from the mean of these three scales, so that a greater score indicated a greater level of SES.

Pubertal status. Pubertal development was assessed with both the self-report and parent-rated eight-item Puberty Development Scale (Petersen, Crockett, Richards, & Boxer, 1988). An average pubertal development scale and a three-level indicator of pubertal development based upon Tanner stage were derived from these scores. There was a 72.3% agreement between parent- and child-reported three-level indicators of pubertal development.

Psychiatric symptomatology. The Trauma Symptom Checklist for Children (TSCC; Briere, 1996) was used to assess acute and chronic posttraumatic symptomatology and other symptom clusters. This 44-item self-report measure has five clinical scales (anger, depression, anxiety, posttraumatic stress, and dissociation) and two validity scales (under- and hyperresponse). Each item is rated on a 4-point scale from *never* to *almost all the time*. Cronbach α for the scales varied from 0.84 to 0.88. In addition, the emotional symptoms, conduct problems, and hyperactivity subscales of the SDQ

(Goodman, 1997), as well as the SDQ total difficulties score were compared across the groups. The SDQ items are rated from *not true* to *certainly true* on a 3-point scale. Cronbach α for the scales varied from 0.77 to 0.81.

Measures of social and emotional functioning. The SDQ (Goodman, 1997) was used to index current social functioning. Cronbach α for this scale was 0.65.

The RSCA (Prince-Embury, 2008), a 64-item self-report measure, was used to assess the personal attributes of the child that have been postulated to relate to resilient functioning. The scale is composed of three global scales capturing emotional reactivity, a sense of mastery, and a sense of relatedness. Each item is rated on a 4-point scale from *never* to *almost always*. Greater scores on the sense of mastery and relatedness scales indicate greater ability to cope with adverse circumstances and capacity to use relationships as a buffer against stress. Greater scores on the emotional reactivity subscale indicate greater arousability that may put an individual at risk in situations of adversity. Cronbach α for the scales varied from 0.77 to 0.89.

Dot-probe experimental task. Sixty-four photographs were selected from the well-validated NimStim set of facial expressions (Tottenham et al., 2009). Photographs included face pairs from 32 different actors (16 of whom were men), each pair presenting two facial expressions: one calm and the other either angry/threatening or happy. Given evidence suggesting that neutral faces may sometime be perceived as threatening (Donegan et al., 2003) especially among maltreated children (Pollak, Cicchetti, Hornung, & Reed, 2000), we used face pairs from a set of 30 calm faces from the NimStim set (Tottenham et al., 2009) as a baseline comparison. The ethnicity of the actors' was 57.14% Caucasian, reflecting a similar ethnic demographic to our study sample (57.40% Caucasian). Image size was standardized and all faces were presented in grayscale.

The experimental trials consisted of face pairs (size 7.5×5.5 cm) from the same actor presented side by side, one picture displaying an emotional expression, either happiness or threat, and the other displaying a calm expression. Each child was presented with one of two possible variations of the task depending on the study in which they were enrolled. They received either a total of 80 trials, 64 of which contained face pairs with an emotional expression, or a total of 72 trials, of which 48 trials contained face pairs with an emotional expression (the latter variation was embedded within a longer experimental protocol). Remaining trials were of calm face pairs. Half of the emotional expression face-pair trials were threatening trials and half were happy trials, and the side on which the emotional expression was displayed was counterbalanced. Order of trial presentation was randomized across participants. All trials began with a 500 ms centrally presented fixation cross and was followed by a face pair presented for 500 ms. Immediately following the presentation of the face pair, a single-asterisk dot probe was presented for 1100 ms on the left or right side of the screen. Subjects were instructed to press either the left or the right arrow button on a keyboard as quickly and as accurately as possible to indicate the location of the probe (right vs. left). The intertrial interval varied randomly between 750 and 1250 ms. Reaction time and accuracy data were recorded.

Analyses of social and emotional functioning

Two sample *t* tests were used within SPSS v.20 (IBM, Armonk, NY), to investigate the main effect of group on the SDQ peer problems scale, as well as the RSCA scales. Group × Sex interactions were investigated using 2×2 analysis of variance (ANOVA) in SPSS. Due to the number of *t* tests and ANOVAS, a false discovery rate correction was performed per behavioral measure to control for multiple comparisons (Benjamini & Hochberg, 1995).

Analysis of dot-probe experimental task

For the dot-probe task, incorrect trials were discarded and trials with latencies of <200 ms or greater than 2 *SD* above each participant's mean latency were also removed, in line with previous studies (Bradley, Mogg, White, Groom, & De Bono, 1999; Mogg & Bradley, 1999; Pine et al., 2005). Participants made incorrect responses, on average, in 3% of trials, and on average 4% of trials involved latencies outside of the latency parameter. In line with previous published data on similar dot-probe paradigms, participants were excluded from analysis if more than 25% of their trials had been discarded due to incorrect responses or excessive latency parameters as described above (Monk et al., 2006; Telzer et al., 2008). This resulted in the exclusion of 11 participants ($n = 5$ maltreated participants).

Attention bias scores were calculated using a standard formula (Dalgleish, Spinks, Yiend, & Kuyken, 2001; Mogg & Bradley, 1999; Pine et al., 2005) involving the subtraction of the participant's mean reaction time on trials where the emotion face (threatening or happy) and probe appeared on the same side of the screen (congruent trials) from the mean reaction time on trials where the emotion face and probe appeared on the opposite side of the screen (incongruent trials).

Positive bias scores reflect the tendency to monitor the emotional stimulus, while negative bias scores reflect the tendency to avoid the emotional stimulus. Independent *t* tests were used to examine group differences in the attentional bias scores. Significance was set at $p < .05$ (two tailed).

MRI acquisition

Participants were scanned with a 1.5 Tesla Siemens (Siemens Medical Systems, Munich, Germany) Avanto MRI scanner with a 32-channel head coil. A high-resolution, three-dimensional T1-weighted structural scan was acquired with a magnetization prepared rapid gradient echo sequence. The imaging parameters were the following: 176 slices; slice thickness = 1 mm; gap between slices = 0.5 mm; echo time = 2730 ms; repetition time = 3.57 ms; field of view = 256 mm × 256 mm; matrix size = 256 × 256; voxel size = 1 × 1 × 1 mm resolution. The scanning time was 5.5 min. Foam padding was used against the sides and the back of the head of the participant to minimize head motion. Ear buds attenuated scanner noise.

MRI processing and analysis

All T1-weighted images were visually inspected for abnormalities and defects, and the quality of each image was rated for quality in contrast and movement artifacts. If the image was thought to represent poor quality, the participant was excluded from the study. From an initial recruitment of 137 participants, a total of 15 participants (MT = 8, Con = 7) were excluded from the analysis due to concerns over image quality, resulting in a final sample of 122 (Table 1).

The structural images were processed using an optimized VBM approach following the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) within Statistical Parametric Mapping Software version 8 (SPM; Wellcome Department of Imaging Neuroscience, London) and the VBM8 toolbox (Christian Gaser, Department of Psychiatry, University of Jena) implemented in MATLAB R2012a (Mathworks, Sherborn, MA). Customized tissue probability maps were created in Montreal Neurological Institute (MNI) space for use with the VBM8 Toolbox. These customized tissue probability maps were produced using the matched template approach of the Template-O-Matic Toolbox based on the NIH study of normal brain development (NIH, Washington DC) for SPM with each participant's age and sex used as defining variables.

The origin of all T1-weighted images were manually set to the anterior commissure. The images were corrected for bias-field inhomogeneities and segmented into gray matter, white matter, and cerebrospinal fluid using the unified segmentation approach within the same generative model (Ashburner & Friston, 2005). A study specific template was generated iteratively using the diffeomorphic registration algorithm implemented in the DARTEL toolbox (Ashburner, 2007). Following this, nonlinear warping of the segmented gray matter images to the DARTEL template in MNI space within the VBM8 Toolbox allowed for high dimensional normalization. The voxel values in the gray matter segments were only multiplied to the nonlinear component of the registration to account for individual differences in brain size and to allow for the measurement of GMV instead of gray matter density. The modulated gray matter images were exported with an isotropic voxel resolution of 1.5 mm^3. Images were then smoothed with an 8-mm full width at half maximum Gaussian kernel. All gray matter images were checked for homogeneity using the covariance structure of each image with all other images to check for cerebral abnormalities or movement artifacts; however, no additional participants were excluded.

The main effect of maltreatment on GMV

Group differences in GMV between the maltreated and comparison groups were assessed using a two-sample t test, in SPM8. The model was implemented with age, sex, and IQ entered into the design matrix as covariates given their known association with brain anatomy (Giedd & Rapoport, 2010) and the trend-level group differences on age and IQ in the present sample.

We took a two-step approach to investigate the main effect of maltreatment exposure on GMV. We first applied a mask to constrain the analysis to a number of anatomical regions specified in our previous VBM analysis, including the amygdala, hippocampus, prefrontal cortex, temporal lobe, and cerebellum (De Brito et al., 2013). These regions of interest (ROI) were defined using the automated anatomical labeling as implemented in WFU Pick-Atlas toolbox (Maldjian, Laurienti, Kraft, & Burdette, 2003). Second, for completeness, we undertook a whole-brain approach to investigate the impact of maltreatment exposure on GMV.

Multiple comparison correction was performed using Monte Carlo simulation with the AFNI program 3dClustSim (http://afni.nimh.nih.gov/afni/), which defines a cluster-based extent threshold to limit the presence of Type 1 errors. At an initial statistical threshold of t (118) = 2.62 and an uncorrected p value of ≤.005, the cluster threshold was defined as 338 contiguous voxels resulting in $\alpha \leq .05$. Nonuniformity inherent in VBM data was addressed by implementing Gaussian random field theory within SPM8. Clusters that were found to be above this threshold were considered significant. An 8-mm ROI sphere around the local maxima of each significant cluster was created, and mean GMV for the region within the sphere was extracted from each subject using the MARSBAR region of interest toolbox (Matthew Brett, MRC Cognition and Brain Unit, Cambridge). These values were then correlated with the behavioral measures of interest, detailed in the Multilevel Data Analysis Strategy section.

Investigating sex differences in the impact of maltreatment on GMV

To investigate sex differences in the impact of maltreatment on cortical structure, two statistical approaches were implemented. First, to investigate whether the significant regions from the main effect of group analysis were driven by an effect in males and females, a 2 × 2 ANOVA was implemented within SPSS on the extracted GMV values displaying significant group differences. Second, to investigate Sex × Group interactions at the level of the whole brain, which may have been occluded in the main effect of group analysis, a flexible factorial model was implemented in SPM.

Within the flexible factorial model, three factors were created for all participants; the first being a "replication" factor defined as "subjects" and group and sex defined as the remaining factors. Age and IQ were included in the model as covariates because of their known association with brain anatomy (Giedd & Rapoport, 2010) and trend-level group differences on age and IQ. The model was rerun excluding the covariates to understand their potential influence on the results. The main effects of each factor as well as the interaction between group and sex were modeled in the design matrix. We performed *t* tests to test the main effect of group, sex, and an ANOVA for Group × Sex interaction on a whole-brain scale. A similar approach to correct for multiple comparisons was implemented, as described previously. Again, mean GMV for regions of significant interaction were extracted by creating an 8-mm ROI around the local maxima.

Multilevel data analysis strategy

Two mediation analyses were conducted; the first investigating the relationship between maltreatment experience and peer problems (with GMV as the potential mediator); and the second investigating the relationship between maltreatment experience and emotional reactivity (with threat bias as the potential mediator). As we recruited a community sample of maltreated and comparison individuals, we focused on a measure of general emotional reactivity, capturing emotional sensitivity, recovery, as well as impairment (Prince-Embury, 2008)

The structural equation modeling package lavaan 0.5-16 was used for these mediation analyses (Rosseel, 2012) and implemented within R software (R Development Core Team, 2013) version 3.02. A maximum likelihood estimate of the indirect effect was estimated as well as a 95% confidence interval using the adjusted bootstrap percentile method (10,000 draws). To examine possible sex differences, we estimated different indirect effects in boys and girls (Model 1) and then constrained the indirect effects to be the same in boys and girls (Model 2). The two models were then compared with a Wald test to test for a significant difference in the indirect effect between boys and girls.

For transparency, we also conducted a set of exploratory correlations within the maltreated sample, on those behavioral outcome measures showing significant differences between the maltreated and comparison groups and (a) attentional threat bias scores and (b) GMV values extracted from regions differing significantly across groups. In addition, we estimated correlations to explore whether individual differences in GMV in five regions associated with maltreatment were associated with threat bias scores.

Results

Sociodemographic variables and psychiatric symptomatology

The maltreated group did not differ from the nonmaltreated group in relation to sex, age, Tanner stage, handedness, IQ, SES, and ethnicity (Table 1). The maltreated relative to the nonmaltreated group did not differ on any of the subscales of the TSCC (Table 1), but did show heightened scores on the conduct problems, $t\ (122) = -4.25$, $p < .001$, hyperactivity, $t\ (122) = -3.62$, $p < .001$, subscales of the SDQ (Table 1; survived false discovery rate $q < .05$).

Social and emotional functioning

The maltreated relative to the nonmaltreated group presented with heightened scores on the peer problems, $t\ (122) = -2.72$, $p = .01$, subscale of the SDQ (Table 1; survived false discovery rate $q < .05$). They also significantly differed from their peers on two subscales of the RSCA, displaying significantly increased emotional reactivity, $t\ (122) = -3.59$, $p < .001$, and significantly decreased mastery, $t\ (122) = 2.37$, $p = .02$ (Table 1; survived false discovery rate $q < .05$). No differences were observed with regard to relatedness, $t\ (122) = 1.44$, $p = .15$. Group and sex did not interact in relation to the total or subscale scores of the SDQ, the TSCC, or the RSCA.

Dot-probe experimental task

Group comparisons showed a significant difference in the bias scores to angry facial expressions between maltreated (mean = −6.79 ms, $SD = 47.28$) and nonmaltreated children (mean = 18.57 ms, $SD = 41.83$), $t\ (97) = 2.80$, $p = .01$; Cohen $d = 0.57$ (Figure 1b), indicating a pattern of attentional bias away from threat in the maltreated group and attentional bias toward threat in the nonmaltreated group. The two groups were not statistically different in their bias scores to happy facial expressions (maltreated children: mean = 2.86 ms, $SD = 39.29$ ms; nonmaltreated children: mean = 4.14 ms, $SD = 44.44$ ms); $t\ (97) = 0.15$, $p = 0.88$; Cohen $d = 0.03$ (Figure 1a). Reaction times on the calm trials were not significantly different for the maltreated and nonmaltreated groups (maltreated children: mean z score = 0.09, $SD = 1.02$; nonmaltreated children: mean z score = −0.08, $SD = 0.98$); $t\ (97) = -0.89$, $p = .54$. However, the accuracy on the dot probe was different between the groups (maltreated children: mean = 90.78%, $SD = 8.75$; nonmaltreated children: mean = 94.79%, $SD = 4.17$); $t\ (97) = 2.98$, $p < .01$. Group and sex did not interact in relation to either happy, $F\ (1, 93) = 1.06$, $p = .31$, or threat, $F\ (1, 93) = 0.71$, $p = .40$, attentional bias scores, indicating no sex differences in task performance.

The impact of maltreatment on GMV

The maltreated and nonmaltreated groups did not differ on global measures of gray matter, white matter, cerebrospinal fluid, and total intracranial volume. Overall gray matter, white matter, cerebrospinal fluid, and total volume were greater in males than in females (Table 2). Sex × Group interactions were not significant for overall gray matter, $F\ (1, 118) = 0.36$, $p = .56$, white matter, $F\ (1, 118) = 2.40$, $p = .12$, cerebrospinal fluid, $F\ (1, 118) = 0.50$, $p = .48$, and total volume, $F\ (1, 118) = 1.48$, $p = .23$.

The main effect of maltreatment exposure on cortical structure

We investigated the main effect of maltreatment exposure on GMV using a set of ROIs. The maltreated group was observed

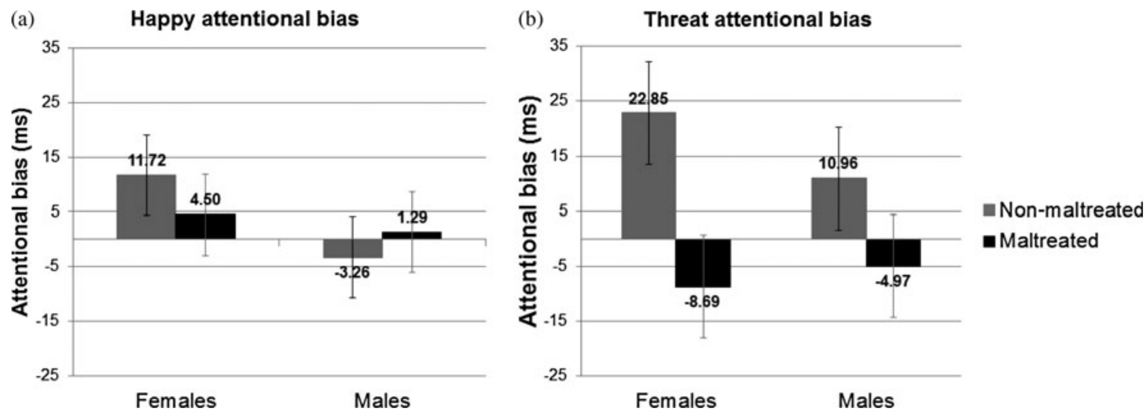

Figure 1. Attentional bias scores for the behavioral dot-probe task in the maltreated and nonmaltreated groups. (a) The maltreated and nonmaltreated group did not differ on attentional bias scores to happy emotional faces on the dot-probe task, t (97) = 0.15, p = .88. (b) The maltreated group showed a significant attentional bias away from threat compared to the nonmaltreated control group, t (97) = 2.80, p = .01. Sex did not interact with group on neither happy nor threat attentional bias scores.

to have significantly reduced GMV within the right middle temporal lobe ($x = 41$, $y = -60$, $z = 12$; $Z = 4.71$; $p = .01$; k [cluster size] = 1615), the left middle temporal lobe ($x = -63$, $y = -19$, $z = -9$; $Z = 4.67$; $p = .03$; $k = 1220$), and the left medial orbitofrontal cortex ($x = -12$, $y = 26$, $z = -21$; $Z = 4.13$; $p = .04$; $k = 875$). No significant differences were observed in relation to cerebellar, hippocampal, or amygdala GMV.

For completeness, we undertook a whole-brain approach to investigate the impact of maltreatment exposure on GMV. The maltreated group was found to have significantly reduced GMV within five regions: the bilateral medial temporal lobe, bilateral supramarginal gyrus, and left medial orbitofrontal cortex. Table 3 details the cluster extents of these five regions. In addition, the maltreated sample displayed significantly increased GMV compared to the nonmaltreated group within the left precentral gyrus ($x = -56$, $y = 5$, $z = 27$; $Z = 4.28$; $p = .02$; $k = 1225$; Table 3; Figure 2). Figure 2 illustrates the cluster extent of the significantly reduced and increased regions of GMV in the maltreated group compared to the nonmaltreated group on a study specific mean structural image.

The influence of sex on the impact of maltreatment on GMV

Our first step in investigating sex differences in the impact of maltreatment on GMV was to identify whether the observed

Table 2. *The global measurements of gray matter, white matter, cerebrospinal fluid (CSF), and total intracranial volume between the maltreated and nonmaltreated groups*

	By Group				
	Control (n = 60)		MT (n = 62)		
	Mean	*SD*	Mean	*SD*	p
Gray matter	771.18	64.85	759.85	64.44	0.34
White matter	479.33	53.16	467.68	45.54	0.20
CSF	171.57	25.61	172.96	26.82	0.77
Total	1422.07	118.42	1400.49	111.63	0.30
	By Sex				
	Males (n = 58)		Females (n = 64)		
	Mean	*SD*	Mean	*SD*	p
Gray matter	795.32	57.59	738.33	58.75	0.00
White matter	490.36	47.55	458.05	46.58	0.00
CSF	179.10	25.14	166.01	25.65	0.01
Total	1464.78	104.50	1362.46	102.41	0.00

Note: All values are measures of volume (mm^3). All p values were derived from t tests.

Table 3. *Whole brain group comparison within the combined sample*

Anatomical Region	Cluster Label	*k*	*p*	Peak Within Cluster *T*	*Z*	MNI Coordinates *x*	*y*	*z*
Controls > Maltreated								
Left medial orbitofrontal gyrus	**A**	**1021**	**0.031**	**4.13**	**3.98**	**−12**	**26**	**−21**
Left orbitofrontal gyrus				3.05	2.98	−11	45	−24
Left inferior frontal gyrus				2.59	2.54	−21	12	−21
Left supramarginal gyrus	**B**	**1319**	**0.021**	**4.7**	**4.49**	**−60**	**−30**	**39**
Left inferior parietal				3.59	3.49	−53	−42	48
NA				3.1	3.03	−56	−49	55
Left middle temporal gyrus	**C**	**1397**	**0.021**	**4.67**	**4.46**	**−63**	**−19**	**−9**
Right supramarginal gyrus	**D**	**1599**	**0.013**	**3.64**	**3.53**	**50**	**−34**	**43**
NA				3.53	2.23	47	−52	62
NA				3.3	3.22	53	−31	62
Right middle temporal gyrus	**E**	**2326**	**0.001**	**4.95**	**4.71**	**41**	**−60**	**12**
Right middle temporal gyrus				4.53	4.34	50	−53	15
Right inferior temporal gyrus				4.23	4.07	50	−55	−6
Controls < Maltreated								
Left precentral gyrus	**F**	**1225**	**0.021**	**4.47**	**4.28**	**−56**	**5**	**27**
Left precentral gyrus				3.59	3.49	−65	2	30
Left precentral gyrus				3.35	3.25	−59	8	39

Note: Cluster maxima are in bold. Cluster labels refer to the SPM clusters visualized in Figure 2. Anatomical locations for cluster maxima were derived from the AAL atlas. K, Cluster size in voxels.

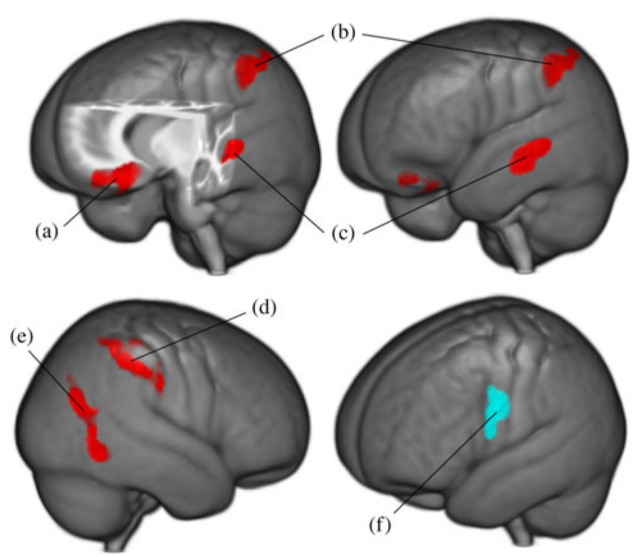

Figure 2. (Color online) Clusters of significantly reduced and increased gray matter volume within the maltreated group compared to the nonmaltreated group. Statistical parametric maps are shown in the clusters of significantly reduced gray matter volume among the maltreated children ($n = 6$) relative to the nonmaltreated children ($n = 60$) in the (a) medial orbitofrontal cortex, (b) left supramarginal gyrus, (c) left middle temporal lobe, (d) right supramarginal gyrus, and (e) right middle temporal lobe. The maltreated group displayed a cluster of significantly increased gray matter volume in the (f) left precentral gyrus. Statistical parametric mappings are overlaid on a mean structural from the 122 participants, visualized in three dimensions using mRIcroGL software. Cluster statistics are shown in Table 3.

group differences reported above were driven equally by females and males. Specifically, Sex × Group interactions were investigated on the extracted GMV values of the significant regions of increase and decrease in the maltreated group compared to the nonmaltreated group: the bilateral middle temporal lobe, bilateral supramarginal gyrus, and left medial orbitofrontal cortex. Sex and group did not significantly interact within the regions of the left middle temporal gyrus, $F(1, 118) = 1.63$, $p = .20$, the right middle temporal gyrus, $F(1, 118) = 2.97$, $p = .09$, or the left medial orbitofrontal cortex, $F(1, 118) = 0.61$, $p = .44$, suggesting no evidence of different effects of exposure to maltreatment on GMV male and female children in these regions.

However, significant Sex × Group interactions were found within the left supramarginal gyrus, $F(1, 118) = 12.57$, $p < .001$ (Figure 3a), and the right supramarginal gyrus, $F(1, 118) = 6.17$, $p = .01$ (Figure 3b). Inspection of the means and post hoc *t* tests indicated that a group difference was only present within the females for the left supramarginal gyrus ($p < .001$; males, $p = .788$) and the right supramarginal gyrus ($p = .01$; males, $p = .99$). In other words, it appears that the females within the maltreated group are driving the main effects of group on the GMV decrease in the bilateral supramarginal gyrus. Including pubertal scale as a covariate in the model did not change the pattern of results, and a significant interaction between sex and group within the left supramarginal gyrus, $F(1, 117) = 13.23$, $p < .001$, and the right supramarginal gyrus, $F(1, 117) = 6.31$, $p = .01$, remained.

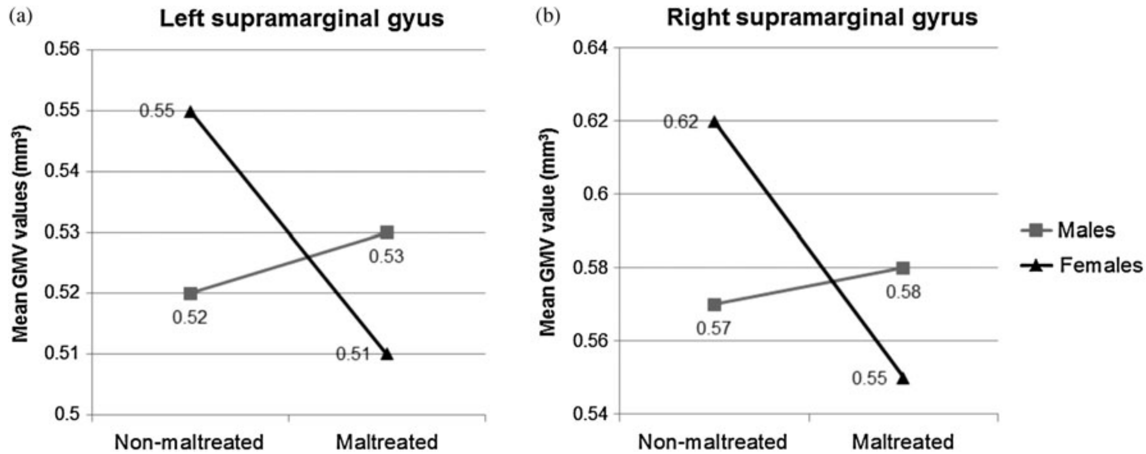

Figure 3. Sex differences in the impact of maltreatment on gray matter volume. Significant reduction in gray matter volume within the left supramarginal gyrus (a) and the right supramarginal gyrus (b) was exhibited only within the maltreated females compared to the nonmaltreated females. Line graphs are for visualization of the interaction between sex and group, therefore the *y*-axis is a different scale between the left (a) and right (b) supramarginal gyrus line graphs.

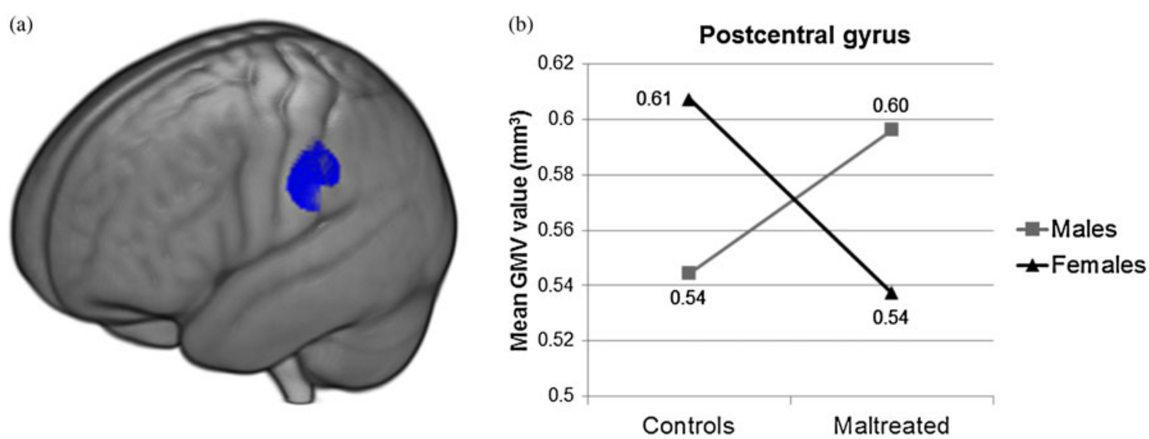

Figure 4. (Color online) Group × Sex interaction in gray matter volume (GMV). (a) A flexible factorial model identified a cluster of significant Group × Sex interaction in GMV within the left postcentral gyrus. The statistical parametric mapping indicates the focus of the significant interaction between group and sex in the left postcentral gyrus ($x = -63$, $y = -13$, $z = 34$; $Z = 3.76$; $\alpha = 0.05$). The statistical parametric mapping is displayed on a mean structural from the 122 participants, visualized in three dimensions using mRIcroGL software. (b) A line chart displays the relationship between group and sex of the mean GMV value extracted from an 8-mm sphere located at the maxima of the postcentral cluster.

Our second step to investigate sex differences was to use a flexible factorial within SPM to model the interaction between the factors, maltreatment experience and sex, on a whole-brain scale to identify regions that may have been occluded in the exploration of main effect of group (i.e., a pattern of increased and decreased GMV in maltreated males and females may have cancelled each other out). This whole-brain analysis revealed a significant cluster within the left postcentral region ($x = -63$, $y = -13$, $z = 34$; $Z = 3.76$; $k = 1671$; $p = .004$; $\alpha = 0.05$; Figure 4) indicating a reduction in GMV in maltreated females compared with nonmaltreated females and an increase in GMV in maltreated males compared with nonmaltreated males. Figure 4 highlights the extent of this cluster on a study-specific mean structural image (n = 122). The GMV values within this cluster were extracted for secondary analyses. The GMV values for males and females within each group were plotted (Figure 4). The model was rerun excluding age and IQ as covariates, and the same significant cluster was observed within the left post central region ($x = -63$, $y = -13$, $z = 33$; $Z = 4.45$; $k = 1911$; $p <$ .001; $\alpha = 0.05$) for the interaction between sex and group; however, the local maxima had shifted one degree in the z-axis and the cluster extent was slightly larger.

The relationship between attentional bias and emotional reactivity

As predicted, attentional threat bias was found to be significantly correlated with the emotional reactivity scale of the RSCA ($\beta = -0.33$, $p = .001$). We then implemented a me-

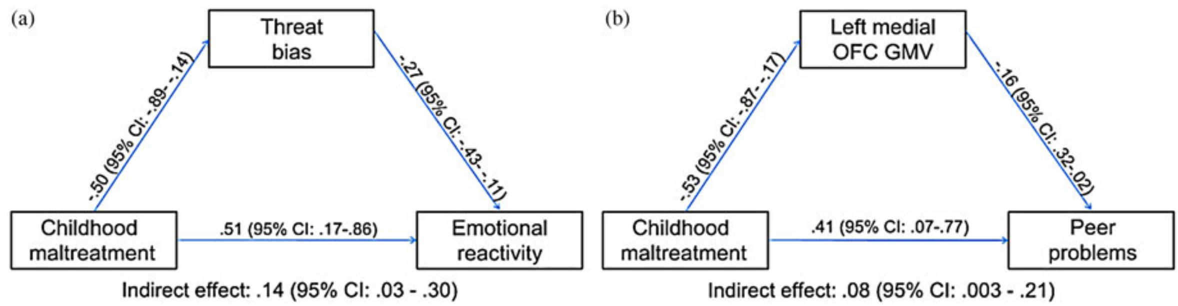

Figure 5. (Color online) Mediation models. (a) Threat bias was found to significantly mediate the relationship between childhood maltreatment and emotional reactivity. (b) Gray matter volume in the left medial orbitofrontal cortex was found to significantly mediate the relationship between childhood maltreatment and peer problems.

diation model in order to investigate whether threat bias mediated the relationship between maltreatment exposure and emotional reactivity. The total effect of maltreatment on the emotional reactivity scale was 0.65 (95% confidence interval [CI]: 0.31–1.00), corresponding to more than 0.5 *SD* increase in peer problems in the maltreated group compared to the control group. The indirect effect through the attentional bias to threat was 0.14 (95% CI = 0.03–0.30), and the confidence interval did not pass through 0, indicating a significant effect (Figure 5a). Approximately 21% of the effect of maltreatment on emotional reactivity was therefore mediated by attentional bias to threat. Similar to the previous model, indirect effects were very comparable in boys and girls, and no significant difference was observed (Wald test = 1.68, $df = 2$, $p = .43$).

The relationship between GMV and peer problems

The relationship between GMV extracted from the significant cluster of the left medial orbitofrontal cortex and the peer problems scale of the SDQ was investigated. In line with our hypothesis, the extracted GMV values from the left mOFC were found to significantly correlate with our measure of social functioning (the peer problems subscale of the SDQ; $\beta = -0.21, p = .02$). We implemented a mediation model investigating the potential mediating influence of mOFC GMV on the relationship between maltreatment exposure and peer problems. The total effect of maltreatment on the peer problem score was 0.49 (95% CI = 0.15–0.85), corresponding to a 0.5 *SD* increase in peer problems in the maltreated group compared to the control group. The indirect effect through the GMV in the medial OFC was 0.08 (95% CI = 0.003–0.21), and the confidence interval did not pass through 0, indicating a significant effect (Figure 5b). Around 17% of the effect of maltreatment on peer problem was therefore mediated by the GMV in the medial OFC. Indirect effects were comparable in boys and girls, and no significant difference was observed (Wald test = 0.92, $df = 2$, $p = .63$).

A set of exploratory correlations was conducted in order to explore the relationship among GMV values, attentional threat bias, and emotional reactivity. We found that threat bias did not correlate with any of the extracted main effect GMV values, or with the region of significant interaction between maltreatment exposure and sex. GMV within the right supramarginal gyrus was found to significantly correlate with the emotional reactivity scale of the RSCA ($r = -32$, $p = .02$).

Discussion

The current study investigated the influence of sex on social, emotional, cognitive, and neural domains in a large community sample of children with documented experiences of abuse. The impact of maltreatment across these domains was largely similar across sexes and suggests that maltreatment is associated with similar putative markers of latent vulnerability in males and females. In addition, our examination of two possible mechanisms that may mediate the relationship between maltreatment and two maladaptive behavioral outcomes were similar across males and females.

Consistent with our predictions, the maltreated group, compared to their nonmaltreated peers, was found to show elevated levels of peer difficulties, greater emotional reactivity, and a reduced sense of mastery. No group differences emerged in relation to social relatedness (thought to reflect perceived access to support, comfort from others, and a sense of trust). Sex differences were not found in relation to these social and emotional functioning outcomes, indicating that maltreatment experience had a similar impact on these domains for boys and girls. At the cognitive level, the maltreated group displayed a significant attentional bias away from threat compared to their nonmaltreated peers; again, there was no interaction with sex. These results support the main findings of Pine et al. (2005), who found a similar pattern in maltreated children with PTSD and suggest that maltreatment alters attentional allocation to threat in a similar fashion for boys and girls. Finally, our investigation into the impact of maltreatment on GMV identified five regions of significantly reduced volume and one region of significantly increased volume associated with maltreatment exposure. Consistent with our predictions, we found maltreatment experience was associated with GMV reductions in the left mOFC and bilateral middle temporal gyri. Sex differences were observed in the bilateral supramarginal gyrus, with GMV reductions being driven primarily by maltreated females. In addition, a region within the postcentral gyrus was found to show significant interaction between sex and exposure to childhood maltreatment. However, it is of note that while we identified a few important sex differences in relation to GMV, the overall pattern that emerged was of similarity in social and emotional functioning, and cognitive and neural profiles for boys and girls who had been exposed to maltreatment.

In our mediation analysis, we explored potential mechanisms linking maltreatment experience and emotional reactivity/peer problems, respectively. First, we found that attentional threat avoidance partly mediated the relationship between maltreatment experience and emotional reactivity. Second, we found that reduction in GMV in the left mOFC partly mediated the relationship between maltreatment experience and peer problems. Similar mediation relationships were observed in both males and females.

The influence of maltreatment and sex differences in social and emotional functioning

As predicted, our maltreated sample presented with greater difficulties with peers, consistent with the impairments in social and peer functioning seen in children reporting experiences of abuse (Bolger & Patterson, 2001; Bolger et al., 1998; Kim & Cicchetti, 2010; Rogosch et al., 1995). Good peer relationships have been shown to act as an important protective factor in the development of trauma symptomatology for both men and women with childhood histories of abuse (Evans et al., 2013; McLewin & Muller, 2006; Pepin & Banyard, 2006), potentially serving to buffer the negative psychological consequences of early adverse experience. We observed a similar pattern of increased peer problems in males and females, suggesting that this may constitute a common risk factor for psychiatric disorder across the sexes. As expected, compared to their peers, maltreated children overall showed higher levels of emotional reactivity, in line with the existing literature indicating a robust association among maltreatment exposure, atypical emotional regulation, and heightened neural activity to threat related cues (Kim & Cicchetti, 2010; Marusak, Martin, Etkin, & Thomason, 2014; Maughan & Cicchetti, 2002; Shields & Cicchetti, 1998). A tendency to experience heightened levels of emotional reactivity accompanied by poor emotional regulation may compromise an individual's ability to effectively negotiate stress and increase risk of future psychiatric symptomatology (Dahl & Gunnar, 2009; Spear, 2009; Swartz, Knodt, Radtke, & Hariri, 2015). In addition, we found that the maltreated group compared to their nonmaltreated peers displayed a significantly reduced sense of mastery, reflecting one's perceived sense of adaptability and optimism (Marusak et al., 2014; Piko, Luszczynska, & Fitzpatrick, 2013; Prince-Embury, 2008). Contrary to predictions, we did not observe a difference in relation to social relatedness, indicating an individual's perception of peer and familial relationships as trustworthy and supportive. One possibility is that the children in the maltreated group were currently receiving improved social support, through either their foster placements or professional networks, in contrast to the historical difficulties likely to have characterized their earlier social environment. That boys and girls did not differ across any of these domains suggests that maltreatment experience exerts a similar influence on these aspects of functioning in both sexes (Infurna, Rivers, Reich, & Zautra, 2015; Masten et al., 1999; Masten & Tellegen, 2012; Prince-Embury, 2008; Southwick, Vythilingam, & Charney, 2005). It remains possible, however, that sex differences may emerge later in development following the onset of psychiatric disorder.

The influence of maltreatment and sex differences in attentional bias to threat

Consistent with Pine et al. (2005), we found that the maltreated children, compared to their nonmaltreated peers, displayed a pattern of attentional avoidance to threat, when completing a visual dot-probe task. This pattern of threat avoidance has been observed in several child and adult studies of PTSD and anxiety, and has been postulated to potentially index difficulties in emotional regulation (Amir et al., 1996; Garner, Mogg, & Bradley, 2006; Helfinstein, White, Bar-Haim, & Fox, 2008; Mansell, Clark, Ehlers, & Chen, 1999; Mathews & Sebastian, 1993). The finding of no sex differences in attentional bias suggests that initial allocation of attention to threat cues is similar for boys and girls, and that any sex differences in threat processing are evident only in downstream processes subsequent to attentional allocation (Andreano, Dickerson, & Barrett, 2014; Thomas et al., 2001).

Emotional reactivity and attentional bias to threat

We formally tested the relationship among maltreatment, attentional allocation to threat, and emotional regulation, with a mediation model. We found that attentional bias in part mediated the relationship between maltreatment exposure and emotional reactivity, in a similar fashion for males and females. Attentional avoidance of threat following maltreatment may therefore represent one potential marker of latent vulnerability for boys and girls.

Understanding the contextual significance and functional implications of attentional bias toward or away from threat in maltreated children remains an important task for future research (Pine et al., 2005; Shechner et al., 2012). It may be that extended exposure to risk environments leads to altered automatic attentional allocation to threat. One possibility is that failure to recalibrate this threat bias in more normative contexts may serve to increase vulnerability to psychiatric disorder in the longer term (Wald et al., 2011, 2013). It is also not clear how this pattern of threat avoidance relates to findings of threat vigilance and recognition in maltreated children (Pollak, 2008). Given that varying the parameters of the dot-probe paradigm, specifically presentation duration, has been shown to influence the directionality of attentional bias in anxious individuals, it may be the case that different tasks (and task parameters) are indexing different aspects of atypical threat processing (Koster, Verschuere, Crombez, & Van Damme, 2005; Onnis, Dadds, & Bryant, 2011). In other words, maladaptive threat processing may be associated with a pattern of both threat avoidance *and* threat vigilance (Koster et al., 2005; Wald et al., 2011), possibly depending on which stage of the processing stream is sampled. This should be systematically explored in maltreated individuals.

The influence of maltreatment and sex differences on GMV

In this study we assessed differences in GMV in, to our knowledge, one of the largest nonclinical sample of children with documented experiences of maltreatment studied to date. Predicted reduced GMV was observed within the OFC and bilateral middle temporal gyrus within the maltreated group compared to their nonmaltreated peers, suggesting that GMV reductions in these regions are robust markers of maltreatment experience (De Brito et al., 2013; Hanson et al., 2010). With connections to limbic regions, the middle temporal lobes are thought to play a key role in autobiographical memory (Dolcos, LaBar, & Cabeza, 2004; Holland, Addis, & Kensinger, 2011; Squire, Stark, & Clark, 2004). Overgeneral autobiographical memory has been implicated as a cognitive risk factor for depression and PSTD (Dalgleish et al., 2001; Schönfeld, Ehlers, Böllinghaus, & Rief, 2007; Williams et al., 2007) and has been postulated to represent another candidate system associated with latent vulnerability linking maltreatment experience and psychiatric vulnerability (McCrory & Viding, 2015). Maltreated children are known to present with a pattern of overgeneral recall (Valentino, Toth, & Cicchetti, 2009), but the functional basis of autobiographical memory processing in maltreated individuals remains to be investigated. The mOFC plays a central role in emotion regulation, reinforcement based decision making and social functioning (Beer, John, Scabini, & Knight, 2006; Ochsner & Gross, 2005; Rempel-Clower, 2007; Rushworth, Behrens, Rudebeck, & Walton, 2007; Schoenbaum, Saddoris, & Stalnaker, 2007); the potential significance of GMV reductions in this region are discussed at length below. Finally, we observed reductions in GMV within bilateral supramarginal gyrus and an increase in GMV within the precentral gyrus in the maltreated group. No differences in GMV were observed in the hippocampus or amygdala, although there is some preliminary evidence for subtle changes in neural structure in these regions in children exposed to early and severe institutionalization (Mehta et al., 2009; Tottenham et al., 2010), and slowed growth of the amygdala in maltreated adolescents (Whittle et al., 2013).

We then explored the possibility of sex differences associated with maltreatment at the group level. It was found that GMV differences in both the mOFC and the middle temporal gyrus were present in both males and females. By contrast, the lower GMV within the bilateral supramarginal gyrus was found to be driven more by maltreated females than by males. Maltreated males did not show a significant GMV decrease in this region compared to their nonmaltreated male peers. The supramarginal gyrus has been associated with emotion recognition (Adolphs, Damasio, Tranel, Cooper, & Damasio, 2000; Adolphs, Tranel, & Damasio, 2001) and certain empathy-related functions including egocentricity and the ability to distinguish oneself from representations of others (Silani, Lamm, Ruff, & Singer, 2013; Singer & Lamm, 2009). In addition, we observed a disordinal interaction between maltreatment exposure and sex within a region of the postcentral gyrus, such that comparison females had greater GMV in this region compared to comparison males with the inverse pattern observed in the maltreated group. This finding is of interest given that reduced GMV in this region appears to correlate with age, such that effects have typically only been reported for adults with childhood histories of abuse and not in children (Lim et al., 2014). It may be that GMV differences in previous studies of children have simply been “cancelled out” by the opposing patterns observed in maltreated males and females. In typical populations, the postcentral gyrus has been found to exhibit a sexually distinct neural role in the processing of emotional content, particularly in memory recall and emotional regulation during cognitive reappraisal (Canli, Desmond, Zhao, & Gabrieli, 2002; Domes et al., 2010), raising the possibility that these GMV differences may have a functional significance in relation to emotional regulation and psychiatric risk (Cicchetti & Lynch, 1995; Kim & Cicchetti, 2010; Leist & Dadds, 2009; Masten et al., 2008; Pollak, 2008; Pollak et al., 2000; Shields, Cicchetti, & Ryan, 1994).

The observed differences in males and females in both the bilateral supramarginal gyrus and the postcentral gyrus may represent possible neural substrates implicated in the differential psychiatric risk trajectories seen in maltreated males and females (Bos et al., 2011; Keyes et al., 2012). However, one must necessarily be cautious in making such inferences given that sex differences in cortical structure or function do not always result in isomorphic behavioral differences (De Vries, 2004; De Vries & Södersten, 2009; Piefke, Weiss, Markowitsch, & Fink, 2005). Because there was an absence of sex differences at cognitive and behavioral levels in the current study, the functional significance of these GMV differences, if any, remains unclear. In view of the role of the supramarginal gyrus and the postcentral gyrus in empathy and empathy-related processes in normative populations (Hooker, Verosky, Germine, Knight, & D’Esposito, 2008; Silani et al., 2013), future studies might usefully explore GMV differences and their association with behavioral and neural aspects of functioning in these domains in maltreated individuals.

Peer functioning and GMV in the mOFC

In a study by Hanson et al. (2010), also recruiting a community sample of maltreated children, reductions in GMV within the orbitofrontal cortex were found to be associated with social difficulties. In line with these findings, we found that reduced GMV within the mOFC mediated the relationship between maltreatment experience and social difficulties, as measured by the peer problems scale of the SDQ. This finding adds weight to the view that cortical alterations in the mOFC, a region which is crucially implicated in social processing, is implicated in the difficulties maltreated individuals can show in social functioning (Alink, Cicchetti, Kim, & Rogosch, 2012; Kim & Cicchetti, 2003; Rogosch et al., 1995). That we observed the same pattern of mediation for males and females points to a common neural substrate for these difficulties. It would be of particular interest in future research to explore the relationship between mOFC GMV and cortisol regulation given the evidence that cortisol functioning is implicated in the impairments in social functioning seen in maltreated children (Alink et al., 2012; Hart, Gunnar, & Cicchetti, 1995).

Summary and implications of sex differences

Because males and females who experience maltreatment are at heightened risk for a broad range of psychiatric disorders, it is not surprising that largely similar patterns of behavioral functioning, attentional bias, and GMV were found across the sexes. In addition, similar patterns across the sexes were observed in our mediation analyses. This suggests that putative markers of latent vulnerability, specifically in relation to attentional avoidance of threat and reduced mOFC GMV, may represent common factors in predisposing to future psychiatric risk. However, it is likely that sex differences in latent vulnerability do exist, but were not detected in the current study, given the differential vulnerability females and males show in relation to internalizing and externalizing disorders following maltreatment (Bos et al., 2011; Keyes et al., 2012). Different patterns of GMV alteration in maltreated males and females in the supramarginal gyrus and postcentral gyrus may represent possible sex-dependent associations with maltreatment experience. It is possible that greater differences in brain structure are evident in maltreated individuals following the emergence of psychiatric disorder (Teicher & Samson, 2013).

From a clinical perspective, the question arises which if any of the parameters associated with maltreatment in the current study are predictive of future disorder. To constitute true markers of latent vulnerability, differences in emotional reactivity, threat avoidance, and GMV would need, within a longitudinal design, to be shown to be predictive of future symptomatology (McCrory & Viding, 2015). We have argued that the identification of reliable markers of latent vulnerability has the potential to directly inform a preventative psychiatry approach, by facilitating the delivery of interventions to the most high-risk children with the aim of offsetting the likelihood of future disorder. The current findings suggest that preventative interventions that either aim to enhance social functioning in line with attachment principles (e.g., Bernard et al., 2012; Cicchetti, Rogosch, & Toth, 2006; Dozier, Peloso, Lewis, Laurenceau, & Levine, 2008; Stronach, Toth, Rogosch, & Cicchetti, 2013) or take a more targeted approach, such as attentional bias modification (Bar-Haim, 2010; Britton et al., 2013; Hakamata et al., 2010), may be promising avenues in targeting pre-clinical vulnerabilities. However, a clearer understanding regarding which neurocognitive correlates of maltreatment experience represent true markers of latent vulnerability, alongside an understanding of their neurocognitive mechanisms, will be important to directly inform us about effective targets for intervention.

Limitations

The current study should be interpreted in light of some limitations. First, data across the multiple levels of analysis was obtained from a cross-sectional design, which precludes the possibility of determining the directionality of effects. The use of longitudinal designs will help determine which of the observed neurocognitive and behavioral differences represent true markers of latent vulnerability, and elucidate possible sex differences in the emergence of psychiatric disorder. Such longitudinal approaches are already bearing fruit in neurodevelopmental studies of attention-deficit/hyperactivity disorder (Shaw et al., 2013). Second, while the current study used official substantiated reports of maltreatment to determine inclusion in the maltreatment group and reporting of maltreatment severity, it would have been of interest to explore how a subjective measure of maltreatment experience relates to the observed structural and cognitive findings.

This study was also characterized by a number of strengths. First, our sample was a community, rather than clinic-referred, group of children, matched with a range of sociodemographic variables with the nonmaltreated group. This provides more confidence in inferring that any observed group differences on behavioral, cognitive, and neural levels are not primarily driven by variations in sociodemographic or psychiatric measures. Second, we were able to take a multilevel approach to explore sex differences in maltreatment impact. We were also able to explore how different maltreatment outcomes related to each other. Such multilevel approaches are vital in progressing the understanding of the pathways from maltreatment to behavioral difficulties and identifying the potential mechanisms that underpin latent vulnerability in the wake of maltreatment (Cicchetti & Dawson, 2002).

Conclusion

This study sought to investigate potential sex differences in how childhood maltreatment impacts social and emotional functioning, as well as cognitive and neurobiological domains. Although a number of sex differences were observed in relation to GMV, the general pattern of findings suggested that the influence of maltreatment experience was remarkably similar for boys and girls.

Our sample of maltreated boys and girls exhibited a similar pattern of elevated peer difficulties and emotional reactivity relative to their nonmaltreated peers. Boys and girls also displayed a similar pattern of attentional avoidance to threat in a visual dot-probe task. That attentional avoidance to threat partly mediated the relationship between maltreatment and emotional reactivity suggests that altered attentional bias to threat may represent one marker of latent vulnerability to future psychiatric disorder (Wald et al., 2011, 2013). It will be important for future studies to systematically explore the longitudinal association between attentional bias and psychopathology in maltreated children.

At the neural level, maltreatment experience was found to be associated with GMV reductions in the mOFC and the middle temporal lobes, suggesting that these represent reliable correlates of maltreatment experience in nonclinical samples of children, even after IQ, SES, and pubertal status have been controlled (De Brito et al., 2013; Hanson et al., 2010; Lim et al., 2014). Sex differences at a neural level were found only within the bilateral supramarginal gyrus (with GMV reductions being primarily driven by maltreated females), and within the postcentral gyrus, which exhibited a disordinal interaction between maltreatment exposure and sex. Functionally, these regions are implicated in empathy and emotional regulation respectively (Domes et al., 2010; Silani et al., 2013; Singer & Lamm, 2009). It is possible that these sex differences in GMV may underpin the differential psychiatric risk trajectories known to characterize males and females following maltreatment experience (Keyes et al., 2012; Mesman, Bongers, & Koot, 2001). The finding that GMV within the mOFC mediated the relationship between maltreatment exposure and peer functioning adds weight to the view that alterations in neural structure in this region are associated with deficits in social functioning following maltreatment (Alink et al., 2012; Hanson et al., 2010; Kim & Cicchetti, 2003; Rogosch et al., 1995), Again, sex was not found to influence this association.

Longitudinal investigations will be crucial in determining which of these behavioral, cognitive, and neural candidates are true markers of latent vulnerability capable of predicting future psychiatric symptomatology. Such work is important if we are to advance our ability to refine and target effective preventative interventions prior to the onset of psychopathology.

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