






# Reduced hippocampal and amygdala volume as a mechanism underlying stress sensitization to depression following childhood trauma

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## Abstract

**Background:** Stressful life events are more likely to trigger depression among individuals exposed to childhood adversity. However, the mechanisms underlying this stress sensitization remain largely unknown. Any such mechanism must be altered by childhood adversity and interact with recent stressful life events, magnifying their association with depression.

**Aim:** This study investigated whether reduced hippocampal and amygdala volume are potential mechanisms underlying stress sensitization following childhood violence exposure.

**Method:** A sample of 149 youth (aged 8–17 years), with ( $N = 75$ ) and without ( $N = 74$ ) exposure to physical abuse, sexual abuse, or domestic violence participated. Participants completed a structural MRI scan and assessments of depression. Approximately 2 years later, stressful life events were assessed along with depression symptoms in 120 participants (57 violence exposed).

**Results:** Childhood violence exposure was associated with smaller hippocampal and amygdala volume. Stressful life events occurring during the follow-up period predicted worsening depression over time, and this association was magnified among those with smaller hippocampal and amygdala volumes. Significant moderated mediation models revealed the indirect effects of violence exposure on increasing depression over time through hippocampal and amygdala volumes, particularly among youths who experienced more stressful life events.

**Conclusions:** These results provide evidence for reduced hippocampal and amygdala volume as potential mechanisms of stress sensitization to depression following exposure to violence. More broadly, these patterns suggest that hippocampal and amygdala-mediated emotional and cognitive processes may confer vulnerability to stressful life events among children who have experienced violence.

## KEYWORDS

brain structure, childhood adversity, early-life stress, maltreatment, threat, trauma

## 1 | INTRODUCTION

Childhood adversity is common and strongly associated with psychopathology, including depression (Kessler et al., 2010; McLaughlin, Conron, Koenen, & Gilman, 2010). Heightened sensitivity to stress is one pathway through which childhood adversity may increase the risk for depression, such that stressful life events (SLEs) are more likely to trigger depressive episodes in those who have experienced childhood adversity (Hammen, Henry, & Daley, 2000). This process—called stress sensitization—has been observed in adults (McLaughlin et al., 2010) and adolescents (Harkness, Bruce, & Lumley, 2006), and in both population-based (McLaughlin et al., 2010) and longitudinal studies (Hammen et al., 2000; Harkness et al., 2006). Despite consistent evidence for stress sensitization to depression following childhood adversity, the mechanisms that underlie this process have rarely been investigated and remain largely unknown. Understanding the neurobiological mechanisms of stress sensitization may inform targets for interventions to prevent and treat depression and reduce stress vulnerability in those who have experienced childhood adversity.

To qualify as a mechanism of stress sensitization, a specific psychological or biological marker must: (a) be associated with childhood adversity and (b) interact with recent SLEs, strengthening their association with depression. Increased reactivity to threat, difficulties with emotion regulation, and low social support have all been proposed as potential psychological mechanisms of stress sensitization (McLaughlin et al., 2017). The first study to investigate a neural mechanism of stress sensitization found that the association between SLEs and depression symptoms several years later was elevated among participants with high amygdala reactivity (Swartz, Knodt, Radtke, & Hariri, 2015). Heightened amygdala reactivity has been consistently associated with childhood adversity (Hein & Monk, 2017), particularly childhood trauma (McLaughlin, Weissman, & Bitrán, 2019). Thus, amygdala reactivity to threat reflects one potential neural mechanism of stress sensitization to depression. Here, we propose that alterations in hippocampal and amygdala volume are additional potential mechanisms of stress sensitization.

Reductions in the volume of the hippocampus and amygdala have been consistently observed in children and adolescents exposed to adversity, particularly following exposure to violence (see McLaughlin et al., 2019 for systematic review). Extensive work in animal models demonstrates the toxic and lasting effects of early-life exposure to stress on the hippocampus (Watanabe, Gould, & McEwen, 1992). Enhanced corticotropin-releasing hormone binding in the hippocampus following early-life stress reduces dendritic spines and branching in hippocampal neurons, and these effects persist with age (Ivy et al., 2010; Magarin & McEwen, 1995). Reductions in hippocampal volume may disrupt hippocampal regulation of the hypothalamic-pituitary-adrenal (HPA) axis, which mediates physiological responses to stress (Frodl & O'Keane, 2013). Similarly, exposure to violence has been consistently associated with reduced amygdala volume and elevated amygdala reactivity in children (McLaughlin et al., 2019). These changes in amygdala structure and function likely promote rapid identification of threats in the

environment (McLaughlin & Lambert, 2017; McLaughlin, Sheridan, & Lambert, 2014), which may be adaptive in dangerous environments but may contribute to heightened stress vulnerability in safe environments or in the face of less severe stressors. Indeed, smaller amygdala volume is associated with increased physiological reactivity to stress (Yang et al., 2008).

Reduced hippocampal and amygdala volume may be a mechanism contributing to stress sensitization, particularly increased vulnerability to depression, among youths exposed to violence. Smaller hippocampal volume is associated with depression in adults in meta-analysis (Schmaal et al., 2016), but findings are less consistent in children and adolescents, with several studies observing a negative association (Caetano et al., 2007; MacMaster & Kusumakar, 2004) but others finding no association (MacMillan et al., 2003; Rosso et al., 2005), or even a positive association (Ellis et al., 2019). Likewise, the association of amygdala volume with depression in children and adolescents is inconsistent across studies (Caetano et al., 2007; MacMillan et al., 2003; Rosso et al., 2005). These discrepant patterns could reflect that the associations of hippocampal and amygdala volume with depression are moderated by factors such as age or SLEs. In the current study, we examine whether hippocampal and amygdala volume each moderate the association of SLEs with depression, such that stressors are more likely to predict increases in depression over time among youth with smaller hippocampal and amygdala volume.

Several prior studies have examined whether reduced hippocampal volume predicts increased vulnerability to depression following SLEs. For example, maternal aggression was associated with greater increases in depressive symptoms over time in early adolescents with smaller hippocampal volume (Whittle et al., 2011). In addition, young adults exposed to violence in childhood had smaller hippocampal volume, which interacted with stress in predicting anxiety, such that recent stressors were associated with elevated anxiety only among participants with small hippocampal volume (Gorka, Hanson, Radtke, & Hariri, 2014). This evidence is promising in suggesting that reduced hippocampal volume may be a mechanism of stress sensitization to depression following childhood violence exposure, although this possibility is largely untested. To our knowledge, no prior research has examined the role of amygdala volume in stress sensitization.

The current study utilized a longitudinal design to evaluate whether reduced hippocampal and amygdala volume are mechanisms underlying stress sensitization to depression in children and adolescents exposed to violence. We expected that the associations of SLEs with increases in depression symptoms over time would be stronger among participants exposed to violence, indicating stress sensitization. In addition, we predicted that youth exposed to violence would have smaller hippocampal and amygdala volume than those who had never experienced violence. We further hypothesized that hippocampal and amygdala volume would interact with SLEs in predicting depression, such that SLEs would be more strongly associated with increases in depression symptoms among participants with smaller hippocampal and amygdala volume. Finally, we estimated moderated

mediation models that evaluated whether an indirect effect of violence exposure on depression symptoms through hippocampal and amygdala volume, was magnified in the context of SLEs.

## 2 | METHOD

### 2.1 | Participants

Participants were 160 children and adolescents ages 8–17 years who participated in a study examining neural development following exposure to violence. Youths and caregivers were recruited at schools, after-school and prevention programs, adoption programs, food banks, shelters, parenting programs, medical clinics, and the general community in Seattle, WA, between January 2015 and June 2017. Recruitment efforts were targeted at recruiting a sample with variation in exposure to violence. To do so, we recruited from neighborhoods with high levels of violent crime, clinics that served a predominantly low-SES catchment area, and agencies that work with families who have been victims of violence (e.g., domestic violence shelters, programs for parents mandated to receive intervention by Child Protective Services). Inclusion criteria for the violence-exposed group included exposure to physical or sexual abuse or direct witnessing of domestic violence. Children in the control group were matched to children in the violence-exposed group on age, sex, and handedness and had never experienced interpersonal violence.

Exclusion criteria included IQ < 80, pervasive developmental disorder, active psychotic symptoms or mania, substance abuse, and presence of safety concerns. Written informed consent was obtained from legal guardians; children provided written assent. All procedures contributing to this study comply with relevant national ethical standards and with the Declaration of Helsinki. All procedures were approved by the University of Washington Institutional Review Board.

Eleven participants were excluded from analysis due to excessive head movement, resulting in 149 participants (75 violence exposed) with usable brain structure data. A total of 120 (57 violence-exposed) of these 149 participants returned for follow-up assessments of SLEs and depression approximately 2 years later ( $M = 643$  days,  $SD = 222$ , 81% retention rate). See Table 1 for sociodemographic characteristics of the final sample.

### 2.2 | Measures

#### 2.2.1 | Violence exposure

We used a multi-informant, multimethod approach for assessing exposure to violence. Participants completed two interviews assessing exposure to violence: the Childhood Experiences of Care and Abuse (CECA) Interview (Bifulco, Brown, & Harris, 1994) and the Violence Exposure Scale for Children-Revised (VEX-R;

Baseline						
	Violence-exposed ( <i>n</i> = 75)		Control ( <i>n</i> = 74)		$\chi^2$	<i>p</i>
	%	<i>n</i>	%	<i>n</i>		
Female	52	39	45	33	0.55	.459
Racial/ethnic minority	61	45	32	24	28.56	<.001
Poverty	34	26	3	2	25.81	<.001
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>t</i>	<i>p</i>
Age	12.84	2.81	12.65	2.56	-0.43	0.666
Hippocampal volume <sup>a</sup>	9.19	0.85	9.94	1.08	-4.69	<.001
Amygdala volume <sup>a</sup>	3.69	0.54	4.02	0.55	-3.66	<.001
Intracranial volume <sup>b</sup>	15.01	1.41	15.97	1.55	-3.97	<.001
Stressful life events	14.97	9.40	5.84	4.20	7.67	<.001
Depression symptoms	12.19	8.71	5.95	4.75	5.44	<.001
Follow-up						
	Violence exposed ( <i>n</i> = 57)		Control ( <i>n</i> = 63)		<i>t</i>	<i>p</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>		
Stressful life events	15.86	11.45	6.87	6.09	5.29	<.001
Depression symptoms	10.96	8.61	5.98	5.10	3.80	<.001

**TABLE 1** Distribution of study variables by violence exposure

<sup>a</sup>Hippocampal and amygdala volumes measured in  $\text{mm}^3 \times 10^3$ .

<sup>b</sup>Intracranial volume measured in  $\text{mm}^3 \times 10^5$ .

Raviv et al., 2001). Children also completed two self-report measures: the Childhood Trauma Questionnaire (CTQ; Bernstein, Ahluvalia, Pogge, & Handelsman, 1997) and the UCLA PTSD Reaction Index (PTSD-RI; Steinberg et al., 2013). Caregivers completed two self-report measures: the Juvenile Victimization Questionnaire (JVQ) lifetime caregiver report (Finkelhor, Hamby, Ormrod, & Turner, 2005), and the caregiver version of the PTSD-RI. Additional details on these scales are in Supporting Information.

Children were classified as experiencing physical or sexual abuse if abuse was endorsed by the child (on the CECA interview, PTSD-RI, or above the validated CTQ threshold) or parent (on the JVQ or PTSD-RI). Otherwise, they were classified as controls. A total of 69 children (46.3%) experienced physical or sexual abuse. Inter-rater reliability was good for child and caregiver reports (82.0% agreement;  $\kappa = 0.62$ ). Exposure to domestic violence (on the VEX-R or PTSD-RI) was determined based on child report only. A total of 58 children (38.9%) reported witnessing domestic violence. Overall, 75 (50%) participants met criteria for violence exposure, defined as exposure to physical abuse, sexual abuse, or domestic violence. Of these 75 participants, violence exposure was reported by both reporters for 60 participants (80%), by the child only for 14 participants (19%), and by the parent only for 1 participant (1%).

## 2.2.2 | Depression

Symptoms of depression were assessed with the Children's Depression Inventory-2 (CDI-2), a recently revised version of the widely used self-report measure of depressive symptoms in children and adolescents (Kovacs, 2011). The CDI-2 is a 27-item scale. For each item, participants choose between three statements that correspond to a three-point scale. Higher scores indicate more severe depression. The CDI-2 demonstrated excellent internal consistency in our sample ( $\alpha = 0.89$ ).

## 2.2.3 | Stressful life events

SLEs occurring in the past year were assessed at both baseline and follow-up using the UCLA Life Stress Interview (Hammen, 1988), a semistructured interview designed to characterize SLEs as objectively as possible. The interview has been extensively validated, adapted for use with children and adolescents, and is widely considered to be the gold standard approach for assessing SLEs (Hammen et al., 2000; Monroe, 2008).

The interview uses a series of structured prompts to query numerous domains of the child's life (peers, parents, household/extended family, neighborhood, school, academic, health, finance, and discrimination). An independent research team objectively codes the likely impact of each event for a child of that age and sex from 1 (*no negative impact*) to 5 (*extremely severe negative impact*) scale, including half-points (e.g., 1.5 and 2.5). These objectively coded impact scores reduce concerns about recall bias or differences in perceptions of

stress that can artificially inflate associations between SLEs and psychopathology. Child participants and a caregiver independently completed the interview and reported on SLEs experienced by the child in the past year. Following prior work, a total impact score was computed by taking the sum of the impact scores of all reported events (excluding those coded as 1), which provides a weighted average of the number and severity of stressors (Hammen et al., 2000). Higher scores indicate a greater frequency and severity of SLEs in the past year.

The interview was administered at both the baseline and follow-up visits, each time probing SLEs occurring in the prior year. Total impact scores based on events reported by parents and children were moderately correlated at both baseline ( $r = .56$ ) and follow-up ( $r = .49$ ). The higher of the child and parent total impact score was used. For more details, see Supporting Information.

## 2.3 | Structural MRI processing

See Supporting Information for information on structural MRI acquisition. Measures of left and right hippocampal, amygdala, and thalamus volume and total intracranial volume were obtained using automatic segmentation in FreeSurfer 5.3. Each segmentation was inspected manually by at least two investigators. No manual edits were performed on subcortical segmentations. Given that there is no consistent pattern of lateralization in the association of childhood violence exposure with hippocampal or amygdala volume (Hanson et al., 2015; McLaughlin et al., 2016; Saxbe et al., 2018), and to reduce multiple comparisons, right and left volumes were summed to create bilateral hippocampal, amygdala, and thalamus volume measures. To keep variables on a similar scale for regression analyses, subcortical volumes were all divided by 1,000, and intracranial volumes were divided by 100,000.

## 2.4 | Data analysis

Linear regression analysis implemented in R version 3.6.1 was used to evaluate the associations of violence exposure and SLEs with depression symptoms at follow-up, and their interaction, to test for stress sensitization. Although the interaction of violence exposure and SLEs did not reach conventional levels of statistical significance, stratified analysis revealed a stress sensitization pattern clearly in our data (see Supporting Information). Because this stress sensitization pattern is well established (Espejo et al., 2007; Hammen et al., 2000; Harkness et al., 2006; McLaughlin et al., 2010) and because it is appropriate to examine a mediation analysis even when the direct effect does not reach conventional thresholds of statistical significance because such a requirement reduces statistical power to detect mediation (Hayes, 2009; MacKinnon, Fairchild, & Fritz, 2007), we conducted analyses to see if violence exposure indirectly contributed to greater sensitivity to stress through alterations in hippocampal and amygdala volume.

To do this, we first evaluated whether violence exposure was associated with hippocampal and amygdala volume. Next, we examined whether hippocampal and amygdala volume were associated with depression at follow-up and moderated the association of SLEs with follow-up depression symptoms. Finally, moderated mediation models were tested with bootstrapped confidence intervals (10,000 iterations) using version 2.13 of the process macro in SPSS. Violence exposure was the independent variable, depression at follow-up was the dependent variable, hippocampal and amygdala volume were each tested as mediators, and SLEs occurring between the baseline and follow-up assessments served as the moderator of the association between hippocampal or amygdala volume and depression at follow-up.

Age, sex, poverty, and racial/ethnic minority status were as covariates in all analyses; total intracranial volume was included in models predicting hippocampal and amygdala volume (see Supporting Information for details). Models predicting depression at follow-up controlled for baseline depression and the time elapsed from baseline to follow-up. To determine if effects were specific to hippocampus and amygdala, we also conducted control analyses using thalamus volume. To rule out confounding by IQ, sensitivity analyses were also conducted controlling for IQ (see Tables S1–S7).

### 3 | RESULTS

#### 3.1 | Descriptive statistics

Descriptive statistics of all variables, separately for violence-exposed and unexposed youth, are presented in Table 1.

#### 3.2 | Stress sensitization and depression symptoms

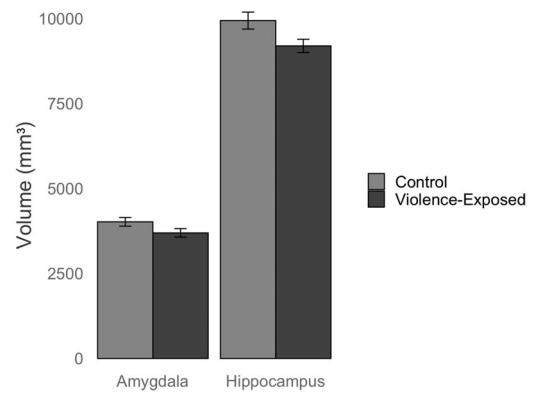
The association between SLEs at follow-up and depression symptoms at follow-up was stronger among participants exposed to violence than those without violence exposure (see Figure S1), but this interaction was not statistically significant ( $B = 0.164$ ,  $SE = 0.130$ ,  $p = .208$ ).

#### 3.3 | Violence exposure and brain structure

Violence exposed participants had significantly smaller hippocampal ( $p = .031$ ) and amygdala ( $p = .047$ ) volume than control participants (Figure 1). Thalamus volume did not differ between violence exposed and unexposed participants ( $p = .843$ ).

#### 3.4 | Brain structure and depression

Hippocampal volume was not associated with depression at follow-up ( $B = -0.563$ ,  $SE = 0.623$ ,  $p = .368$ ). A similar lack of associations



**FIGURE 1** Smaller hippocampal and amygdala volumes in violence-exposed youth. Violence exposed youth have significantly smaller hippocampal and amygdala volumes than youth never exposed to violence. Error bars represent 95% confidence intervals

were observed for amygdala volume with depression at follow-up ( $B = -1.04$ ,  $SE = 1.10$ ,  $p = .349$ ).

#### 3.5 | Stressful life events, brain structure, and depression symptoms

SLEs occurring during the follow-up period interacted with hippocampal volume ( $B = -0.118$ ,  $SE = 0.057$ ,  $p = .042$ ) and amygdala volume ( $B = -0.222$ ,  $SE = 0.102$ ,  $p = .031$ ) in predicting depression at follow-up (Table 2). Simple slopes revealed that the association between SLEs occurring between the baseline and follow-up with increases in depression symptoms over time was strongest among participants with small to average hippocampal and amygdala volumes and not significant among participants with larger hippocampal and amygdala volumes (Figure 2).

The interaction between thalamus volume and SLEs in predicting depression was not significant ( $B = -0.010$ ,  $SE = 0.043$ ,  $p = .812$ ).

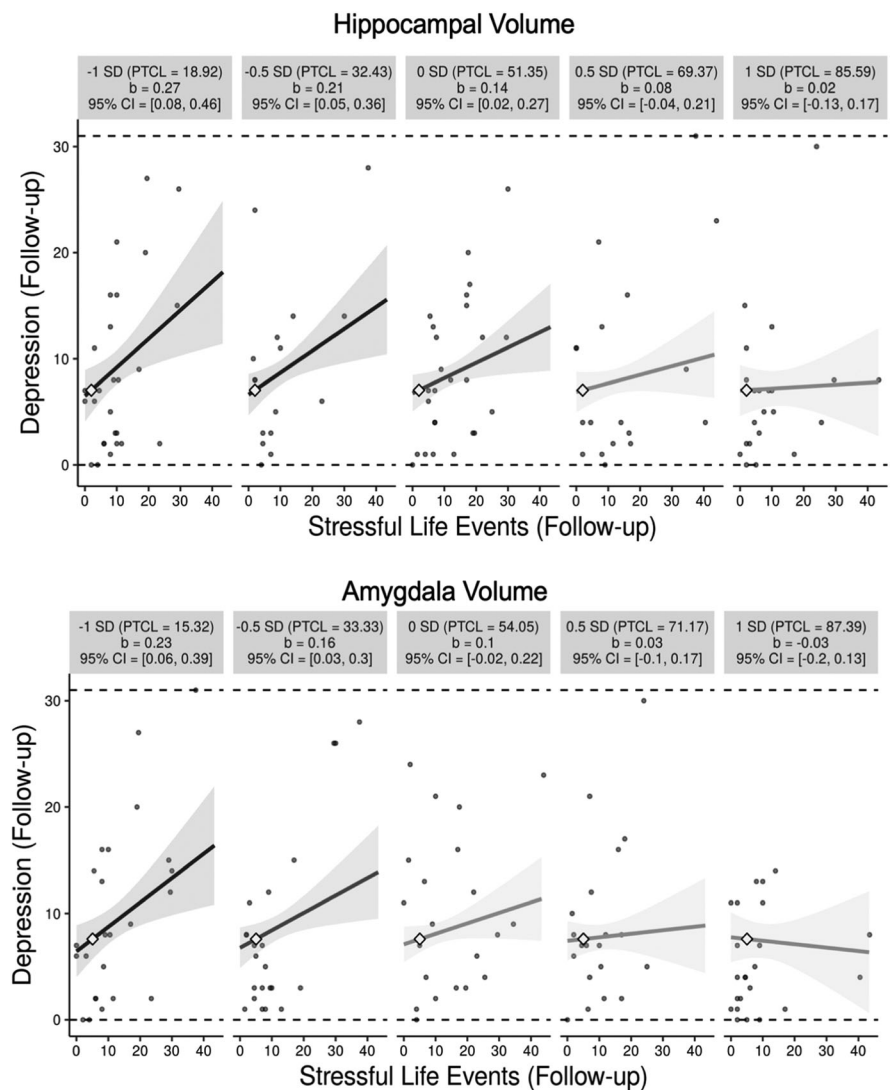
#### 3.6 | Moderated mediation

Moderated mediation analyses revealed a conditional indirect effect of violence exposure on depression at follow-up, via hippocampal volume, conditional on past-year SLEs at follow-up (Figure 3). A similar indirect effect of violence exposure on depression at follow-up was observed via amygdala volume, conditional on recent SLEs (Figure 3). The bootstrapped 95% confidence interval of the standardized index of moderated mediation for the model with hippocampal volume (0.061; 95% CI, 0.010–0.149) and the model with amygdala volume (0.064; 95% CI, 0.011–0.160) did not include zero, suggesting a significant conditional indirect effect in both models.

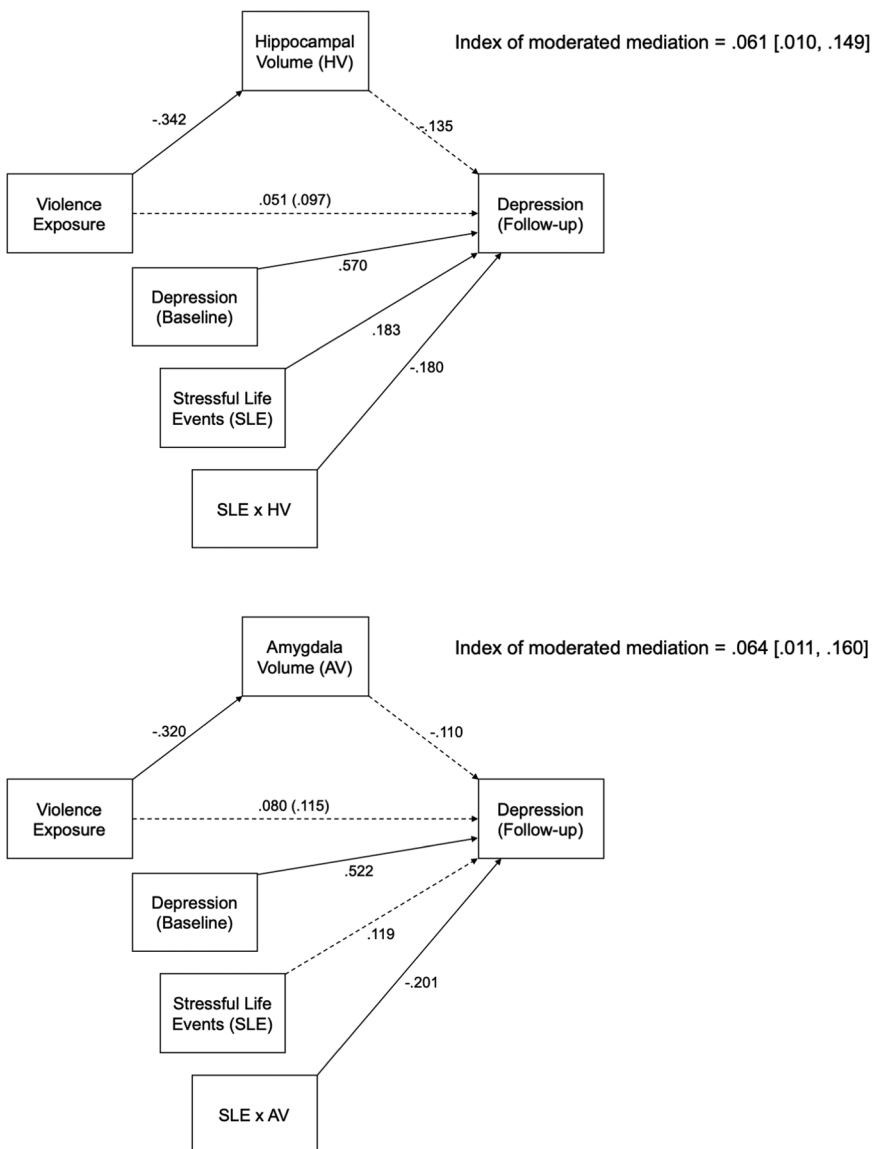
**TABLE 2** Interaction of stressful life events with hippocampal and amygdala volume in relation to depression

Predictors	Depression (follow-up)							
	Hippocampus				Amygdala			
	B	SE	t	p	B	SE	t	p
Sex	1.15	1.29	0.89	.375	1.16	1.29	0.90	.370
Age	0.173	0.210	0.82	.412	0.257	0.207	1.24	.217
Time elapsed (years)	-0.573	0.840	-0.68	.497	-0.615	0.840	-0.73	.465
Racial/ethnic minority	0.15	1.12	0.14	.891	0.15	1.13	0.14	.892
Poverty	-1.39	1.49	-0.93	.355	-0.86	1.50	-0.57	.568
Depression (baseline)	<b>0.568</b>	<b>0.080</b>	<b>7.05</b>	<b>&lt;.001</b>	<b>5.33</b>	<b>0.082</b>	<b>6.52</b>	<b>&lt;.001</b>
Violence exposure	0.57	1.42	0.59	.556	1.32	1.38	0.96	.339
Intracranial volume	0.706	0.512	1.38	.171	0.538	0.491	1.10	.275
Stressful life events (SLE) at follow-up	<b>0.142</b>	<b>0.060</b>	<b>2.37</b>	<b>.020</b>	0.092	0.057	1.62	.108
Hippocampal or amygdala volume	-1.05	0.63	-1.66	.099	-1.39	1.08	-1.28	.103
Hippocampal or amygdala volume × SLE	<b>-0.118</b>	<b>0.057</b>	<b>-2.06</b>	<b>.042</b>	<b>-0.222</b>	<b>0.102</b>	<b>-2.18</b>	<b>.032</b>

Parameters where the effect was significant at  $p < .05$  are in bold.



**FIGURE 2** Moderation of the relation between stressful life events and depression by hippocampal and amygdala volume. Stressful life events at follow-up are positively associated with depression symptoms at follow-up, controlling for baseline depression, in participants with small to average hippocampal volume but not larger (0.5 SD above the mean and higher) hippocampal volume and in participants with small (-0.5 SD below the mean and smaller) but not average or larger amygdala volume. Figure produced using the interactive data visualization tool (McCabe, Kim, & King, 2018)



**FIGURE 3** Moderated mediation models of hippocampal and amygdala volumes as mechanisms of stress sensitization. Results of regression-based moderated mediation models of the indirect effect of violence exposure on follow-up depression via hippocampal and amygdala volume, conditional on stressful life events at follow-up, and controlling for baseline depression. Sex, age, time elapsed between visits, poverty, racial/ethnic minority status, and total intracranial volume are not shown, but were also included as covariates. All coefficients are standardized. 95% bootstrapped confidence intervals are based on 10,000 iterations. Solid lines indicate significant relations. Dotted lines indicate nonsignificant relations

## 4 | DISCUSSION

We provide novel evidence that smaller hippocampal and amygdala volume among youths exposed to violence may contribute to increased vulnerability to depression symptoms following SLEs. Prior work has consistently shown that children and adolescents who have experienced adversity, including violence exposure, are at elevated risk for depression following SLEs later in life (Espejo et al., 2007; Harkness et al., 2006), but the mechanisms underlying this stress sensitization pattern have rarely been investigated. Here we provide evidence that smaller hippocampal and amygdala volume among youths exposed to violence are associated with increased vulnerability to depression symptoms following SLEs. These findings replicate prior work demonstrating that violence-exposed children and adolescents have smaller hippocampal and amygdala volume (McLaughlin et al., 2019) and extend it by demonstrating that these reductions in hippocampal and amygdala volume are associated with

increased vulnerability to the emergence of depression symptoms following SLEs in a longitudinal design. This provides compelling evidence that differences in hippocampal and amygdala structure following violence exposure may alter the way youth respond to stressors in their environment, contributing to risk for depression.

Violence exposure did not interact with SLEs to predict increases in depression symptoms over time in our data. However, stress sensitization patterns are well-replicated in larger samples (Hammen et al., 2000; Harkness et al., 2006; McLaughlin et al., 2010). Although stress sensitization effects did not reach conventional levels of significance in our sample, we did find evidence of stress sensitization operating indirectly via reduced hippocampal and amygdala volume. Thus, the results of this study suggest that reductions in hippocampal and amygdala volume are potential mechanisms of stress sensitization to depression in violence-exposed youth.

Our findings are consistent with prior studies examining the relation between trauma exposure and hippocampal and amygdala

volume in children and adolescents (Hanson et al., 2015; McLaughlin et al., 2016; Saxbe et al., 2018). Although neither hippocampal nor amygdala volume were associated with depression, both hippocampal and amygdala volume interacted with SLEs to predict depression symptoms, such that smaller volume was associated with depression only among youth who experienced additional SLEs. Reduced hippocampal and amygdala volume following childhood violence exposure may therefore reflect a latent vulnerability (McCrorry & Viding, 2015) that only manifests in increases in depression when youth encounter additional stressors.

Alterations in stress reactivity and emotion regulation may explain the role of hippocampal and amygdala volume in stress sensitization. Smaller amygdala volume is associated with greater physiological reactivity to stress (McLaughlin et al., 2016; Trotman, Gianaros, Zanten, van Williams, & Ginty, 2019; Yang et al., 2008). This increased reactivity to acute, episodic stressors may contribute to greater vulnerability to depression over time. Reductions in hippocampal volume may disrupt hippocampal regulation of the HPA axis, altering physiological responses to stress (Frodl & O'Keane, 2013). Atypical HPA axis function is well-documented in individuals with depression (Burke, Davis, Otte, & Mohr, 2005; Knorr, Vinberg, Kessing, & Wetterslev, 2010). Reduced hippocampal and amygdala volume among youth exposed to violence may therefore contribute to heightened physiological reactivity in the face of novel stressors, magnifying vulnerability to depression following SLEs.

Although this study has numerous strengths, some limitations constrain interpretability and suggest potential future directions for research. First, the distribution of the number and severity of SLEs, as well as racial/ethnic minority status and poverty, differed systematically between violence exposed and unexposed participants. While this is consistent with patterns in the general population, it led to differential restrictions to the range of SLEs in the two groups. Race/ethnicity and poverty were controlled for in all analyses, but there may nonetheless be some residual confounding. Second, higher levels of depression have the potential to bias retrospective recall of violence exposure. However, these concerns are reduced by the high level of agreement between child and parent reports of violence exposure in this sample, and recent work suggests that recall bias does not explain associations between retrospective reports of childhood trauma and psychopathology (Danese & Widom, 2020). Next, because hippocampal and amygdala volume was measured after violence exposure occurred, it is impossible to establish whether or not differences in hippocampal volume preceded the violence exposure. Prospective longitudinal designs among families at high risk for violence exposure could potentially more clearly establish the causal link between violence exposure and hippocampal and amygdala volume. Indeed, one study has shown that an intervention aimed at enhancing supportive parenting in adolescents from low socioeconomic status families prevented reductions of hippocampal and amygdala volume (Brody et al., 2017). In addition, the absence of a significant interaction between violence exposure and stressful life events in relation to depression challenges the characterization of reduced hippocampal and amygdala volume as a mechanism of stress

sensitization to some degree. Although we do not replicate this more distal interaction effect found in larger samples (Hammen et al., 2000; Harkness et al., 2006; McLaughlin et al., 2010), our findings do clearly demonstrate that violence exposure is associated with reduced hippocampal and amygdala volume, which in turn interacts with stressful life events in relation to depression. Recent large, developmental studies of brain structure and function, such as the Adolescent Brain Cognitive Development study (Casey et al., 2018) and the Human Connectome Project in Development (Somerville et al., 2018) may provide opportunities to examine whether both the distal interaction between violence exposure stressful life events and the more proximal interactions between stressful life events and hippocampal and amygdala volume replicate in the same sample. Finally, future work examining behavioral and neurophysiological indicators of hippocampal and amygdala functioning in relation to hippocampal and amygdala volume and stress sensitization could further elucidate how reduced hippocampal and amygdala volume acts as mechanisms of stress sensitization to depression and identify behavioral targets for intervention.

## 5 | CONCLUSION

Childhood violence exposure is associated with smaller hippocampal and amygdala volume, which, in turn, is associated with increases in the emergence of depressive symptoms over time in youth who experience SLEs. Smaller hippocampal and amygdala volume is therefore a plausible mechanism of stress sensitization and have the potential to serve as a biomarker of risk following exposure to violence.

## ACKNOWLEDGMENTS

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## CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Open Science Framework at <https://doi.org/10.17605/OSF.IO/5HPC6>.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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