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Self-reported neglect, amygdala volume, and symptoms of anxiety in adolescent boys

Marissa C. Roth*, Kathryn L. Humphreys, Lucy S. King, Ian H. Gotlib

Department of Psychology, Stanford University, Stanford, CA, USA

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ABSTRACT

Experiences of psychosocial neglect affect the developing brain and may place individuals at increased risk for anxiety. The majority of research in this area has focused on children who have experienced severe psychosocial deprivation; it is not clear whether typical variation in neglect experienced in community samples would have the same neurobiological consequences as those documented in extreme samples. The present study examined the associations among self-reported childhood neglect, amygdala volume, and anxiety symptoms in a community sample of 138 adolescents ages 9–15 years (43% male). Linear mixed modeling yielded a three-way interaction of neglect, sex, and brain hemisphere, reflecting a significant positive association between neglect and right amygdala volume in boys. Additional analyses indicated that right amygdala volume significantly mediated the association between neglect and anxiety symptoms in boys. These findings are consistent with previous reports of larger amygdala volumes in previously institutionalized children, and with documented associations between caregiving deprivation and anxiety symptoms. The results suggest that the effects of childhood neglect on limbic structures are sex-specific and lateralized, and provide support for a neural mechanism relating childhood neglect to later difficulties in emotional functioning.

1. Introduction

Child neglect is common; indeed, in the United States neglect accounts for more than 75% of the over 700,000 children with validated child welfare cases each year. Worldwide, it is likely that experiences of neglect are proportionally even more prevalent, with war, famine, natural disasters, and epidemics leaving many children without caregivers. Indeed, a United Nations report indicated that 8 million children worldwide are living in institutions (United Nations, 2006), under conditions known to be associated with severe psychosocial neglect (Zeanah et al., 2006). Not surprisingly, a large body of work has documented the association between experiences of neglect and adverse cognitive and socioemotional outcomes (Calem et al., 2017; De Bellis, 2005; Glaser, 2000; Gould et al., 2012; Humphreys, Fox, Nelson, & Zeanah, 2017). Given the consistency of these findings, there is now growing interest in identifying the mechanisms by which neglect leads to poorer functioning.

In this context, researchers have documented that the lack of a sensitive and reliable caregiver early in life has lasting neuroanatomical consequences (Humphreys & Zeanah, 2015; Humphreys, King, & Gotlib, 2018; McLaughlin, Sheridan, & Nelson, 2017; Sheridan & McLaughlin, 2014; Tottenham & Sheridan, 2009). Experiences of child neglect have been found to be associated with anomalous limbic system structure and connectivity, particularly involving the amygdala, which coordinates behavioral and physiological responses to threat (Ledoux, 2003). Many neural pathways connect sensory brain regions to the amygdala, enabling its

* Corresponding author at: Department of Psychology, Stanford University, 450 Serra Mall, Jordan Hall, Rm #155, Stanford, CA 94305, USA.
E-mail address: rothm@stanford.edu (M.C. Roth).

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central role in fear learning (Davis, 2006); indeed, increased amygdala reactivity has been linked consistently with anxiety disorders (Shin & Liberzon, 2010). Despite evidence from non-human work that maternal deprivation is associated with alterations in the amygdala (Kikusui & Mori, 2009; Ladd, Thrivikraman, Huot, & Plotsky, 2005; Ono et al., 2008; Teicher et al., 2004), data from human research are mixed. For example, two studies found that previously institutionalized children showed increased amygdala volumes relative to never-institutionalized controls (Mehta et al., 2009; Tottenham et al., 2010) and, further, that time spent in institutional care was linearly and positively associated with amygdala volume (Tottenham et al., 2010). In contrast, two other studies found that children who spent time in institutions had smaller left amygdala volumes than did children who had not experienced neglect (Hanson et al., 2015; Hodel et al., 2015); Hodel et al. (2015) found only a trend-level effect for right amygdala volume. Further, in the Bucharest Early Intervention Project, children with and without a history of institutional care did not differ from each other in amygdala volume (Sheridan, Fox, Zeanah, McLaughlin, & Nelson, 2012).

Studies of adults using retrospective dimensional self-report measures to examine the effects of neglect occurring outside the context of institutional care on neural outcomes have also yielded inconclusive findings (Calem, Bromis, McGuire, Morgan, & Kempton, 2017; Hanson et al., 2015; Pechtel, Lyons-Ruth, Anderson, & Teicher, 2014). Two studies found no association between childhood abuse and neglect, considered together, and amygdala volume in adults (Calem et al., 2017; Dannlowski et al., 2012). In two studies that assessed neglect separately from abuse, investigators either found no association with amygdala volume (Pechtel et al., 2014), or found that early neglect was associated with smaller amygdala volume (Hanson et al., 2015).

These inconsistencies may be due to possible sex differences or hemispheric interactions that were not examined in these studies. While some studies did explicitly examine sex differences (e.g., Mehta et al., 2009; Tottenham et al., 2010), other researchers controlled for sex without describing potential differences between boys and girls (Calem et al., 2017; Dannlowski et al., 2012; Hanson et al., 2015; Hodel et al., 2015; Lyons-Ruth, Pechtel, Yoon, Anderson, & Teicher, 2016; Sheridan et al., 2012). Importantly, it is possible that boys are less resilient to experiences of abuse and neglect than are girls (Humphreys, Miron et al., 2017; Rutter, 1987). For example, in a large sample of adults who as children had experienced abuse and neglect, maltreated males were less likely than were maltreated females to meet threshold criteria for resilience measured across eight domains of functioning, an effect that remained significant even when investigators controlled for domains that may disproportionately affect males (e.g., criminality) (McGloin & Widom, 2001). Further, it is noteworthy that non-human animal studies have found sex differences in amygdala development following maternal separation: male mice, but not female mice, showed premature amygdala myelination (Kikusui & Mori, 2009), which may contribute to increases in amygdala volume in males (see Uematsu et al., 2012). These results suggest that in non-human animals, the amygdala may be more sensitive to early experiences of deprivation in males than in females. Given these findings, it is possible that sex moderates the observed neuroanatomical consequences of neglect, such that the association is stronger in boys than in girls.

Findings are similarly equivocal with respect to the association between neglect and laterality of its effect on amygdala volume. While several investigators did not report examining hemisphere differences (e.g., Sheridan et al., 2012), studies in which hemisphere-specific effects of neglect on amygdala volume were found have yielded inconsistent findings. For example, whereas in one study early deprivation was associated with larger right than left amygdala volumes (Mehta et al., 2009), in two other studies early neglect was associated with reductions in left but not in right amygdala volume (Hanson et al., 2015; Hodel et al., 2015), and a third study reported no significant association between neglect and either right or left amygdala volume (Pechtel et al., 2014). Inconsistencies in the findings of these studies may be due to measurement differences in the assessment and classification of neglect. For example, Pechtel et al. (2014) used the MACE Scale to assess childhood maltreatment and found a significant positive association between severity of maltreatment and right amygdala volume but no significant association between the neglect subscale of the MACE Scale and amygdala volume. It is possible that this approach to measuring neglect may have limited range, given that only physical and emotional neglect are assessed. Hanson et al., Hodel et al., and Mehta et al. all assessed neglect in a binary manner (i.e., previously institutionalized compared to never institutionalized), rather than using a continuous measure of neglect. Given that children likely experience different forms and degrees of neglectful behavior within the same institutional environments (Zeanah, Smyke, & Settles, 2006), using a dimensional measure of neglect may yield more consistent results with respect to a possible dose-response relation between childhood neglect and amygdala volume.

The present study was designed to examine the association between neglect and amygdala volume, and to address gaps in the literature concerning participant sex and amygdala laterality. Rather than using an extreme-groups approach (i.e., comparing those with and without a history of institutional care), we used a dimensional measure of neglect (i.e., self-reported neglect) that includes a range of neglect experiences (i.e., physical, emotional, and supervisory) in a community sample of adolescents. Although extant findings concerning the relation between neglect and amygdala volume are mixed, most studies that did report a directional effect found a positive association between these two variables (Mehta et al., 2009; Tottenham et al., 2010). Therefore, we hypothesized that higher levels of neglect would be associated with larger amygdala volume in our sample. Given possible sex- and hemisphere-related differences in amygdala volume following neglect, we examined both sex and hemisphere as potential moderators of the association between neglect and amygdala volume.

Based on findings that boys are less resilient to psychosocial deprivation than are girls (Humphreys, Miron et al., 2017; McGloin & Widom, 2001; Rutter, 1987) and that maternal separation is associated with growth-related changes in male, but not in female, amygdalae (Kikusui & Mori, 2009; Ono et al., 2008), we hypothesized that the effect of neglect on amygdala volume would be larger in boys than in girls. Based on the results of previous studies that examined hemispheric interactions (Mehta et al., 2009; Pechtel et al., 2014) and on recent evidence that stress has lateralized effects on the brain that often implicate the right side (Ocklenburg, Korte, Peterburs, Wolf, & Güntürkün, 2016), we hypothesized that neglect would be associated more strongly with right than with left amygdala volume, and again, to a greater extent in boys than in girls. Finally, given the link between neglect and anxiety

Table 1
Demographic and Clinical Variables by Participant Sex (N = 138).

	Girls	Boys	t or χ^2
Age	11.93 (1.70)	12.41 (1.30)	−1.88
Pubertal Stage	2.64 (1.17)	2.38 (1.16)	1.33
Race/Ethnicity			7.26
White/Caucasian	37%	40%	
African American	13%	3%	
Hispanic	6%	10%	
Asian	10%	18%	
Native American	1%	3%	
Pacific Islander	1%	2%	
Other	30%	22%	
No response given	1%	2%	
Mother Education			2.84
< High School	1%	0%	
High School	1%	0%	
Some College	24%	29%	
College Degree	48%	40%	
Graduate Degree	25%	31%	
Father Education			6.24
< High School	2%	0%	
High School	4%	2%	
Some College	18%	30%	
College Degree	49%	28%	
Graduate Degree	27%	40%	
Family Income			6.68
Less than $25,000	10%	3%	
$25,001-$75,000	12%	12%	
$75,001-$150,000	33%	47%	
More than $150,000	33%	35%	
No response given	12%	3%	
Income-to-needs ratio	1.28 (0.59)	1.38 (0.48)	−1.03
Neglect Score	2.9 (3.2)	2.0 (2.7)	1.65
Anxiety Symptoms (MASC Score)	21.0 (12.3)	19.1 (11.2)	0.91
Left Amygdala Volume	1451.2 (196.2)	1606.6 (225.9)	−4.30***
Right Amygdala Volume	1552.6 (225.4)	1653.5 (256.6)	−2.42*

Note. M (SD) or %.
* $p < .05$.
*** $p < .001$.

(Humphreys, Gabard-Durnam et al., 2017; Zeanah et al., 2009) and given that amygdala plays an important role in anxiety in individuals with (Gee et al., 2013; Tottenham et al., 2010; Tottenham et al., 2011) and without (Barrós-Loscertales et al., 2006; De Bellis et al., 2000) histories of neglect, we examined whether amygdala volume would mediate the association between self-reported neglect and symptoms of anxiety.

2. Methods

2.1. Participants

Participants were 138 children (60 boys, 78 girls) ages 9.11–15.58 years (M age = 12.14 years, SD = 1.55) who were recruited from the San Francisco Bay Area community with the goal of obtaining a sample of children who had experienced a range of severity of early life stress. Pubertal stage was assessed via child report; Tanner Stage ranged from 1 to 5 (M = 2.53, SD = 1.18), with the goal of recruiting boys and girls that, as groups, did not differ significantly in pubertal stage (see Table 1). Children self-reported race/ethnicity: 38% White/Caucasian, 14% Asian, 9% African American, 8% Hispanic, 2% Native American, 1% Pacific Islander, 26% Other (primarily children who identify as multiracial), and 1% not provided. Parents reported on annual household income: 7% reported < $25,000, 12% reported $25,001–$75,000, 39% reported $75,001–$150,000, 34% reported > $150,000, and 8% not provided. Given the high cost of living in the area in which these participants live, we also calculated the income-to-needs ratio for participants who provided income information (n = 127, *M* = 1.33, *SD* = 0.54), and found that 27% of the sample would be categorized as “low income” (i.e., income-to-needs ratio < 1.0). These and additional details about the demographic characteristics of the sample are presented in Table 1. The study was approved by the Stanford University Institutional Review Board; participants and their parents gave assent and informed consent, respectively. Participants were screened for initial inclusion/exclusion criteria through a telephone interview; potentially eligible individuals were then invited to the laboratory for in-person interviews and assessments. The measure of neglect was added midway through data collection for Wave 1 of a longitudinal study. Because we included neglect data in this study only from the first time this construct was assessed for each participant, for 80 participants their neglect data were obtained at Wave 1 and for 58 participants their neglect data were obtained at Wave 2, which occurred approximately two years following the baseline assessment. Thus, all participants provided one measure of neglect and amygdala volume data that was obtained at the same time. At baseline, inclusion criteria were that children be between the ages of 9 and 13 years and be proficient in English. Exclusion criteria were factors that would preclude MRI scan (e.g., metal implants, braces), a history of major neurological or medical illness, severe learning disabilities that would make it difficult for participants to comprehend the study procedures. Females who reported having started menses were excluded, and boys were matched to girls on pubertal stage (Marshall & Tanner, 1968). Participants who provided usable structural MRI scans in which either or both amygdala volumes were obtained were included in the present study.

2.2. Procedure

Participants visited the laboratory and completed self-report measures assessing experiences of neglect, as well as other measures and interviews not included here. Participants also returned to the MRI center within two weeks of their laboratory visit, where structural scans were obtained. Participants were compensated for their participation.

2.3. Measures

2.3.1. Multidimensional neglectful behavior scale (MNBS)

To assess neglect, participants completed the MNBS (Adult Recall Short Form; Straus, Kinard, & Williams, 1995), an 8-item self-report measure of neglectful behavior designed to be completed by adolescents and adults regarding neglectful behavior by their caretakers during childhood. The MNBS yields data on the four dimensions of neglect: cognitive, emotional, physical, and supervisory; responses are scored on a 4-point scale, from 0 (*strongly disagree*) to 3 (*strongly agree*) (see Appendix for subscale descriptive statistics). The total score can range from 0 to 24, with higher scores indicating greater neglect. In our sample, the MNBS demonstrated good internal consistency ($\alpha = 0.89$). Scores greater than 2 SD from the mean were winsorized and replaced with the next closest value.

2.3.2. Multidimensional anxiety scale for children (MASC)

To assess anxiety, participants completed the MASC, 2nd edition (March, Parker, Sullivan, Stallings, & Connings, 1997), a self-report measure that assesses a broad range of symptoms of anxiety in children ages 8–19 years (Fraccaro, Stelnicki, & Nordstokke, 2013; March et al., 1997). Items are scored on a 4-point scale, from 0 (*never true about me*) to 3 (*often true about me*), with higher scores indicating greater anxiety symptoms. The MASC has high internal consistency ($\alpha = 0.92$; Fraccaro et al., 2013) and has strong psychometric properties (Baldwin & Dadds, 2007; Wood, Piacentini, Bergman, McCracken, & Barrios, 2002). Because the MASC measures symptoms and yields scale scores that correspond to DSM-IV criteria and categorization of anxiety disorders in children, it has been found to have widespread utility in clinical and research contexts (Wood et al., 2002). The MASC yields data on four scales of anxiety; in order to reduce participant burden in this study, only the Social Anxiety and Physical Symptoms scales were administered. The scores from these two scales were summed to obtain a total anxiety score.

2.4. MRI data acquisition

MRI scans were acquired at the Center for Cognitive and Neurobiological Imaging at Stanford University using a 3T Discovery MR750 (GE Medical Systems, Milwaukee, WI, USA) equipped with a 32-channel head coil (Nova Medical, Wilmington, MA, USA). Whole-brain T1-weighted images (T1w) were collected using the following spoiled gradient echo (SPGR) pulse sequence: 186 sagittal slices; TR (repetition time)/TE (echo time)/TI (inversion time) = 6.24/2.34/450 ms; flip angle = 12°; voxel size = 0.9 mm × 0.9 mm × 0.9 mm; scan duration = 315 s.

2.5. Amygdala segmentation

To obtain volumes from T1w images, we used the FreeSurfer software suite (v5.3; available at: http://surfer.nmr.mgh.harvard.edu/) for automated segmentation of subcortical volumes (Fischl et al., 2002). This segmentation approach is widely used, is robust against anatomic variability, has comparable accuracy to manual labeling techniques (Fischl & Dale, 2000; Fischl et al., 2002) and has acceptable scan-rescan reliability (Jovicich et al., 2009). Using the FreeView image viewer, amygdala segmentations were visually inspected for processing and segmentation errors. Only individuals with usable left (n = 137) or right (n = 134) amygdala volumes were included.

2.6. Data analysis

To examine the association of self-reported neglect and amygdala volume, we used linear mixed modeling (LMM) given that individuals provided both left and right volume measurements and LMM accounts for the non-independence of nested measures within individuals. We used restricted maximum likelihood estimation in Mixed Models in SPSS (version 23, IBM Corporation),

Table 2
Linear Mixed Model Results.

	df	*F*	*p*
Intercept	1, 119.34	2.37	.126
Race (white = 1)	**1, 114.30**	**4.75**	**.031**
Income-to-needs ratio	1, 115.21	.22	.640
Age	1, 114.47	3.30	.072
Pubertal stage	1, 114.47	1.46	.229
Intracranial volume	**1, 124.87**	**32.45**	**< .001**
Neglect	1, 117.25	1.40	.239
Sex (male = 1)	1, 116.05	0.59	.446
Hemisphere	**1, 116.67**	**7.35**	**.008**
Neglect x sex	1, 116.06	1.11	.294
Neglect x hemisphere	**1, 118.46**	**5.53**	**.020**
Sex x hemisphere	**1, 116.66**	**9.04**	**.003**
Neglect x sex x hemisphere	**1, 118.42**	**8.91**	**.003**

Note. Bold indicates statistical significance.

specifying fixed and random intercepts. Neglect, sex, and hemisphere were included as main effects and in two- and three-way interactions. Age, pubertal stage, income-to-needs ratio, and race (dummy-coded as White/Caucasian vs. else) and intracranial volume (ICV) were included as covariates. Degrees of freedom were calculated using the Satterthwaite method (Satterthwaite, 1946), which can yield fractional values.

To test whether amygdala volume mediated the association between self-reported neglect and anxiety symptoms, we conducted a single-step mediation analysis using the PROCESS macro (Hayes, 2013) in SPSS. To assess the significance of the indirect effect, we implemented a non-parametric bootstrap procedure using sampling with replacement (n = 1000) and 95% bias correction, and calculated accelerated confidence intervals (CIs) for coefficients. If the CI does not include zero, the indirect effect is considered statistically significant. Age, pubertal stage, and ICV were included as covariates.

3. Results

Demographic and variables of interest assessed in this study are presented in Table 1 as a function of sex. Boys and girls did not differ on demographic variables or neglect. As expected, boys had greater left and right amygdala volumes than did girls.

3.1. Neglect and amygdala volume

We conducted a single LMM to test the association between neglect and amygdala volume, with sex and hemisphere included as potential moderators of interest, and covarying for age, pubertal stage, income-to-needs ratio, race, and ICV. As predicted, this analysis yielded a significant three-way interaction of neglect, sex, and hemisphere (see Table 2). As shown in Fig. 1, the three-way interaction was driven by differences in right and left amygdala volume in boys as a function of neglect, such that higher levels of self-reported neglect were associated with significantly larger right (compared to left) amygdala volume in boys. Post-hoc analyses using linear regression within the sample of boys indicated that neglect explained 7 percent of variance in right amygdala volume (p = .009) over and above the effects of age, pubertal stage, income-to-needs ratio, race, and ICV.

3.2. Test of mediation

We tested whether larger right amygdala volume mediated the association between neglect and anxiety in males, given that a hierarchical linear regression analysis supported an association between right amygdala volume and anxiety symptoms after

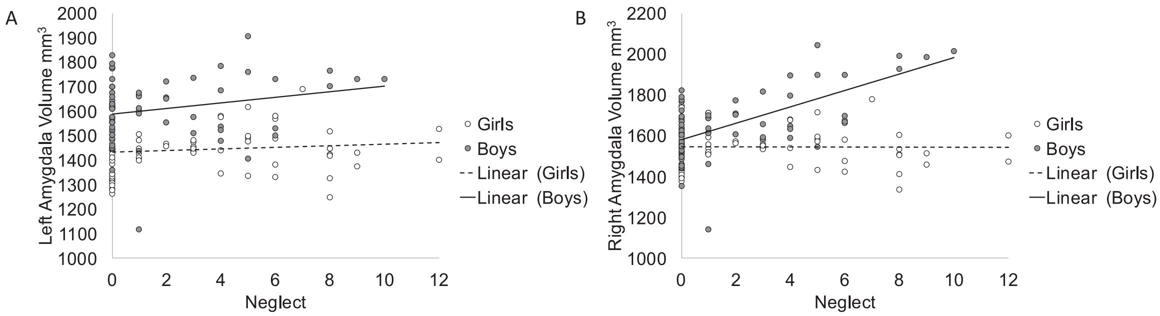

Fig. 1. Amygdala volume as a function of neglect and sex for left (A) and right (B) hemispheres.

controlling for age, pubertal stage, income-to-needs ratio, race, and ICV (β = 0.39, t(47) = 2.09, p = .042, ΔR^2 = 0.08). Using a single-step mediation with age, pubertal stage, and ICV as covariates, there was no significant direct effect of the self-reported neglect on anxiety symptoms (B = 0.39, SE = 0.65 [95%CI: −0.92, 1.71], p = .548); however, right amygdala volume significantly mediated the association between neglect and anxiety symptoms (indirect effect = 0.46, SE = 0.31 [95% CI: 001, 1.27]), indicating that the variance between self-reported neglect and anxiety symptoms in boys is partially explained by increased right amygdala volume. When income and race were included as covariates, the sample size was reduced (n = 54) and the estimate of the indirect effect was similar (indirect effect = 0.43, SE = 0.32), but the confidence interval no longer indicated that the effect reached statistical significance (95% CI: −0.025, 1.16).

4. Discussion

In a community sample of 138 adolescents, we found that higher levels of self-reported neglect were significantly associated with larger volume of the right amygdala in boys. These results are consistent with previous reports that early experiences of adversity are related to greater amygdala volume (Mehta et al., 2009; Pechtel et al., 2014; Tottenham et al., 2010). Importantly, the present findings are also consistent with reports of larger amygdala volumes in children who experienced neglect in the form of institutional rearing, a severe form of psychosocial deprivation, suggesting that the association between neglect and increased amygdala volume is evident even in less severe forms of neglect experienced by children in the community (i.e., who are not referred for maltreatment). Thus, our findings support the utility of considering neglect along a continuum (Humphreys et al., 2018) in examining the association between experiences of deprivation and neurobiological outcomes. Further, we provide support that, in boys, right amygdala volume mediates the association between self-reported neglect and anxiety symptoms.

Notably, the current findings were sex-specific: only in boys was neglect associated with amygdala volume. Previous reports have found sex-specific neurobiological correlates of adverse childhood experiences (De Bellis & Keshavan, 2003; Teicher et al., 2003, 2004). Further, boys have been found to exhibit greater amygdala functional connectivity and reactivity to emotional material than do girls (Cahill et al., 2004; Kilpatrick, Zald, Pardo, & Cahill, 2005; Schneider et al., 2011). Our results indicate that early experiences of deprivation may affect neural structure differentially in males and females.

Sex differences in the behavioral consequences of early adversity have been well documented, arguably starting 40 years ago with findings of greater vulnerability in boys than in girls in response to family discord (Rutter, 1987). Boys faced with an emotional challenge may elicit more negative responses from parents, due to increased oppositional or disruptive behavior (Rutter, 1987). Gender differences in coping strategies may also contribute to sexually dimorphic responses to psychosocial stress. In general, males are less likely than are females to engage in adaptive coping strategies (see Tamres, Janicki, & Helgeson, 2002 for review). In particular, boys are less likely to seek social support or use problem-solving strategies in response to stressful situations, and are more likely to use avoidant coping mechanisms (Eschenbeck, Kohlmann, & Lohaus, 2007). Thus, it is possible that sex and gender-related differences in family dynamics and coping styles have downstream effects on the amygdala, given that boys showed a more pronounced effect of neglect on amygdala volume than was observed in girls. While previous research has tended to focus on females' vulnerability to early adversity based on immunological or hormonal pathways (e.g. Cordero, Ansermet, & Sandi, 2013; Machado et al., 2013; Palanza, 2001; Ruttle, Shirtcliff, Armstrong, Klein, & Essex, 2015), our findings suggest that males may be more vulnerable to the negative effects of neglect than are females, and are consistent with other work examining sex differences in outcomes in children with histories of neglect (Humphreys, Miron et al., 2017; McGloin & Widom, 2001).

Further, because the limbic system undergoes considerable development over adolescence, it is possible that sex-specific responses to early experiences of neglect are mediated by sex hormones such as estrogens and androgens (Rose et al., 2004; Tottenham & Sheridan, 2009; Uematsu et al., 2012). Indeed, amygdala volume has been found to be positively associated with higher levels of circulating testosterone in adolescent boys (M age = 11.70 years) (Neufang et al., 2009); moreover, the amygdala has a high proportion of androgen receptors relative to other brain regions (Martini & Melcangi, 1991). Given the host of changes in neural structure and circuitry that occur during adolescence and the critical role of sex hormones in myelination (Arain et al., 2013), it is possible that early experiences of deprivation convey sexually dimorphic effects through the neuroendocrine system. Further research is needed to explore the mechanisms by which testosterone may potentiate sex differences in amygdala volume in typical and atypical development.

The present results indicate that the effects of neglect on amygdala volume in boys are moderated by hemisphere: higher levels of neglect were associated with larger right, but not left, amygdala volume in boys. This finding is consistent with earlier reports of sex-specific hemispheric lateralization of amygdala connectivity and reactivity (Cahill, Uncapher, Kilpatrick, Alkire, & Turner, 2004; Kilpatrick et al., 2005); more specifically, compared to girls, boys have been found to exhibit greater functional connectivity of the right amygdala and greater activation of the right amygdala in response to emotionally arousing stimuli. Laterality differences in amygdala volume have been found to be associated with a wide range of stressors (e.g., Barry et al., 2017; Hill et al., 2001; Lyons-Ruth et al., 2016; Woon & Hedges, 2008; Woon & Hedges, 2009). In particular, larger right amygdala volume has been associated with trauma exposure and PTSD in adults (Woon & Hedges, 2009), suggesting that trauma contributes to asymmetrically lateralized amygdala volumes. Our finding that neglect only explained variation in right amygdala volume are consistent with these findings, but not with other studies that found different patterns of lateralization in other groups at heightened risk for psychological difficulties. For example, Lyons-Ruth et al. (2016) found that disorganized attachment was associated with increased left amygdala volume in adults. The functional significance of these asymmetries in response to stress, however, is far from clear, and is an important question to be addressed in future research.

Our results underscore the importance of examining possible neurobiological consequences of neglect. Previous research has typically assessed structural differences in relation to maltreatment, irrespective of type of maltreatment. For example, in a meta-analysis of brain structure in adults with and without early experiences of adversity, Calem et al. (2017) found no association between level of adversity and amygdala volume. Importantly, this report did not consider the type of adversity, but instead examined global effects of child maltreatment on structural outcomes. Given that early neglect appears to be sufficiently potent to confer neural alterations independent of experiences of other types of adversity, these divergent results may be explained by the fact that Calem et al. did not distinguish neglect from other forms of maltreatment. Researchers and theorists examining child maltreatment have emphasized the importance of differentiating environments that lack adequate input (e.g., neglect) from environments that are characterized by the presence of harmful input (e.g., abuse) (Humphreys & Zeanah, 2015; McLaughlin, Sheridan, & Lambert, 2014; Sheridan & McLaughlin, 2014; Zeanah & Sonuga-Barke, 2016). For instance, although abuse and neglect often co-occur (Dong, Anda, & Felitti, 2004), amygdala volume may be differentially affected by different types of stressors. Indeed, caregiving deprivation appears to affect the amygdala in particular. Lupien et al. (2011) found that children who were exposed to maternal depressive symptomatology, which is associated with reduced caregiving sensitivity, had larger bilateral amygdala volumes compared with children who had not been exposed to maternal depressive symptoms. Further, greater maternal symptom severity was associated with larger amygdala volume in offspring. No equivalent effect was found for the hippocampus, indicating that the amygdala may be uniquely sensitive to inadequate care.

Increased amygdala volume may have functional significance; we found preliminary evidence that amygdala volume mediates the association between self-reported neglect and anxiety symptoms in boys, although the finding was attenuated in a smaller sample size that included additional covariates. This finding is consistent with an earlier report that documented associations between previous institutionalization and amygdala volumes, and between amygdala volumes and internalizing behavior, but did not explore a possible mediation because of limited sample size (Tottenham et al., 2010). Previous research has demonstrated a positive association between amygdala volumes and anxiety in both pediatric and adult samples (Barrós-Loscertales et al., 2006; De Bellis et al., 2000), and a growing literature suggests that the amygdala mediates the association between adversity and difficulties in self-regulation. Children rely on caregivers as external sources of emotion regulation until they develop their own internal mechanisms of regulation (Atzil & Gendron, 2017); further, the amygdala is instrumental in fear learning and threat processing (Duvarci & Pare, 2014; Tovote, Fadok, & Lüthi, 2015). Taken together, previous evidence suggests that inadequate input from caregivers may result in altered development of amygdala circuitry (McLaughlin et al., 2014; Tottenham & Sheridan, 2009), amplifying neural activation in response to threatening and fearful stimuli (Maheu et al., 2010) and ultimately increasing the likelihood of psychopathology (Humphreys & Zeanah, 2015).

We should note several limitations of this study. First, the children in our sample reported mild to moderate levels of neglect, indicating that our sample represents a restricted range in terms of neglect experience. The majority of our sample was relatively high income, which likely limited the range of neglect we observed. Given the association between income and early adversity, more research is needed to determine whether income level and neglect experience contribute independently to neuroanatomical changes. Importantly, however, finding an association between neglect severity and amygdala volume even in this restricted sample indicates that even more minor forms of neglect may have measureable neuroanatomical consequences. Second, while our community sample was reasonably diverse with respect to race and ethnicity (see Table 1), the relatively small sample size within each identified racial group limits our ability to assess differences in self-reported neglect or amygdala volume in terms of race. Race is an important factor that may be associated with the likelihood of experiencing neglect given inequitable social conditions for minorities; the most recent report on child maltreatment cases in the U.S. finds that American Indian and African American children are at the greatest risk for maltreatment (U.S. Department of Health & Human Services, 2018). Third, we relied on adolescent self-report to assess neglect and anxiety. Self-report has some advantages over parent report for this construct, given concerns regarding bias due to potential social desirability. Nevertheless, adolescent report is not without potential for bias given difficulty in accurately reporting on experiences in very early life (i.e., infantile amnesia) and the potential for psychopathology to result in inflated perceptions of neglect (Chae, Goodman, Eisen, & Qin, 2011). Fourth, the MNBS does not provide information regarding the timing of exposure. This is an important area for future research given previous reports documenting the importance of timing and chronicity of early adversity on brain development (Pechtel et al., 2014; Tottenham & Sheridan, 2009). Finally, while we found differences in amygdala volume associated with variations in neglect, the correlational nature of these associations makes it difficult to draw causal conclusions. Given evidence from non-human animal studies and other studies in humans (e.g., children with institutional care histories), we believe that it is likely that neglect affects brain development. Nevertheless, future research is needed to replicate and extend these findings in order to increase confidence in our obtained pattern of results.

In conclusion, we document a positive association between self-reported neglect in adolescent boys reared outside of institutional settings and right amygdala volume and, in addition, provide evidence that right amygdala volume mediates the association between neglect and symptoms of anxiety in boys. Early caregiver deprivation has been found to increase children's risk for psychological difficulties later in life; we suggest that the amygdala plays a key role in mediating this association given its importance in emotional functioning, especially in threat responding and fear conditioning. Because neglect occurs on a continuum even among typical community families, and increased exposure to neglect confers risk for negative outcomes, policy efforts to reduce exposure to neglect should be a priority.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.chiabu.2018.03.016.

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