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

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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

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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