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Evidence for a sensitive period in the effects of early life stress on hippocampal volume

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Abstract

Exposure to stress has been causally linked to changes in hippocampal volume (HV). Given that the hippocampus undergoes rapid changes in the first years of life, stressful experiences during this period may be particularly important in understanding individual differences in the development of the hippocampus. One hundred seventy-eight early adolescents (ages 9–13 years; 43% male) were interviewed regarding exposure to and age of onset of experiences of stress; the severity of each stressful event was rated by an objective panel. All participants underwent structural magnetic resonance imaging, from which HVs were automatically segmented. Without considering the age of onset for stressful experiences, there was a small but statistically significant negative association of stress severity with bilateral HV. When considering the age of onset, there was a moderate and significant negative association between stress severity during early childhood (through 5 years of age) and HV; there was no association between stress severity during later childhood (age 6 years and older) and HV. We provide evidence of a sensitive period through 5 years of age for the effects of life stress on HV in adolescence. It will be important in future research to elucidate how reduced HV stemming from early life stress may contribute to stress-related health outcomes.

KEYWORDS
adversity, early life stress, hippocampus, sensitive period

1 | INTRODUCTION

Early life stress (ELS) is a potent risk factor for later negative mental and physical health outcomes (Shonkoff & Garner, 2012). The hippocampus, a structure that is involved in emotion, memory, and learning (Phelps, 2004), has a high concentration of glucocorticoid receptors (Jacobson & Sapolsky, 1991). Exposure to glucocorticoids reduces synaptogenesis and neurogenesis (Teicher, 2008), and non-human animal research indicates that such exposure, which is increased by stress, affects hippocampal gray matter volume (Karl, Schaefer, Malta, Dörfel, Rohleder, & Werner, 2006; Kim, Pellman, & Kim, 2015; Shi, Liu, Zhou, Yu, & Jiang, 2009) . Early research with humans examined adult outcomes of retrospectively reported stress, and found that experiences of trauma in childhood predicted reduced hippocampal volume (HV) in adults (Bremner, Randall, Vermetten, Staib, Bronen, Mazure, & Charney, 1997; Stein, Koverola, Hanna, Torchia, & McClarty, 1997). This work was followed by studies of children and adolescents who were broadly identified as having experienced ELS, typically using an extreme-group approach. This research yielded mixed findings concerning the effects of ELS on subsequent HV; whereas some studies demonstrated reduced HV in those with ELS (Hanson, Nacewicz, Sutterer, Cayo, Schaefer, Rudolph, & Davidson, 2015; Hodel, Hunt, Cowell, Heuvel, Gunnar, Thomas, & Thomas, 2015), others found no significant association (Frodl, Janowitz, Schmaal, Tozzi, Dobrowolny, Stein, & Grabe, 2017; Mehta, Golembo, Nosarti, Colvert, Mota, Williams, &

Sonuga-Barke, 2009; Sheridan, Fox, Zeanah, McLaughlin, & Nelson, 2012; Tottenham, Hare, Quinn, McCarry, Nurse, Gilhooly, & Casey, 2010). These mixed findings may be due in part to issues related to measurement, age of assessment (e.g., because the rate of hippocampal growth may be affected by adverse experience (Ellwood-Lowe, Humphreys, Ordaz, Camacho, Sacchet, & Gotlib, 2018)), and the timing of exposure to stress.

Because of the high density of glucocorticoid receptors, researchers have focused on this structure in examining the effects of stress during sensitive periods in development (Teicher, 2008). Indeed, research in adults suggesting that variation in HV is more strongly attributable to early life events than to normative aging processes (Lupien, Evans, Evans, Lord, Miles, Pruessner, Pike, & Pruessner, 2007) underscores the importance of elucidating the effects of the timing of stress on hippocampal development. Andersen, Tomada, Vincow, Valente, Polcari, and Teicher (2008) examined whether the age at which sexual abuse occurred was related to HV in adulthood. Women who experienced sexual abuse in the preschool age period (i.e., age 3–5 years) had significantly smaller HV than did women who experienced no abuse or who experienced abuse at older ages. Similarly, children who were adopted to the United States following early institutional care had smaller HV in early adolescence than did their counterparts who were raised in their biological homes (Hodel et al., 2015), suggesting an early sensitive period for hippocampal development. In concert with findings indicating that early life experiences may be particularly influential on HV, Luby and colleagues (Luby, Belden, Harms, Tillman, & Barch, 2016) found that maternal support in the preschool, but not in the school-age, period predicted growth in HV from school age into early adolescence. These longitudinal findings provide evidence for a sensitive period in early childhood during which life experiences may have a unique impact on HV.

There is also a growing understanding that how ELS is assessed and quantified may be important for identifying the sequelae of such experiences. Researchers examining the impact of stress on development frequently use an extreme-group or "threshold" approach, in which experiences of stress are grouped based on the presence or absence of a severe stressful event or experience. Within these extreme groups, however, there is often significant variability. For example, even in samples of previously institutionalized children, variability in the amount of time spent in adverse caregiving environments is associated with differences in outcome (Nelson, Fox, & Zeanah, 2014). In contrast to an extreme-group approach, capturing how stressors vary in severity allows for a finer-grained characterization of the experiences of children. In addition, simple models that weight all stressful events equally in severity are problematic (as discussed in Humphreys & Zeanah, 2015; McLaughlin & Sheridan, 2016; Zeanah & Sonuga-Barke, 2016). Psychometrically, summing the count of all stressful event treats each event with equal weight (i.e., with a weight of 1) and, therefore, does not distinguish between two individuals with the same number of endorsed events but who differ significantly in the severity of these events. There is an evidence that the severity of stressors (i.e., beyond a simple count) is associated with HV in adolescence (Hanson et al., 2015). Such an approach attempts to take into account both the number of stressful events *and* severity of stressors. In this context, the quantification of stress *severity* can take at least two approaches: (a) the sum of severity across all stressful events endorsed; or (b) the severity of the event rated to be most stressful. In the present study, we examine both of these approaches. The sum of stress severity may be most consistent with an allostatic load approach to stress, such that repeated activation of the stress response system accumulates in the long-term impact (McEwen, 1998). The second, in which a single stressful event is associated with long-term changes, is consistent with other work on physiological markers of stress exposure (e.g., telomere length following the death of a close family member; Parks, Miller, McCanlies, Cawthon, Andrew, Deroo, & Sandler, 2009). Importantly, no study has combined these approaches in the assessment of stress severity during the child's life with a measure of the *timing* of these stressful events.

In the present study, we examined whether the severity (i.e., objective severity rating of the most stressful experience reported) and timing of life stress (i.e., age of onset) are associated with HV in a community sample of early adolescents. Our sample was not selected on the basis of severe adversity, and has therefore the ability to advance our understanding of the potential sensitivity of response to typical stressors. We selected the hippocampus a priori as our region of interest given prior theoretical and empirical work indicating the stress sensitivity of this brain region (Teicher, 2008; Teicher, Andersen, Polcari, Anderson, Navalta, & Kim, 2003; Tottenham & Sheridan, 2009). We hypothesized that severity of stress, regardless of age of onset, would be associated with smaller HV and, further, that the association between stress severity and HV would be stronger in early childhood (through 5 years of age) than in later childhood (after age 6 years).

RESEARCH HIGHLIGHTS

- Severity of stress in childhood is associated with reduced left and right hippocampal volume.
- Stress severity in early childhood, but not later in childhood, appears to be responsible for the association between stress severity and hippocampal volume.
- Stress severity persists as a statistical predictor of reduced hippocampal volume after covarying for the number of stressful events experienced.

2 | METHODS

2.1 | Participants

Participants were 178 children (77 boys, 101 girls) aged 9.11–13.98 years (M age = 11.39 years, SD = 1.04) who were recruited to take part in a longitudinal study examining ELS and

psychopathology across the pubertal transition (see Humphreys, Kircanski, Colich, & Gotlib, 2016 for more information about the sample). In brief, participants were selected from the community with the goal of obtaining a range of severity of ELS. The study was approved by the Stanford University Institutional Review Board; participants and their parents gave assent and informed consent, respectively. Demographic information is presented in Table 1. The average income of the sample was quite high, as the cost of living in Santa Clara county is among the highest in the nation ($101,173; U.S. Census Bureau, https://www.census.gov/quickfacts/fact/table/santaclaracountycalifornia,US/PST045216). Thus, an income-to-needs ratio (i.e., household income/Santa Clara county low income limit for the number of people in household) may better reflect socioeconomic status (SES). Based on having an income-to-needs ratio <1 (cutoff determined based on reccomendations based on U.S. Census Bureau, 2004), 30% of families in the sample were low-income. 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. 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 Tanner stage, in order to obtain participants in early puberty. In total, 214 individuals participated in our study, of whom 202 (94%) reported a stressful event with an identified age of onset; all of these events were rated for severity (see Supporting Information Table S1 for frequency of event endorsed by age period). Individuals who reported no events or only events without an age of onset (n = 12) were not included in subsequent analyses. Of the remaining 202 participants, 20 were not scanned and 4 did not provide usable structural scans, resulting in available HV information for 178 participants (88%).

TABLE 1 Descriptive statistics for the sample

	Full sample (n = 178)
Age	11.39 (1.04)
Sex (% male)	43%
Race/ethnicity	49% Caucasian 23% Mixed/Other 13% Asian 8% Hispanic 7% African American
Household income[a]	1% Less than $5,000 2% $5,001–$10,000 1% $10,001–$15,000 4% $15,001–$25,000 2% $25,001–$35,000 6% $35,001–$50,000 9% $50,001–$75,000 12% $75,000–$100,000 27% $100,001–$150,000 37% $150,000 or greater
Income-to-needs[a]	1.29 (0.55)
Average tanner stage	2.04 (0.74)
Number of stress events	4.75 (3.28)
Lifetime stress severity	1.59 (0.78)
Stress severity ages 0–5 years[b]	1.42 (0.96)
Stress severity age 6 years and older[b]	1.33 (0.70)
Left hippocampal volume (mm^3)	4,256.80 (433.02)
Right hippocampal volume (mm^3)	4,226.50 (419.80)

Notes. Mean (*SD*).
[a]Available for 169. [b]For those with a stressful event occurring during this age period.

2.2 | Procedure

Participants were interviewed about experiences of life stress and completed other measures and tasks not reported here. Participants were compensated for their participation.

2.3 | Measures

2.3.1 | Life stress

Children were interviewed about their stressful life experiences using a modified version of the Traumatic Events Screening Inventory for Children (TESI-C) (Ribbe, 1996). Modifications are described in detail elsewhere (King, Colich, LeMoult, Humphreys, Ordaz, Price, & Gotlib, 2016); briefly, children responded to questions about 30 types of stressful events (e.g., moving, parental divorce, parental arguments). Interviewers obtained details about the events, including the age of onset provided based on the child's recollection. A panel of three coders, blind to the children's reactions and behaviors during the interview, rated the objective severity of each type of stressful event endorsed using a modified version of the UCLA Life Stress Interview coding system (Rudolph & Hammen, 1999) on a scale of 1–5, increasing in half-point increments (1 = non-event or no impact [e.g., viewing remnants of a car accident]; 5 = extremely severe impact [e.g., witnessing a violent death]; ICC = 0.99). Events given a score of 1 were not included, and subsequently 1.5 was subtracted from all values in order to create a range of severity from 0 to 3.5.

Our primary measurement of stress severity was the rating given to the most severe stressful event reported. We considered stress severity based on the timing of the stress onset, including examining events that occurred in early life (i.e., birth through 5 years), an age cutoff based on our own and others' previous work on ELS (Furniss, Beyer, & Müller, 2009; Humphreys et al., 2016). That is, stress severity in each age period was determined as the most severe stress occurring during that period. The nature of our stress interview meant that we obtained integer values for the age at

which each event occurred; thus, in order to split events based on developmental status we had to make a determination using year cutoffs. A sizable number of participants (n = 112 [63%]) reported a stressful event prior to age 6 years; using an earlier cut point would have resulted in a significantly reduced sample. Thus, the selection of a particular age split (e.g., 0 vs. 1+, 0–1 vs. 2+, etc.) was not only influenced by current age cutoffs used in the field of infant mental health but also sample size considerations. Almost all participants (n = 175 [98%]) reported at least one stressful event that occurred later in childhood (i.e., from age 6 until their interview date). The type and subjective quality of stressful events may vary based on developmental stage; in Supporting Information Table S1 we present the overall rates of different types of stressful events endorsed based on age of onset. For those with stressful events during both age periods (n = 109 [61%]), there was a significant correlation between stress severity in early childhood with stress severity in later childhood ($r(107) = 0.26$, $p = 0.006$). Additionally, we obtained a count of the number of stressful events and a cumulative measure of stress that takes into account both the number and the severity of stressful events (see King et al., 2016), which we also included as alternative predictors of HV.

Parents completed a questionnaire version of the TESI regarding their children's experience of potentially stressful or traumatic events. The same items as those included in the child report were assessed, including the presence or absence of, and age of onset for, each event. We did not rate severity of stressors because parents were not asked to provide details about each event (as children provided through interviews) to allow for panel ratings.

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. The SPGR sequence was repeated up to two additional times if the first acquisition did not yield clear images. For each participant with multiple acquisitions, the single SPGR image with the clearest structural boundaries (i.e., that was free from motion or other artifacts) was used for further analysis.

2.5 | Segmentation of the hippocampus and thalamus

We used the FreeSurfer software suite (v5.3; available at: http://surfer.nmr.mgh.harvard.edu/) for the automated segmentation of subcortical volumes from the T1w images (Fischl, Salat, Busa, Albert, Dieterich, Haselgrove, & Dale, 2002). Automated segmentation of HV using this pipeline has been shown to be robust against anatomic variability and to have comparable accuracy to manual labeling techniques (Fischl et al., 2002; Fischl & Dale, 2000; Morey, Petty, Xu, Pannu Hayes, Wagner, Lewis, & McCarthy, 2009) and acceptable scan-rescan reliability (Jovicich, Czanner, Han, Salat, Kouwe, Quinn, & Fischl, 2009). All participants were physically healthy per our recruitment criteria; there were no brain anomalies with the exception of arachnoid cysts (n = 9) and grossly asymmetrical lateral ventricles (n = 2). T1w images that failed registration or were poorly skull-stripped were manually corrected by a co-author with extensive experience with FreeSurfer (MCC) and re-run through FreeSurfer's recon-all pipeline to ensure accurate estimated ICV (Buckner, Head, Parker, Fotenos, Marcus, Morris, & Snyder, 2004). Using the FreeView image viewer, all hippocampal segmentations were visually inspected for processing and segmentation errors. Segmentation errors included over-extension of the lateral hippocampal segmentation and incomplete segmentation of the hippocampal body. As noted above, only those with usable left (n = 163; 92%) or right (n = 175; 98%) HV were included. In supplemental analyses to examine the specificity of associations of stress and HV, we analyzed volume of the thalamus (a region that is less likely to be affected by stress severity; Aronsson, Fuxe, Dong, Agnati, Okret, & Gustafsson, 1988; Frodl, Reinhold, Koutsouleris, Reiser, & Meisenzahl, 2010; Sah, Pritchard, Richtand, Ahlbrand, Eaton, Sallee, & Herman, 2005) as a control region. More information about these analyses can be found in Supporting Information.

2.6 | Data analysis

A Pearson's correlation was conducted to assess concordance between counts of child and parent reported stressors in early childhood (i.e., through 5 years of age). Separate left and right HV values were regressed on age, sex, and ICV (see Supporting Information Table S2); all HV values presented are thus residual values from this initial linear regression. We used linear regressions to examine the association of lifetime stress severity (a dimensional measure in which higher scores indicate greater stress severity) with HV measured in early adolescence, examining each hemisphere separately. We examined both linear and quadratic terms for stress severity, given the possibility that the association between stress and outcomes would follow an inverted U-shaped function (see Lupien, Maheu, Tu, Fiocco, & Schramek, 2007). Next, we tested whether stress severity during specific age periods (i.e., early childhood, through 5 years of age, vs. later childhood, age 6 years or older) predicted HV. Finally, we examined the predictive impact of stress severity over and above alternative metrics of stress (i.e., number of stressors and cumulative measurement of stress). Given the exploratory nature of the study, we did not correct for multiple comparisons.

3 | RESULTS

Demographic and clinical variables assessed in this study are presented in Table 1. Given limitations in self-report for early life events, we examined the association between child- and parent-reported

events in early childhood. We found a moderate, positive association (r (176) = 0.42, $p < 0.001$), supporting the validity of child report of stressful events.

3.1 | Lifetime stress severity and hippocampal volume

We conducted a linear regression to test the association between stress severity across both early and late childhood periods and residual values for HV (controlling for age, sex, and ICV). There was a significant association between lifetime stress severity and left HV ($\beta = -0.19$, t (161) = −2.44, $p = 0.016$, $R^2 = 0.04$). Similarly, there was a significant association between lifetime stress severity and right HV ($\beta = -0.16$, $t(173) = -2.17$, $p = 0.032$, $R^2 = 0.03$). Sex did not moderate these associations, and the quadratic term for stress severity did not significantly improve model fit and therefore this term was not included in the model.

3.2 | Stress severity and hippocampal volume by age of stress onset

To test whether the association between stress severity and HV differed as a function of the age of stress onset, we conducted separate linear regressions based on stress severity during the two age periods (i.e., through 5 years of age or age 6 or older). There was a significant association between stress severity in early childhood and left HV ($\beta = -0.28$, $t(103) = -2.93$, $p = 0.004$, $R^2 = 0.08$; Figure 1a), as well as right HV ($\beta = -0.31$, $t(107) = -3.39$, $p < 0.001$, $R^2 = 0.10$; Figure 1c). For severity of stress experienced in later childhood, there was no significant association between stress severity and HV (left: $\beta = -0.10$, $t(158) = -1.21$, $p = 0.229$, $R^2 = 0.01$; right: $\beta = -0.01$, $t(170) = -0.11$, $p = 0.922$, $R^2 < 0.001$; Figure 1b,d). Sex did not moderate these associations, and the quadratic term for stress severity did not significantly improve model fit.

To further clarify the specific effect of stress severity in early childhood, we conducted an additional regression analysis for the subset of participants who reported stressors in both age periods ($n = 109$) in which we regressed HV on early childhood stress severity when controlling for later childhood stress severity. For left HV, stress severity in early childhood remained a significant predictor above and beyond later childhood stress severity ($\beta = -0.26$, $t(99) = -2.59$, $p = 0.011$, $R^2 = 0.06$, $p = 0.011$; Full model: $F(2, 99) = 4.71$, $p = 0.011$); stress severity in later childhood did not significantly predict HV ($\beta = -0.10$, $t(99) = -1.00$, $p = 0.320$, $R^2 = 0.01$, $p = 0.320$). Similarly, for right HV, stress severity in early childhood was a significant predictor above and beyond later childhood stress severity ($\beta = -0.33$, $t(103) = -3.37$, $p = 0.001$, $R^2 = 0.10$, $p < 0.001$; Full model: $F(2, 103) = 5.74$, $p = 0.004$); stress severity in later childhood did not significantly predict HV ($\beta = 0.05$, $t(103) = -0.55$, $p = 0.581$, $R^2 = 0.003$, $p = 0.581$). To examine whether these two associations differed from one another, we conducted a test of the difference between two dependent correlations with one variable in common (Lee & Preacher, 2013) using Fisher's r-to-z transformation in all participants; this analysis yielded a statistically significant difference in the correlations between stress severity during early and later childhood with right HV ($z = -2.68$, $p = 0.007$); this difference did not reach statistically significance for left HV ($z = -1.59$, $p = 0.112$).

3.3 | Considering different indices of stress

In our approach we used the severity ratings based on the stressful event rated as most severe, but this is only one way to assess experiences of stress dimensionally. We used this approach because summed counts of events do not take into account the severity of the events. Severity of lifetime stress remained a significant predictor even after including the number of stressors reported in the child's life (left: $\beta = -0.22$, $t(160) = -2.32$, $p = 0.021$, $R^2 = 0.03$; Full model: $F(2, 160) = 3.15$, $p = 0.045$; right: $\beta = -0.20$, $t(172) = -2.12$, $p = 0.035$, $R^2 = 0.03$; Full model: $F(2, 172) = 2.54$, $p = 0.082$). For stress in early life, we also found that severity of stress during this period remained a significant predictor even after including the number of stressors reported through 5 years of age (left: $\beta = -0.37$, $t(102) = -3.41$, $p < 0.001$, $R^2 = 0.10$; Full model: $F(2, 102) = 5.82$, $p = 0.004$; right: $\beta = -0.40$, $t(106) = -3.72$, $p < 0.001$, $R^2 = 0.12$; Full model: $F(2, 106) = 7.02$, $p < 0.001$).

Further, we should point out that we used severity of the most severe stressful event over an approach in which a sum of severity ratings is computed across different types of events (King et al., 2016). We made this choice largely because using cumulative severity ratings can result in participants who experienced either several relatively low-level stressful events or a single very severe stressful event receiving the same score. The severity of the most severe lifetime stressful event was no longer a significant predictor of HV when including cumulative lifetime stress severity as a covariate (left: $\beta = -0.20$, $t(160) = -1.64$, $p = 0.104$, $R^2 = 0.02$; Full model: $F(2, 160) = 2.95$, $p = 0.055$; right: $\beta = -0.19$, $t(172) = -1.61$, $p = 0.108$, $R^2 = 0.02$; Full model: $F(2, 172) = 2.37$, $p = 0.096$). However, the severity of the most severe stressful event in early life remained a significant predictor when including the cumulative severity of stressful events reported through 5 years of age as a covariate (left: $\beta = -0.35$, $t(102) = -2.30$, $p = 0.024$, $R^2 = 0.05$; Full model: $F(2, 102) = 4.46$, $p = 0.014$; right: $\beta = -0.44$, $t(106) = -2.76$, $p = 0.007$, $R^2 = 0.06$; Full model: $F(2, 106) = 6.10$, $p = 0.003$).

Given that family financial problems (see Supporting Information Table S1) was a stressor type included in the stress interview, we did not consider current family income as a predictor. We did, however, examine whether current income-to-needs ratio was associated with experiences of stress in early life. Children who had experienced a stressor before age 6 years had, on average, a lower current income-to-needs ratio scores than did children who did not experience a stressor prior to age 6 years ($t(145.45) = 3.20$, $d = 0.51$, $p = 0.002$).

4 | DISCUSSION

In the present study we provide evidence of a sensitive period for the effect of stress severity on HV in a sample of 178 early adolescents.

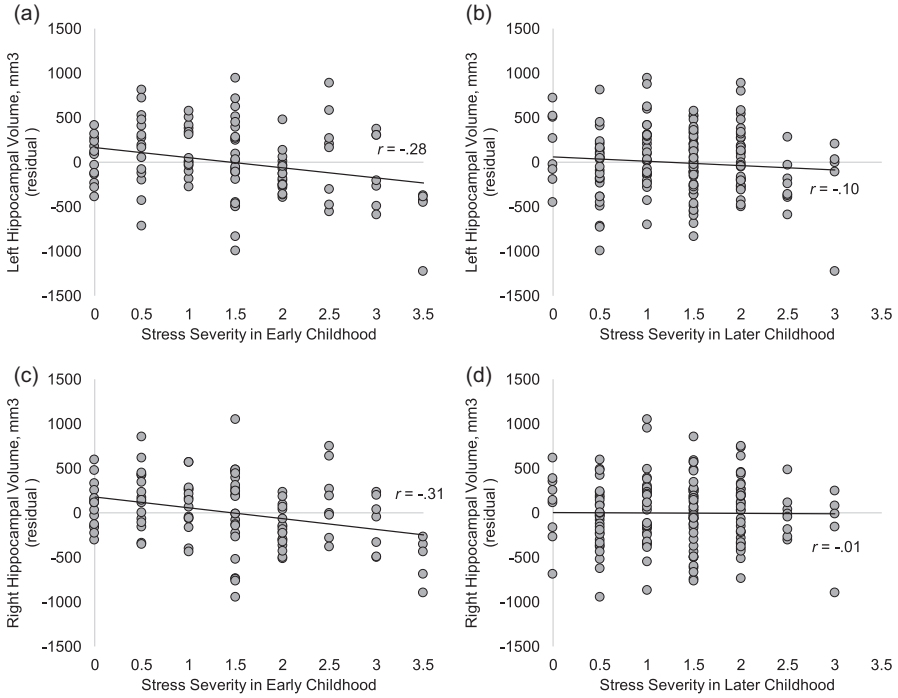

FIGURE 1 Left hippocampal volume by stress severity in early childhood (a) and later childhood (b). Right hippocampal volume by stress severity in early childhood (c) and later childhood (d)

Our approach indicated that HV varied as a function of naturally occurring variation in severity of ELS, over and above metrics assessing simple count of stressful experiences or cumulative exposure to stress. Although severity of stress across the child's lifetime was associated with HV, this relation was driven by the severity of stress in early life (birth through 5 years of age) rather than in later childhood. Specifically, whereas stress severity in early childhood was negatively associated with bilateral HV, there was no such association for stress severity experienced in later childhood. Further, cumulative stress, as quantified by the total number of stressful experiences reported and the cumulative objective severity of these experiences, did not explain the unique effect of the most severe stressful experience in early life on HV. While we observed a small effect size for the association between severity of lifetime stress and HV, we observed a medium effect size for the association between stress severity in early life and HV (Cohen, 1992). Our findings have important clinical implications given that smaller HV has been prospectively linked to a number of outcomes, including vulnerability to psychopathology following trauma (Gilbertson, Shenton, Ciszewski, Kasai, Lasko, Orr, & Pitman, 2002), poorer antidepressant treatment response (Colle, Dupong, Colliot, Deflesselle, Hardy, Falissard, & Corruble, 2016), and memory deficits (Zheng, Li, Xiao, He, Zhang, & Li, 2017).

While many studies have documented an association between life stress and HV (Hanson et al., 2015; Hodel et al., 2015; Zimmerman, Ezzati, Katz, Lipton, Brickman, Sliwinski, & Lipton, 2016), not all have (Frodl et al., 2017; Mehta et al., 2009; Sheridan et al., 2012; Tottenham et al., 2010), and among those that have reported a significant association there is variability in the magnitude of the effect size. Discrepancies in past research may be due in part to the timing of the stressors assessed. Investigators who consider timing in relation to environmental experiences on HV, rather than simple group or count-based approaches to ELS without considering age, have reported results consistent with the current findings. For example, early caregiving quality in the form of maternal support was found to predict both absolute HV (Luby, Barch, Belden, Gaffrey, Tillman, Babb, & Botteron, 2012) and increased growth of the hippocampus (Luby et al., 2016). Taken together with findings from the present study, and early work in this area (Andersen et al., 2008), there is growing evidence that there is a sensitive period in the first years of life for the effects of stress on hippocampal development. An alternative explanation, however, is that the impact of early stress on the observed outcomes in early adolescence may be a function of a longer developmental timescale, as the effects of stress more proximal to the age at assessment may require more time to have observable effects.

In addition to the age at which stressful events occurred, the age at which HV is assessed is also relevant; researchers have posited that the impact of ELS on the hippocampus is not evident until adolescence or adulthood (Andersen & Teicher, 2004; Carrion, Weems, & Reiss, 2007; Lupien, Parent, Evans, Tremblay, Zelazo, Corbo, & Séguin, 2011; Tottenham & Sheridan, 2009). These formulations are based, in part, on findings that smaller HV has been found in adults, but not in children, with post-traumatic stress disorder (Woon & Hedges, 2008). The present study provides evidence of ELS-associated differences in HV in early adolescence; it is possible, of course, that later developmental periods are also relevant for the effects of ELS on HV. For example, in their small study of childhood sexual assault survivors, Andersen et al. (2008) identified the adolescent period as a time of vulnerability for the effects of ELS on HV. The hippocampus changes throughout adolescence (Bramen, Hranilovich, Dahl, Forbes, Chen, Toga, & Sowell, 2011; Goddings, Mills, Clasen, Giedd, Viner, & Blakemore, 2014; Satterthwaite, Vandekar, Wolf,

Ruparel, Roalf, Jackson, & Gur, 2014). Many researchers have suggested that adolescence, and in particular, the transition through puberty, is a sensitive period in development (Blakemore, Burnett, & Dahl, 2010; Fuhrmann, Knoll, & Blakemore, 2015; Teicher, 2008). Because adolescence is also a time of heightened risk for many forms of psychopathology (F. S. Lee, Heimer, Giedd, Lein, Šestan, Weinberger, & Casey, 2014), it is a critically important developmental period during which to study the neurobiological underpinnings of maladaptive cognitions and behaviors. Certainly, further longitudinal research is required to understand precisely how early stress may influence HV across adolescence. Further, variations in HV set in motion in early life may not have behavioral implications until later in development, and later events may lead to brain alterations in regions and functional networks outside of the hippocampus. Thus, the present results should not be taken to indicate that *only* events early in life are meaningful. Prospective studies with repeated assessments of stress, HV, and behavior are needed to examine possible bidirectional influences and consequences of stress.

Recruiting and assessing a community sample of adolescents with a range of severity of stressful experiences, rather than including only children with and without severe stress, allowed us to examine the sensitivity of the hippocampus to stressful events occurring in the normative, or typical, range. Our method for measuring stress was important for our ability to identify a link between experiences of stress in early life and HV. We conducted supplemental analyses using an index of cumulative stress through early life, as well as a count of stressful events, as covariates in models with the severity of the most severe stressor reported. These analyses support the theory that the most severe stressor is the likely consequential for HV. There are, however, alternative approaches that may be useful. In contrast to the present findings, Hanson et al. (2015) found that panel-rated cumulative stress severity predicted smaller HV. In addition, perceived stress may also be a useful indicator in stress measurement for HV (Zimmerman et al., 2016). It is worth noting that the events reported (see Supporting Information Table S1) vary in their chronicity and duration—two factors not explicitly examined here given the sample size. As a field, we do not yet agree on the specific aspects of stress that are most important; it is likely that different ways of categorizing and quantifying stressful experiences will be differentially impactful depending on the outcome examined. The present findings support our hypothesis that stressors in early life have a greater impact on HV than do stressors in later childhood; however, we cannot determine precisely why this may be the case. There are three explanations that may account for this association. First, the hippocampus may be more stress sensitive earlier in development. Second, the types and severity of stressors in early life may differ from those experienced in later life (as seen in Supporting Information Table S1). And third, even stressors of the same type and perceived severity may be experienced differently as a function of the child's cognitive maturity (Masten & Narayan, 2012).

There is increasing interest in understanding the role that income or socioeconomic status may play in child development. Current theories propose that the mechanisms by which SES affects child outcomes include both increased exposure to stress and reduced resources (Duncan, Magnuson, & Votruba-drzal, 2017). We explicitly included stressful events that stemmed from family financial problems; this item was included in the original stress interview assessment. Given that there may be unique neurobiological correlates of threat in comparison to deprivation (McLaughlin, Sheridan, & Lambert, 2014; Sheridan & McLaughlin, 2014), we expect that any link between SES and HV may be due to the increased stress associated with poverty (as opposed to non-stress related correlates of poverty posited to affect other brain regions). Our finding indicate that children who experienced stress in early life had a lower current income-to-needs ratio than did children who reported no stress during this age period highlights that stress is not randomly distributed. While in practice it is difficult to disentangle the mechanisms responsible for increased negative outcomes associated with children from lower SES families, increased stress and fewer financial resources are likely to be have unique associations with negative outcomes (Farah, Betancourt, Shera, Savage, Giannetta, Brodsky, & Hurt, 2008; Humphreys & Zeanah, 2015).

In closing, we should note four limitations of this study. First, although our assessments of ELS were conducted in early adolescence, they are nevertheless retrospective in nature and were divided into two main age groupings on the basis of self-reported age of stress onset. Possible biases in memory, as well as infantile amnesia, may lead to reports that deviate from actual experiences. Nevertheless, the magnitude of the correlation between parent and child reports of the number of stressful experiences in early life lends credibility to these self reports. Informant agreement is generally low (De Los Reyes & Kazdin, 2005), and the moderate positive effect size may be larger than expected based on similar work (Dohrenwend, 2006). Further, biases in memory themselves may be related to HV; given the correlational nature of this study, we cannot rule out the possibility that individuals who grow up with small HV could interpret various situations as being more or less stressful than do individuals with larger HV. Although the use of objective severity ratings rather than subjective responses mitigates some of this concern, it is nevertheless likely that some events were not reported and, therefore, could not be considered in our ratings of stress severity. Similarly, experiences of stress are cumulative, if not correlated, across the lifespan: individuals who experience high levels of ELS in their first years of life are likely to experience higher levels of stress over subsequent years. Our approach did not separate repeated or chronic stress from the age at which the first stress occurred; however, given that stress severity in early childhood remained significant after accounting for both number of stressful experiences reported and severity of stress in later childhood, it is likely that earlier rather than repeated or later stress is most influential. Further, researchers in the field of infant mental health typically consider birth to 5 years of age as “early life” (Zero to Three, 2016), but because development is continuous, there is more similarity between 5- and 6-year-olds than between 1- and 5-year-olds.

Second, as we alluded to above, important changes in hippocampal development occur during adolescence, and longitudinal research is needed to determine whether the observed effects are

long-lasting, are mutable by experiences, and what, if any, implications there are of reduced HV. Third, we focused on the hippocampus as an a priori region of interest. Notably, analyses examining the effects of stress severity on the thalamus, a region considered to be less stress sensitive than is the hippocampus, did not yield any significant associations, supporting the hypothesis that the hippocampus is more stress sensitive than are other brain regions. In this context, the hippocampus is one of several brain regions posited to be altered by stress exposure (Teicher, 2008) and, even within the hippocampus, there is heterogeneity in terms of subfield differences in maturation and normative age-related change (Gogtay, Nugent, Herman, Ordonez, Greenstein, Hayashi, & Rapoport, 2006). Examining hippocampal subfields is an important next step; one study in adults found that perceived stress, measured dimensionally, was most strongly associated with CA2/CA3 and CA/dentate gyrus (Zimmerman et al., 2016). In addition, we used automated processes to segment the hippocampus, which may have led to inaccuracies, although researchers have documented comparability of manual and automated segmentation (Morey et al., 2009; Suh, Wang, Das, Avants, & Yushkevich, 2011). Finally, this community sample was relatively high-income; therefore, our findings should be replicated in more economically diverse samples.

Despite these limitations, the present study is important in documenting that the severity of stressful experiences in early life is associated with smaller bilateral HV in early adolescence. Importantly, no such association was found for the severity of stress occurring later in childhood, suggesting that there is a sensitive period for the effects of stress on hippocampal development. These findings add to a growing body of research underscoring the importance of early life experiences in influencing the course of brain development. Future work will benefit from examining prospective associations and the effects of stress during adolescence (and across the pubertal transition) to identify long-term changes and potential targets for intervention. Finally, extending this line of work to examine potential of HV in predicting the functional outcomes in childhood and adolescence remains an important step in identifying mechanisms by which early adversity affects later health outcomes.

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REFERENCES

Andersen, S. L., & Teicher, M. H. (2004). Delayed effects of early stress on hippocampal development. *Neuropsychopharmacology*, *29*(11), 1988–1993. https://doi.org/10.1038/sj.npp.1300528.

Andersen, S. L., Tomada, A., Vincow, E. S., Valente, E., Polcari, A., & Teicher, M. H. (2008). Preliminary evidence for sensitive periods in the effect of childhood sexual abuse on regional brain development. *Journal of Neuropsychiatry*, *20*(3), 292–301. https://doi.org/10.1176/appi.neuropsych.20.3.292.

Aronsson, M., Fuxe, K., Dong, Y., Agnati, L. F., Okret, S., & Gustafsson, J. A. (1988). Localization of glucocorticoid receptor mRNA in the male rat brain by in situ hybridization. *Proceedings of the National Academy of Sciences*, *85*(23), 9331–9335. https://doi.org/10.1073/pnas.85.23.9331.

Blakemore, S. J., Burnett, S., & Dahl, R. E. (2010). The role of puberty in the developing adolescent brain. *Human Brain Mapping*, *31*(6), 926–933. https://doi.org/10.1002/hbm.21052.

Bramen, J. E., Hranilovich, J. A., Dahl, R. E., Forbes, E. E., Chen, J., Toga, A. W., … Sowell, E. R. (2011). Puberty influences medial temporal lobe and cortical gray matter maturation differently in boys than girls matched for sexual maturity. *Cerebral Cortex*, *21*(3), 636–646. https://doi.org/10.1093/cercor/bhq137

Bremner, J. D., Randall, P., Vermetten, E., Staib, L., Bronen, R. A., Mazure, C., … Charney, D. S. (1997). Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse—a preliminary report. *Biological Psychiatry*, *41*(1), 23–32. https://doi.org/10.1016/S0006-3223(96)00162-X

Buckner, R. L., Head, D., Parker, J., Fotenos, A. F., Marcus, D., Morris, J. C., & Snyder, A. Z. (2004). A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: Reliability and validation against manual measurement of total intracranial volume. *NeuroImage*, *23*(2), 724–738. https://doi.org/10.1016/J.NEUROIMAGE.2004.06.018

Carrion, V. G., Weems, C. F., & Reiss, A. L. (2007). Stress predicts brain changes in children: A pilot longitudinal study on youth stress, posttraumatic stress disorder, and the hippocampus. *Pediatrics*, *119*(3), 509–516. https://doi.org/10.1542/peds.2006-2028

Cohen, J. (1992). A power primer. *Psychological Bulletin*, *112*(1), 155–159. https://doi.org/10.1037/0033-2909.112.1.155

Colle, R., Dupong, I., Colliot, O., Deflesselle, E., Hardy, P., Falissard, B., … Corruble, E. (2016). Smaller hippocampal volumes predict lower antidepressant response/remission rates in depressed patients: A meta-analysis. *The World Journal of Biological Psychiatry*, *19*(5), 360–367, https://doi.org/10.1080/15622975.2016.1208840

De Los Reyes, A. & Kazdin, A. E. (2005). Informant discrepancies in the assessment of childhood psychopathology: A critical review, theoretical framework, and recommendations for further study. *Psychological Bulletin*, *131*, 483–509. https://doi.org/10.1037/0033-2909.131.4.483

Dohrenwend, B. P. (2006). Inventorying stressful life events as risk factors for psychopathology: Toward resolution of the problem of intracategory variability. *Psychological Bulletin*, *132*(3), 477–495. https://doi.org/10.1037/0033-2909.132.3.477

Duncan, G. J., Magnuson, K., & Votruba-drzal, E. (2017). Moving beyond correlations in assessing the consequences of poverty. *Annual Review of Psychology*, *68*(1), 413–434, https://doi.org/10.1146/annurev-psych-010416-044224

Ellwood-Lowe, M. E., Humphreys, K. L., Ordaz, S. J., Camacho, M. C., Sacchet, M. D., & Gotlib, I. H. (2018). Time-varying effects of income on hippocampal volume trajectories in adolescent girls. *Developmental Cognitive Neuroscience*, *30*, 41–50. https://doi.org/10.1016/j.dcn.2017.12.005

Farah, M. J., Betancourt, L., Shera, D. M., Savage, J. H., Giannetta, J. M., Brodsky, N. L., … Hurt, H. (2008). Environmental stimulation, parental nurturance and cognitive development in humans. *Developmental Science*, *11*(5), 793–801. https://doi.org/10.1111/j.1467-7687.2008.00688.x

Fischl, B., & Dale, A. M. (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences of the United States of America*, *97*(20), 11050–11055. https://doi.org/10.1073/pnas.200033797

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., … Dale, A. M. (2002). Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. *Neuron*, *33*(3), 341–355. https://doi.org/10.1016/S0896-6273(02)00569-X

Frodl, T., Janowitz, D., Schmaal, L., Tozzi, L., Dobrowolny, H., Stein, D. J., … Grabe, H. J. (2017). Childhood adversity impacts on brain subcortical structures relevant to depression. *Journal of Psychiatric Research*, *86*, 58–65. https://doi.org/10.1016/j.jpsychires.2016.11.010

Frodl, T., Reinhold, E., Koutsouleris, N., Reiser, M., & Meisenzahl, E. M. (2010). Interaction of childhood stress with hippocampus and prefrontal cortex volume reduction in major depression. *Journal of Psychiatric Research*, *44*(13), 799–807. https://doi.org/10.1016/j.jpsychires.2010.01.006

Fuhrmann, D., Knoll, L. J., & Blakemore, S.-J. (2015). Adolescence as a Sensitive Period of Brain Development. *Trends in Cognitive Sciences*, *19*(10), 558–566. https://doi.org/10.1016/j.tics.2015.07.008. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/26419496

Furniss, T., Beyer, T., & Müller, J. M. (2009). Impact of life events on child mental health before school entry at age six. *European Child and Adolescent Psychiatry*, *18*(12), 717–724. https://doi.org/10.1007/s00787-009-0013-z

Gilbertson, M. W., Shenton, M. E., Ciszewski, A., Kasai, K., Lasko, N. B., Orr, S. P., & Pitman, R. K. (2002). Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nature Neuroscience*, *5*(11), 1242–1247. https://doi.org/10.1038/nn958

Goddings, A. L., Mills, K. L., Clasen, L. S., Giedd, J. N., Viner, R. M., & Blakemore, S. J. (2014). The influence of puberty on subcortical brain development. *NeuroImage*, *88*, 242–251. https://doi.org/10.1016/j.neuroimage.2013.09.073

Gogtay, N., Nugent, T. F., Herman, D. H., Ordonez, A., Greenstein, D., Hayashi, K. M., … Rapoport, J. L. (2006). Dynamic mapping of normal human hippocampal development. *Hippocampus*, *16*(8), 664–672. https://doi.org/10.1002/hipo.20193

Hanson, J. L., Nacewicz, B. M., Sutterer, M. J., Cayo, A. A., Schaefer, S. M., Rudolph, K. D., … Davidson, R. J. (2015). Behavioral problems after early life stress: Contributions of the hippocampus and amygdala. *Biological Psychiatry*, *77*(4), 314–323. https://doi.org/10.1016/j.biopsych.2014.04.020

Hodel, A. S., Hunt, R. H., Cowell, R. A., Van Den Heuvel, S. E., Gunnar, M. R., Thomas, K. M., … Thomas, K. M. (2015). Duration of early adversity and structural brain development in post-institutionalized adolescents. *NeuroImage*, *105*, 112–119. https://doi.org/10.1016/j.neuroimage.2014.10.020

Humphreys, K. L., Kircanski, K., Colich, N. L., & Gotlib, I. H. (2016). Attentional avoidance of fearful facial expressions following early life stress is associated with impaired social functioning. *Journal of Child Psychology and Psychiatry*, *10*(10), 1174–1182. https://doi.org/10.1111/jcpp.12607

Humphreys, K. L., & Zeanah, C. H. (2015). Deviations from the expectable environment in early childhood and emerging psychopathology. *Neuropsychopharmacology*, *40*(1), 154–170. https://doi.org/10.1038/npp.2014.165

Jacobson, L., & Sapolsky, R. (1991). The role of the hippocampus in feedback regulation of the hypothalamic-pituitary-adrenocortical axis. *Endocrine Reviews*, *12*(2), 118–134. https://doi.org/10.1210/edrv-12-2-118

Jovicich, J., Czanner, S., Han, X., Salat, D., van der Kouwe, A., Quinn, B., … Fischl, B. (2009). MRI-derived measurements of human subcortical, ventricular and intracranial brain volumes: Reliability effects of scan sessions, acquisition sequences, data analyses, scanner upgrade, scanner vendors and field strengths. *NeuroImage*, *46*(1), 177–192. https://doi.org/10.1016/j.neuroimage.2009.02.010

Karl, A., Schaefer, M., Malta, L. S., Dörfel, D., Rohleder, N., & Werner, A. (2006). A meta-analysis of structural brain abnormalities in PTSD. *Neuroscience & Biobehavioral Reviews*, *30*(7), 1004–1031. https://doi.org/10.1016/j.neubiorev.2006.03.004

Kim, E. J., Pellman, B., & Kim, J. J. (2015). Stress effects on the hippocampus: a critical review. *Learning & Memory*, *22*(9), 411–416. https://doi.org/10.1101/lm.037291.114

King, L. S., Colich, N. L., LeMoult, J., Humphreys, K. L., Ordaz, S. J., Price, A. N., & Gotlib, I. H. I. (2016). The impact of the severity of early life stress on diurnal cortisol: The role of puberty. *Psychoneuroendocrinology*, *77*, 68–74. https://doi.org/10.1016/j.psyneuen.2016.11.024

Lee, F. S., Heimer, H., Giedd, N., Lein, E. S., Šestan, N., Weinberger, D. R., & Casey, B. J. (2014). Adolescent mental health—Opportunity and obligation. *Science*, *346*(6209), 547–549. https://doi.org/10.1126/science.1260497

Lee, I. A., & Preacher, K. J. (2013). Calculation for the test of the difference between two dependent correlations with one variable in common. http://doi.org/http://quantpsy.org/corrtest/corrtest2.htm

Luby, J. L., Barch, D. M., Belden, A., Gaffrey, M. S., Tillman, R., Babb, C., … Botteron, K. N. (2012). Maternal support in early childhood predicts larger hippocampal volumes at school age. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(8), 2854–2859. https://doi.org/10.1073/pnas.1118003109

Luby, J. L., Belden, A., Harms, M. P., Tillman, R., & Barch, D. M. (2016). Preschool is a sensitive period for the influence of maternal support on the trajectory of hippocampal development. *Proceedings of the National Academy of Sciences*, *113*(20), 5742–5747. 10.1073/pnas.1601443113

Lupien, S. J., Evans, A., Lord, C., Miles, J., Pruessner, M., Pike, B., & Pruessner, J. C. (2007). Hippocampal volume is as variable in young as in older adults: Implications for the notion of hippocampal atrophy in humans. *NeuroImage*, *34*(2), 479–485. https://doi.org/10.1016/j.neuroimage.2006.09.041

Lupien, S. J., Maheu, F., Tu, M., Fiocco, A., & Schramek, T. E. (2007). The effects of stress and stress hormones on human cognition: Implications for the field of brain and cognition. *Brain and Cognition*, *65*(3), 209–237. https://doi.org/10.1016/j.bandc.2007.02.007

Lupien, S. J., Parent, S., Evans, A. C., Tremblay, R. E., Zelazo, P. D., Corbo, V., … Séguin, J. R. (2011). Larger amygdala but no change in hippocampal volume in 10-year-old children exposed to maternal depressive symptomatology since birth. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(34), 14324–14329. https://doi.org/10.1073/pnas.1105371108

Masten, A. S., & Narayan, A. J. (2012). Child Development in the Context of Disaster, War, and Terrorism: Pathways of Risk and Resilience. *Annrual Review of Psychology*, *63*, 227–257. https://doi.org/10.1146/annurev-psych-120710-100356

McEwen, B. S. (1998). Stress, adaptation, and disease. Allostasis and allostatic load. *Annals of the New York Academy of Sciences*, *840*, 33–44. https://doi.org/10.1111/j.1749-6632.1998.tb09546.x

McLaughlin, K. A., & Sheridan, M. A. (2016). Beyond cumulative risk: A dimensional approach to childhood adversity. *Current Directions in Psychological Science*, *25*(4), 239–245. https://doi.org/10.1177/0963721416655883

McLaughlin, K. A., Sheridan, M. A., & Lambert, H. K. (2014). Childhood adversity and neural development: Deprivation and threat as distinct dimensions of early experience. *Neuroscience and Biobehavioral Reviews*, *47*(11), 578–591. https://doi.org/10.1016/j.neubiorev.2014.10.012

Mehta, M. A., Golembo, N. I., Nosarti, C., Colvert, E., Mota, A., Williams, S. C. R., … Sonuga-Barke, E. J. S. (2009). Amygdala, hippocampal and corpus callosum size following severe early institutional deprivation: The English and Romanian Adoptees study pilot. *Journal*

of Child Psychology and Psychiatry, *50*(8), 943–951. https://doi.org/10.1111/j.1469-7610.2009.02084.x

Morey, R. A., Petty, C. M., Xu, Y., Pannu Hayes, J., Wagner, H. R., Lewis, D. V., … McCarthy, G. (2009). A comparison of automated segmentation and manual tracing for quantifying hippocampal and amygdala volumes. *NeuroImage*, *45*(3), 855–866. https://doi.org/10.1016/j.neuroimage.2008.12.033

Nelson, C. A., Fox, N. A., & Zeanah, C. H. (2014). *Romania's Abandoned Children: Deprivation, Brain Development, and the Struggle for Recovery*. Cambridge, MA: Harvard University Press.

Parks, C. G., Miller, D. B., McCanlies, E. C., Cawthon, R. M., Andrew, M. E., Deroo, L. A., & Sandler, D. P. (2009). Telomere length, current perceived stress, and urinary stress hormones in women. *Cancer Epidemiology Biomarkers and Prevention*, *18*(2), 551–560. https://doi.org/10.1158/1055-9965.EPI-08-0614

Phelps, E. A. (2004). Human emotion and memory: Interactions of the amygdala and hippocampal complex. *Current Opinion in Neurobiology*, *14*(2), 198–202. https://doi.org/10.1016/j.conb.2004.03.015

Ribbe, D. (1996). Psychometric review of traumatic event screening instrument for children (TESI-C). *Measurement of Stress, Trauma, and Adaptation*, 386–387.

Rudolph, K. D., & Hammen, C. (1999). Age and gender as determinants of stress exposure, generation, and reactions in youngsters: A transactional perspective. *Child Development*, *70*(3), 660–677. https://doi.org/10.1111/1467-8624.00048

Sah, R., Pritchard, L. M., Richtand, N. M., Ahlbrand, R., Eaton, K., Sallee, F. R., & Herman, J. P. (2005). Expression of the glucocorticoid-induced receptor mRNA in rat brain. *Neuroscience*, *133*(1), 281–292. https://doi.org/10.1016/j.neuroscience.2005.01.066.

Satterthwaite, T. D., Vandekar, S., Wolf, D. H., Ruparel, K., Roalf, D. R., Jackson, C., Gur, R. C. (2014). Sex differences in the effect of puberty on hippocampal morphology. *Journal of the American Academy of Child and Adolescent Psychiatry*, *53*(3), 341–350.e1. https://doi.org/10.1016/j.jaac.2013.12.002

Sheridan, M. A., Fox, N. A., Zeanah, C. H., McLaughlin, K. A., & Nelson, C. A. (2012). Variation in neural development as a result of exposure to institutionalization early in childhood. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(32), 12927–12932. https://doi.org/10.1073/pnas.1200041109

Sheridan, M. A., & McLaughlin, K. A. (2014). Dimensions of early experience and neural development: Deprivation and threat. *Trends in Cognitive Sciences*, *18*(11), 580–585. https://doi.org/10.1016/j.tics.2014.09.001

Shi, F., Liu, B., Zhou, Y., Yu, C., & Jiang, T. (2009). Hippocampal volume and asymmetry in mild cognitive impairment and Alzheimer's disease: Meta-analyses of MRI studies. *Hippocampus*, *19*(11), 1055–1064. https://doi.org/10.1002/hipo.20573

Shonkoff, J. P., & Garner, A. S. (2012). The lifelong effects of early childhood adversity and toxic stress. *Pediatrics*, *129*(1), e232–e246. https://doi.org/10.1542/peds.2011-2663

Stein, M. B., Koverola, C., Hanna, C., Torchia, M. G., & McClarty, B. (1997). Hippocampal volume in women victimized by childhood sexual abuse. *Psychological Medicine*, *27*(4), 951–959. https://doi.org/10.1017/S0033291797005242

Suh, J.W., Wang, H., Das, S., Avants, B., & Yushkevich, P.A. (2011). Automatic Segmentation of the Hippocampus in T1-Weighted MRI with Multi-Atlas Label Fusion Using Open Source Software: Evaluation in 1.5 and 3.0T ADNI MRI. In Proc Int Soc Magn Reson Med. Retrieved from https://stage.nitrc.org/docman/view.php/443/912/Abstract_JungSuh.pdf

Teicher, M. H. (2008). Stress, sensitive periods and maturational events in adolescent depression. *Trends in Neurosciences*, *31*(4), 183–191. https://doi.org/10.1016/j.tins.2008.01.004

Teicher, M. H., Andersen, S. L., Polcari, A., Anderson, C. M., Navalta, C. P., & Kim, D. M. (2003). The neurobiological consequences of early stress and childhood maltreatment. *Neuroscience and Biobehavioral Reviews*, *27*(1–2), 33–44. https://doi.org/10.1016/S0149-7634(03)00007-1

Tottenham, N., Hare, T. A., Quinn, B. T., McCarry, T. W., Nurse, M., Gilhooly, T., … Casey, B. J. (2010). Prolonged institutional rearing is associated with atypically large amygdala volume and difficulties in emotion regulation. *Developmental Science*, *13*, 46–61. https://doi.org/10.1111/j.1467-7687.2009.00852.x

Tottenham, N., & Sheridan, M. A. (2009). A review of adversity, the amygdala and the hippocampus: A consideration of developmental timing. *Frontiers in Human Neuroscience*, *3*(January), 68. https://doi.org/10.3389/neuro.09.068.2009

U.S. Census Bureau. (2004). Current population survey: definitions and explanations. Retrieved from http://www.census.gov/population/www/cps/cpsdef.html

Woon, F. L., & Hedges, D. W. (2008). Hippocampal and amygdala volumes in children and adults with childhood maltreatment-related posttraumatic stress disorder: A meta-analysis. *Hippocampus*, *18*(8), 729–736. https://doi.org/10.1002/hipo.20437

Zeanah, C. H., & Sonuga-Barke, E. J. S. (2016). Editorial: The effects of early trauma and deprivation on human development—from measuring cumulative risk to characterizing specific mechanisms. *Journal of Child Psychology and Psychiatry*, *57*(10), 1099–1102. https://doi.org/10.1111/jcpp.12642

Zero to Three (2016). *DC:0–5: Diagnostic Classification of Mental Health and Developmental Disorders of Infancy and Early Childhood*. Washington, DC: Zero to Three.

Zheng, Z., Li, R., Xiao, F., He, R., Zhang, S., & Li, J. (2017). Sex Matters: Hippocampal Volume Predicts Individual Differences in Associative Memory in Cognitively Normal Older Women but Not Men. *Frontiers in Human Neuroscience*, *11*, 93. https://doi.org/10.3389/fnhum.2017.00093.

Zimmerman, M. E., Ezzati, A., Katz, M. J., Lipton, M. L., Brickman, A. M., Sliwinski, M. J., & Lipton, R. B. (2016). Perceived stress is differentially related to hippocampal subfield volumes among older adults. *PLoS ONE*, *11*(5), e0154530. https://doi.org/10.1371/journal.pone.0154530

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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