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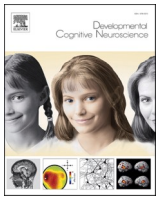

Threat experiences moderate the link between hippocampus volume and depression symptoms prospectively in adolescence

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ABSTRACT

Identifying neuroimaging risk markers for depression has been an elusive goal in psychopathology research. Despite this, smaller hippocampal volume has emerged as a potential risk marker for depression, with recent research suggesting this association is moderated by family income. The current pre-registered study aimed to replicate and extend these findings by examining the moderating role of family income and three dimensions of environmental experience on the link between hippocampus volume and later depression. Data were drawn from the Adolescent Brain Cognitive Development (ABCD) study and were comprised of 6693 youth aged 9–10 years at baseline. Results indicated that psychosocial threat moderated the association between right hippocampus volume and depression symptoms two years later, such that a negative association was evident in low-threat environments (std. beta=0.15, 95% CI [0.05, 0.24]). This interaction remained significant when baseline depression symptoms were included as a covariate, though only in youth endorsing 1 or more depression symptoms at baseline ($\beta = 0.13$, 95% CI = [0.03, 0.22]). These results suggest that hippocampus volume may not be a consistent correlate of depression symptoms in high risk environments and emphasize the importance of including measures of environmental heterogeneity when seeking risk markers for depression.

1. Introduction

The variation in core dimensions of experience across high and low socioeconomic contexts are posited to shape brain development. A growing body of research has established positive relations between socioeconomic status, indexed as family income or caregiver education, with global brain volumes, in addition to cortical thickness and surface area (Johnson et al., 2016; Mackey et al., 2015; McDermott et al., 2019). In addition to global alterations, the volume of a number of individual brain regions of interest, including limbic structures like the hippocampus, have been positively associated with socioeconomic status (Hanson et al., 2011; McDermott et al., 2019). Importantly, socioeconomic status is not a proximal mechanism that directly influences neurobehavioral development. Instead, environmental experiences associated with high and low socioeconomic status are likely to be, in part, responsible for individual differences in brain development. Among these experiences, chronic stressors such as environmental deprivation, exposure to threat, and lower levels of caregiver social support are one set of factors associated with altered brain volumes (Brody et al., 2017; Kok et al., 2015; Machlin et al., 2023; Mackes et al., 2020; McLaughlin et al., 2019). These experiences have also been linked with psychopathology risk, with several theoretical perspectives and empirical findings implicating chronic stress as an environmental risk factor for depression (Belleau et al., 2019; Monroe and Harkness, 2005).

The associations between chronic stress, brain structure, and depression risk converge upon similar mechanisms. Exposure to stressful environments can lead to the secretion of stress hormones, known as glucocorticoids, that feedback to affect the brain directly (Joels and Baram, 2009; McEwen, 2012; McEwen et al., 2015). The hippocampus is particularly sensitive to these changes in hormone levels as it is rich in glucorticoid receptors (Joels and Baram, 2009; McEwen et al., 2015). Accordingly, smaller hippocampal volumes have been associated with the environmental exposures associated with low socioeconomic status (McDermott et al., 2019) and are among the most replicated neural risk markers of depression (Kempton et al., 2011; Koolschijn et al., 2009; Treadway et al., 2015). For example, previous work in the ABCD study,

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from which data for these analyses were drawn, neighborhood poverty was significantly associated with decreased right hippocampus volume (Taylor et al., 2020). Similarly, in one large meta-analysis examining the volume of several subcortical regions of interest, only smaller hippocampal volumes were found to differ between individuals experiencing depression and those who were not (Schmaal et al., 2016). While the link between hippocampal volume and depression risk has been well established in the literature, little research has empirically examined the converging effects of socioeconomic status on this association.

In a previous study in a different sample, we combined socioeconomic status, depression symptoms, and hippocamus volume into the same empirical framework to assess whether the link between depression and hippocampus volume was consistent across the family income gradient. Using data from a nearly two-decade long study of the neurobehavioral sequelae of preschool depression, we showed that early life family income-to-needs ratio moderated the relationship between preschool depression symptoms and later hippocampal volume (Herzberg et al., 2022). Specifically, the expected negative association between depression symptoms and hippocampal volume was evident in high- but not low-income youth. Our results converged with prior research that had reported that family income was associated with hippocampal volume before, but not after, the onset of depressive episodes (Ellwood-Lowe et al., 2018). Similar moderating effects have also been found in non-clinical applications, including evidence that adverse experiences in childhood affect putamen volumes only in low-income contexts (Herzberg et al., 2022). Taken together, these results suggest that environmental heterogeneity may be an important contributer to the difficulties in identifying valid and clinically useful neuroimaging markers of psychopathology risk. This may be especially true in the context of stressful environments known to impact the markers of risk for psychopathology, potentially disrupting their link to psychopathology and possibly rendering the markers less useful in populations that might benefit most from improved prevention or intervention efforts.

The current study sought to replicate and extend the prior findings suggesting moderation of the links between hippocampus volume and depression symptoms by environmental experiences. A weakness of the prior literature in this area has been the blunt assessment of environmental experiences, as most researchers have used standard socioeconomic status indexes such as family income or caregiver education as proxy measures of youth environment. However, emergent research has shown that different aspects of adverse experiences may have unique impacts (McLaughlin et al., 2019, 2021). To address this limitation, this study used three dimensions of environmental experience, in addition to family income, as potential moderators of the association between hippocampal volume and depression symptoms. Importantly, these additional dimensions of experience—material and economic deprivation, psychosocial threat, and caregiver social support—were adjusted for systematic demographic reporting biases, ensuring that they represented the same latent construct across participants with different sociodemographic profiles. In a series of pre-registered models, we tested the predictions that family income-to-needs ratio would moderate the association between baseline hippocampus volume and depression symptoms 2 years later in the Adolescent Brain Cognitive Development (ABCD) Study, such that high- but not low-income youth would exhibit a negative association between hippocampus volume and depression symptoms. We further predicted that the dimensions of experience would play a similar moderating role, with only more benign or supportive conditions being associated with the expected link between hippocampus volume and depression symptoms.

2. Methods

2.1. Participants

Participants were 9448 youth from the Adolescent Brain Cognitive Development (ABCD) study sample with usable structural MRI data. The ABCD study is a prospective longitudinal sample of over 11,000 youth beginning when participants were 9 – 10 years of age. Recruitment and data collection were completed at 21 sites using a probability sampling technique in U.S. schools in an effort to minimize systematic bias in sampling (Garavan et al., 2018). Study procedures received approval from local institutional review boards at each site and participants and their legal guardians provided informed consent. Table 1 includes a demographic summary of the sample used in these analyses.

Data included in the analytic sample for this analysis were from ABCD Release 4.0 and downloaded from the National Institute of Mental Health (NIMH) Data Archive (https://nda.nih.gov/abcd/). Only participants with usable structural MRI data as indicated by the ABCD Recommended Image Inclusion data file (abcd_imgincl01), longitudinal behavioral data, and complete sociodemographic data were included, resulting in the final analytic sample (N = 6693). The number of observations in each model varies as a function of small changes in the amount of available data on the questionnaires used to define the dimensions of environmental experience, which are described below. As such, the number of observations included in each model are provided with the regression tables. See Figure S1 for an accounting of missing data from the full ABCD sample.

2.2. Measures

2.2.1. Family income-to-need ratio and caregiver education

Family income and parental education data were retrieved from the ABCD Parent Demographics Survey (pdem02). As family income was collected using 10 income bins (< $5,000; $5,000 - $11,999; $12,000 - $15,999; $16,000 - $24,999; $25,000 - $34,999; $35,000 - $49,999; $50,000 - $74,999; $75,000 - $99,999; $100,000 - $199,999; $200,000 or more), family income-to-need ratio was approximated by picking the average of each bin, dividing this the federal poverty line for the year in which the income was collected and adjusting for family size. Caregiver education was defined as the greatest number of years of education reported between two caregivers or as the value reported for the sole caregiver if second caregiver education was not reported. Years of caregiver education were used as a continuous variable.

2.2.2. Dimensions of environmental experiences

To increase the specificity of the analyses, three previously created factor scores indexing key dimensions of children's environmental experiences across the socioeconomic gradient were used (see DeJoseph et al., 2022). Specifically, moderated nonlinear factor analysis (MNLFA; Bauer, 2017; Bauer and Hussong, 2009; Curran et al., 2014) was leveraged to generate invariant measures of *material deprivation, psychosocial threat,* and *caregiver social support*. MNLFA scores empirically adjusts for measurement non-invariance (i.e., bias) across sociodemographic characteristics, affording a common and unbiased scale of measurement across demographic groups and age. This method results in person-specific factor scores that enhance individual variation as well as measurement precision (Curran et al., 2014; DeJoseph et al., 2021).

Table 1
Participant demographics.

	N (%)
Sex	
Female	4565 (48.32)
Male	4883 (51.68)
Race	
Black	1211 (12.82)
Hispanic	1917 (20.29)
Other	1166 (12.34)
White	5154 (54.55)
	M (SD)
Caregiver Education (years)	20.33 (2.49)
Income-to-Needs	3.79 (2.42)
Child age (months)	119.13 (7.48)

MNLFA scores were created using items from several ABCD measures. *Material and economic deprivation* was indexed via seven items originating from the parent-reported Financial Adversity Questionnaire (Diemer et al., 2013). Items assessed the degree to which a family experienced several economic hardships over the past 12 months (e.g., could not afford food, could not pay rent or mortgage, were evicted). The factor analysis establishing the unidimensionality of the material and economic deprivation score exhibited good model fit ($\chi 2 = 22,534.32$, p =0.000, CFI=0.966, RMSEA = 0.075). *Psychosocial threat* was indexed via nine items from the youth-reported Family Conflict subscale of the ABCD Family Environment Scale (Moos, 1994; Zucker et al., 2018). Items assessed youths' perceived conflict within their family (e.g., 'We fight a lot in our family'; 'Family members sometimes get so angry they throw things'). Reliability of the Family Conflict subscale of the Family Environment Scale has been shown to be generally acceptable in adolescents (Boyd et al., 1997), though it has shown slightly less than acceptable internal consistency in the full ABCD sample to date ($\alpha = 0.68$; Gonzalez et al., 2021), with $\alpha > 0.70$ considered acceptable (Tavakol and Dennick, 2011). Internal consistency of the Family Conflict scale in our subsample is comparable to the full ABCD sample ($\alpha = 0.68$ for youth-report and $\alpha = 0.67$ for parent-report). The MNLFA approach, however, ameliorates this concern through its ability to test and subsequently adjust for non-invariance (i.e., bias) to ensure the items function similarly across demographic groups—thus improving reliability and generalizability of the measure for a more diverse population. Once again, the factor analysis assessing the psychosocial threat construct fit the data well ($\chi 2 = 16532.77$, p =0.00, CFI = 0.95 RMSEA =.053). *Caregiver social support* was indexed via five items from the ABCD Children's Report of Parental Behavior Inventory (CRPBI). Only items corresponding to the primary caregiver (85% biological mother) were used to maximize available data and assessed youth's perceptions of support from their caregiver (e.g., 'Makes me feel better after talking over my worries with him/her'; 'Believes in showing his/her love for me'). The CRPBI has been shown to have good reliability in prior work, be associated with dimensionally assessed internalizing symptoms, and has acceptable internal consistency in the full ABCD sample ($\alpha = 0.71$; Brieant et al., 2021; Gonzalez et al., 2021; Margolies and Weintraub, 1977; Safford et al., 2007). In our subsample, the internal consistency of the CRPBI Support scale is slightly lower ($\alpha = 0.66$). The factor analysis assessing the social support construct also fit the data well ($\chi 2 = 176.27$, p =0.00, CFI = 0.99, RMSEA = 0.054).

See DeJoseph et al. (2022) for further details about how these MNLFA scores were computed.

2.2.3. Measurement of youth depression symptoms

Raw scores from the Child Behavior Checklist (CBCL; Achenbach, 2009) depression symptoms scale were used as a parent-reported measure of youth depression. Parents completed the CBCL annually beginning at the baseline ABCD assessment (Barch et al., 2018). Only scores from the baseline and two-year assessments were used in this study.

2.2.4. Youth self-report of internalizing symptoms

Youth-reported internalizing symptoms were assessed using the Brief Problem Monitor (Achenbach, 2009) at the two-year follow-up assessment (this was not administered at baseline). Raw scores from the internalizing scale were used in these analyses.

2.3. Magnetic resonance imaging

2.3.1. Image acquisition

The magnetic resonance imaging procedures in the ABCD study have been detailed in depth in previous publications (Casey et al., 2018). One of three 3 T scanner models were used for image acquisition, depending on site, and included Prisma (Siemens Corporation), Discovery MR750 (GE Healthcare, Chicago, IL), or Achieva dStream (Philips, Amsterdam, Netherlands). All sites and scanners used a 32-channel head-coil for data acquisition. Structural scans included a T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) and a T2-weighted fast spin echo scan, each with a 1 mm^3 resolution (Casey et al., 2018; Hagler et al., 2019). The T1-weighted MPRAGE was used for cortical and subcortical segmentation.

2.3.2. Image processing and segmentation

Left and right hippocampus and total intracranial volume for each participant were retrieved from the tabulated structural MRI data included in ABCD Annual Release 4.0 (abcd_smrip10201). These data were extracted from T1-weighted MPRAGE images that had been visually inspected by trained technicians and preprocessed using the ABCD pipeline, which included gradient distortion correction, intensity inhomogeneity correction, registration to standard space, and motion correction (Hagler et al., 2019). Subcortical segmentation of the hippocampus was completed using FreeSurfer v5.3 and an automated, atlas-based segmentation process (Dale et al., 1999; Fischl, 2012; Fischl et al., 2002). Full details of the ABCD image processing procedures can be found elsewhere (Hagler et al., 2019).

2.4. Data analysis

2.4.1. Pre-registered analyses

The intended sample, measures, and primary outcome models were pre-registered on Open Science Framework (osf.io/6g9ab) prior to any data exploration or analysis. A series of pre-registered multi-level regression models were fit in R version 4.2.1 (R Core Team, 2020) and followed up in a series of exploratory analyses. Multi-level regression models were used in this study as they are well-equipped for applications to longitudinal and clustered data, have been used in much of the prior literature using this sample, and recommended for researchers using the ABCD study data (Bosker and Snijders, 2011; Dick et al., 2021; Freeman et al., 2022; Heeringa and Berglund, 2020; Holt-Gosselin et al., 2023; O'Brien et al., 2020; Saragosa-Harris et al., 2022). Pre-registered models included multi-level models with raw CBCL depression scores at the two-year assessment as the dependent variable. The first models attempted to replicate the effects observed by Herzberg et al. (2022) in a different sample using the interaction of hippocampus volume and family income-to-needs as the predictor of interest, while subsequent models extended the previous methods to include the dimensions of environmental experience described above in the interaction of interest. Covariates included age, sex, race, caregiver education, and intracranial volume in all models. Random effects of family nested within site were included to account for clustering in the data. Two deviations from the pre-registered models occurred. First, the regression models were fit using zero-inflated Poisson distributions in the glmmTMB package in R (Brooks et al., 2017) due to the low level of depression symptom endorsement in the first two years of the ABCD study. These models were appropriate as models fit without a zero-inflation term underfit zeros (ratio of observed:predicted zeroes = 0.90 for each independent variable of interest), which can result in biased regression estimates, but were not over dispersed (all dispersion ratios < 1). Second, caregiver education was inadvertently omitted as a covariate in each regression model in the preregistration but must be included due to the use of the MNLFA scores, which incorporate demographic variation. Best practice using MNLFA scores requires that each demographic characteristic adjusted for is included in subsequent statistical modelling (Bauer, 2017). Follow-up models including baseline CBCL depression symptoms to assess change from baseline to the two-year assessment were also pre-registered. Simple slopes analysis and Johnson-Neyman plotting were used for interaction decomposition and interpretation. Following model fitting, analyses revealing interaction effects were repeated excluding outliers with a standardized residual +/−3sd of the mean to eliminate the possibility of highly influential data points.

2.4.2. Exploratory analyses

A series of exploratory analyses were completed after the pre-registered models had been fit. First, in order to investigate the effects of early endorsement of depression symptoms, models with baseline depression symptoms as a covariate were fit in youth endorsing baseline depression symptoms and in youth without baseline symptom endorsement separately. This analysis was completed to better understand whether youth who endorse depression symptoms prior to age 10 years represent a higher risk group than their peers who do not. Next, the pre-registered analyses were also completed using youth-reported internalizing symptoms assessed with the Brief Problem monitor to assess potential differences in youth- vs. parent-report of internalizing symptoms. Similarly, parent-reported psychosocial threat was assessed as an alternative to the youth-reported psychosocial threat score to address differences in reporter using raw sum scores from the Conflict subscale of the Family Environment Scale. No such exploratory analyses were completed for the economic and material deprivation score nor the caregiver social support score as there were not equivalent variables with a different reporter in these domains of the ABCD study. Finally, two robustness checks were included to test the specificity of the observed effects to the CBCL depression symptoms scores and assessing whether variation in sociodemographic factors across sites affected the results. The exploratory models are presented with false discovery rate correction for multiple comparisons (FDR; Benjamini and Hochberg, 1995) as they were not pre-registered.

3. Results

3.1. Pre-registered model results

A table reporting the means and standard deviations of each variable as well as the correlations between all of the independent variables and outcomes of interest can be found in Table S1.

3.1.1. Family income-to-needs

Family income-to-needs did not moderate the association between baseline left nor right hippocampus volume and depression symptoms two years later ($\beta = -0.01$, 95% CI = [−0.05, 0.03] and $\beta = -0.00$, 95% CI = [−0.04, 0.03], respectively). See Tables S2 and S3 in the supplementary material for full model results.

3.1.2. Dimensions of environmental experience

The interaction between psychosocial threat and right hippocampus volume was longitudinally associated youth depression symptoms two years later ($\beta = 0.15$, 95% CI = [0.05, 0.24], see Table 2 and Fig. 1). Simple slopes analysis indicated that the longitudinal relationship between right hippocampus volume and youth depression symptoms was significant at 1 standard deviation below the psychosocial threat mean (slope estimate = −0.90, $p = 0.01$) but not at the mean or 1 standard deviation above the mean of psychosocial threat (slope estimate = −0.08, $p = 0.32$ and slope estimate = 0.75, $p = 0.38$, respectively; see Table S4). A Johnson-Neyman plot of the psychosocial threat by right hippocampus interaction can be found in Figure S2. This relationship held when outliers with standardized residuals ±3 standard deviations from the mean were removed (see Table S5 and Figure S3). The interaction between psychosocial threat and left hippocampus volume was not associated with depression symptoms at the 2-year assessment ($\beta = 0.08$, 95% CI = [−0.03, 0.19], see Table S6). Neither dimensions of material and economic deprivation nor social support interacted with hippocampus volumes to associate with depression symptoms (see Tables S7 – S10). An additional set of analyses assessing the possibility that variations in family income or exposure across sites masked true effects using independent variables mean-centered within site resulted in nearly identical results (see Supplemental Results and Tables S11 – S18).

Table 2
Full model results of a zero-inflated Poisson multi-level model including depression symptoms at the 2-year assessment and the interaction of psychosocial threat and right hippocampus volume as the term of interest. Random effects of family nested within site were included.

Outcome Variable: 2-year Follow-up Depression Symptoms						
Model Component	**Predictor**	**B**	**SE**	**t**	**p**	**95% CI**
Fixed Effects	**Intercept**	**0.76**	**0.25**	**3.09**	**0.00**	**[0.28, 1.24]**
Fixed Effects	**Psychosocial Threat**	**-0.48**	**0.21**	**-2.26**	**0.02**	**[−0.89, −0.06]**
Fixed Effects	Right Hippocampus	-0.05	0.06	-0.82	0.41	[−0.16, 0.07]
Fixed Effects	**Age**	**0.01**	**0.00**	**4.54**	**0.00**	**[0.01, 0.02]**
Fixed Effects	Female	-0.03	0.04	-0.73	0.47	[−0.11, 0.05]
Fixed Effects	**Black**	**-0.40**	**0.07**	**-5.51**	**0.00**	**[−0.54, −0.26]**
Fixed Effects	Hispanic	-0.11	0.06	-1.79	0.07	[−0.22, 0.01]
Fixed Effects	Other Race	0.03	0.06	0.49	0.62	[−0.09, 0.15]
Fixed Effects	**Caregiver Education**	**-0.02**	**0.01**	**-2.26**	**0.02**	**[−0.04, 0.00]**
Fixed Effects	ICV	-0.00	0.00	-0.48	0.63	[0.00, 0.00]
Fixed Effects	**Psychosocial Threat x Right Hipp.**	**0.15**	**0.05**	**2.86**	**0.00**	**[0.05, 0.24]**
Zero-Inflation	**ZI Intercept**	**-0.77**	**0.05**	**-14.60**	**0.00**	**[−0.88, −0.67]**
Random Effects	Family ID	0.70				[0.67, 0.73]
Random Effects	Site	0.18				[0.12, 0.26]

Number of Observations = 6677.

3.1.3. Covarying baseline depression symptoms

In a series of pre-registered follow-up models, baseline depression symptoms from the Child Behavior Checklist were included to investigate change in depression symptoms from the initial assessment to the two-year assessment. As the absence of baseline depression symptoms were expected to be related to the absence of 2-year follow-up depression symptoms (e.g., stability in low symptom load over time), baseline depression symptoms were included in the zero-inflation component of the model specification. As expected, baseline depression symptoms were strongly associated with zero values at the 2-year assessment in all models including baseline depression symptoms as a covariate (all p's $<$ 0.01). When controlling for baseline depression symptoms, the interaction of psychosocial threat and right hippocampus volume remains longitudinally associated with 2-year follow-up depression symptoms ($\beta = 0.10$, 95% CI = [0.01, 0.18]; Table S19). As when baseline depression symptoms were not included, the interaction of psychosocial threat with left hippocampus volume was not associated with 2-year follow-up depression symptoms, nor did family income-to-needs, material deprivation or social support models result in statistically significant effects (Tables S20 – S26).

3.2. Exploratory analyses

3.2.1. Effects in those who endorsed depression at baseline vs. non-endorsers

A set of exploratory analyses investigated the interaction effect in only participants endorsing depression symptoms at baseline and only in participants without baseline endorsement. Among participants who had endorsed depression symptoms at baseline only, the interaction of psychosocial threat and right hippocampus remained a strongly associated with depression symptoms at 2-year follow-up, with baseline

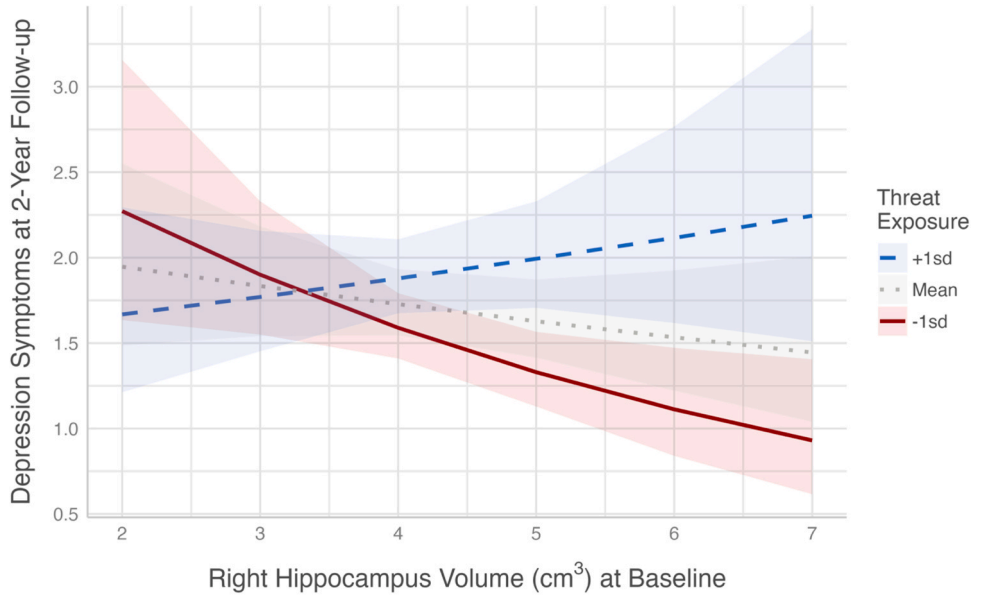

Fig. 1. Model predicted depression symptoms at 2-year follow-up as a function of right hippocampus volume and threat exposure at the baseline assessment. Low levels of psychosocial threat are associated with a negative association between right hippocampus volume and later depression symptoms, while mean and high levels of psychosocial threat exposure are not.

depression symptoms included as a covariate (β = 0.13, 95% CI = [0.03, 0.22]; Table S27 and Figures S4 – S5). The interaction effect was not longitudinally associated with 2-year depression symptoms in youth who did not endorse depression symptoms at baseline (β = −0.04, 95% CI = −0.24, 0.16]; Table S28). No zero-inflation was evident in the non-endorsement group, so no zero-inflation model component was included in this follow-up model.

3.2.2. *Youth-reported internalizing symptoms as outcome variable*

Youth-reported internalizing symptoms on the Brief Problem Monitor were also used as the outcome of interest in a set of exploratory models. Interactions between psychosocial threat and both left and right hippocampus volumes were significantly associated with youth-reported internalizing symptoms two years later (β = 0.09, 95% CI = [0.02, 0.17]; and β = 0.10, 95% CI = 0.03, 0.17], respectively; Tables S29 & S30). The pattern of results for the right hippocampus was

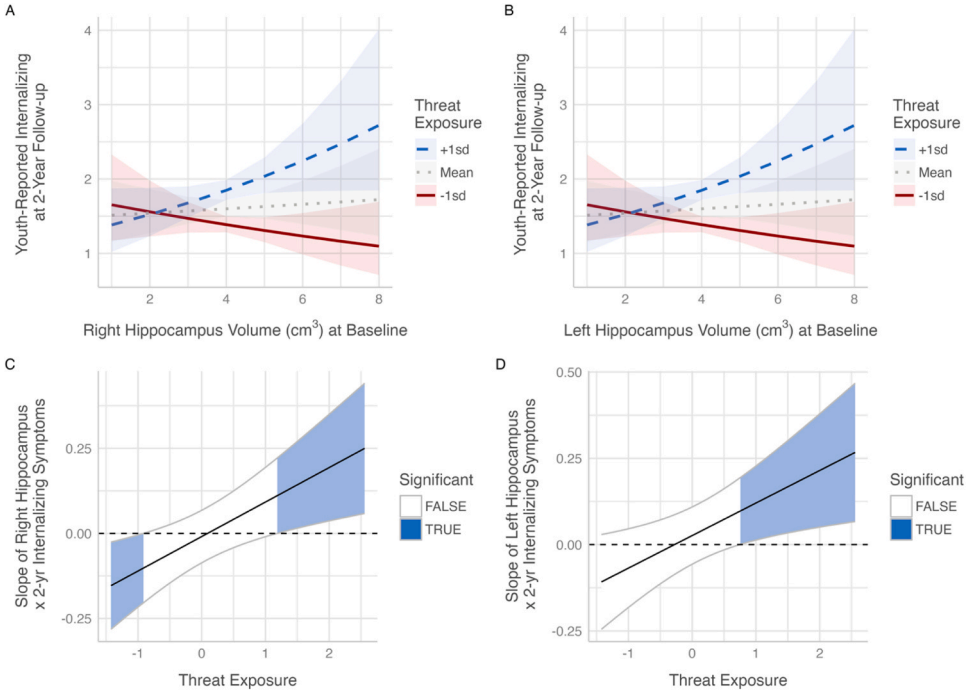

Fig. 2. A. Model predicted youth-reported internalizing symptoms at 2-year follow-up as a function of left hippocampus volume and psychosocial threat exposure at the baseline assessment. High levels of psychosocial threat were associated with a positive association between hippocampus volume and internalizing symptoms. B. Model predicted youth-reported internalizing symptoms at 2-year follow-up as a function of baseline right hippocampus volume and psychosocial threat exposure. A negative association between hippocampus volume and internalizing symptoms was observed in low threat conditions and the opposite is true in high threat conditions. C & D. Johnson-Neyman plots exhibiting the regions of significance in the models depicted in panels A and B, respectively.

largely similar to models that included parent-reported depression symptoms as the outcome variable, with a slightly larger positive association between hippocampus volume and internalizing symptoms in high threat conditions (See Figs. 2B and D). Unlike parent-reported depression symptoms, however, a positive association between left hippocampus volume and youth-reported internalizing symptoms was observed in high threat conditions (see Figs. 2A and C). The interactions between hippocampus volumes and family income, material and economic deprivation, and social support once again were not longitudinally associated with internalizing symptoms. See the supplementary information for full model results (Tables S31 – S36).

3.2.3. Parent-reported psychosocial threat

Parent-reported sum scores from the Conflict subscale of the Family Environment Scale were also investigated as a measure of psychosocial threat to assess the specificity of results to youth report. Neither left nor right hippocampus volumes interacted with parent-reported psychosocial threat to predict youth depression symptoms two years later (see Tables S37 & S38).

3.2.4. Additional robustness checks

A final set of robustness checks assessed the specificity of the pattern of results to the CBCL depression scale in comparison to other CBCL internalizing scales. The results were specific to the depression scale of the CBCL (see the Supplemental Results and Tables S39 – S41).

4. Discussion

In this preregistered study, we endeavored to replicate and extend prior work in a large independent sample that demonstrated the moderating role of family income on the association between preschool depression and later hippocampal volumes. Unlike the prior research (Herzberg et al., 2022), we did not find that family income-to-need ratio moderated the association between hippocampal volume and later depression symptoms. However, our analyses revealed a significant interaction between psychosocial threat experiences and right hippocampus volume that was longitudinally associated with parent-reported depression symptoms two years later. This interaction remained significant in the right hippocampus when youth-reported internalizing symptoms were used in place of the parent-reported scores and was shown to be specific to depression symptoms when using parent report. Further, when controlling for previous symptom endorsement, the moderation was specific to youth who had reported depression symptoms at baseline; non-endorsers at baseline did not show the same pattern of results. Exeperiences of material deprivation and social support did not moderate the link between hippocampus volume and depression symptoms two years later.

While the prior research had suggested a role for early environmental experiences as a moderator of psychopathology risk in adolescence, the use of family income-to-need ratio as a proxy for such environmental experience reduced the specificity of the results. In this study, we assessed the role of more direct dimensions of experience implicated across the socioeconomic gradient to address this problem. Our results demonstrated that experiences of psychosocial threat as particularly important to determining which youth are at risk of developing depression symptoms as a function of hippocampus volume. This result converges with our prior findings using income-to-needs ratio as the environmental moderator (Herzberg et al., 2022) in that low levels of threat were associated with the expected association between hippocampal volume and depression symptoms—a pattern similar to that seen in high-income environments. Conversely, experiencing high levels of psychosocial threat, like low family income in the previous study, may have reduced the relationship between hippocampal volume and later depression symptoms, perhaps via well-established stress-related mechanisms that alter hippocampal volume independent of depression risk (Joels and Baram, 2009; McEwen, 2015). Why the results identified in this study are specific to right hippocampus when using CBCL depression symptoms is not easily explained in the context of the prior literature. While volumetric asymmetries are known to be a normative phenomenon in the hippocampus during adolescence (Giedd et al., 1996), there is little evidence to suggest that hippocampus asymmetry is an important marker of depression risk. Though one study has identified hippocampus asymmetry as a potential factor in the experience of prodromal psychosis symptoms in adolescence (Okada et al., 2018), such main effects provide little context to the interactive effects observed in this study.

There were no hemisphere-specific effects when using youth-reported internalizing symptoms, with interactive effects observed in the left and right hemispheres, suggesting that the hemisphere-specific effects observed here may be due to chance differences in sampling or other sources of variance. Like in the primary models, youth reported internalizing symptoms were longitudinally associated with right hippocampus volume and psychosocial threat specifically, further suggesting that hippocampus volume is only linked to youth internalizing symptoms in the context of relatively low levels of environmental stress. It should be noted, however that a slightly different pattern emerged in the left hippocampus. In high-threat contexts, left hippocampus volume was positively associated with youth-reported internalizing symptoms. We also investigated the specificity of effects to youth-reported psychosocial threat and found that parent-reported psychosocial threat did not interact with hippocampus volumes to predict depression symptoms two years later. It may be that youth-reported psychosocial threat is more related to future depression symptoms or that individual perceptions of threat are important for understanding the neurobiological consequences of stress, as has been suggested in the theoretical literature (Smith and Pollak, 2021). Despite the inconsistency between left and right hippocampus when examining youth-reported internalizing symptoms and in the interactive effect when using parent-report measures of threat, our results suggest that hippocampus volume is not a specific marker of psychopathology risk in all environmental contexts. This result necessitates consideration of individual experiences in the future development of improved markers of risk.

Our results indicate that hippocampus volume continues to be associated with depression symptoms two years later in low threat environments even when controlling for baseline depression symptoms. This relationship held only in youth who endorsed depression symptoms at the baseline assessment; youth who did not endorse baseline depression symptoms did not exhibit an association between hippocampus volume and depression symptoms at any level of psychosocial threat exposure. The distinction between baseline endorsers and those that did not endorse depression symptoms at baseline is consistent with prior research reporting early endorsement of depression symptoms as a risk factor for future symptom development (Köhler et al., 2019; Luby, 2010). Additionally, in light of the prior theoretical and empirical literature, the differences between baseline endorsers and non-endorsers reported here suggest that neurobiological risk factors may not only be specific to environmental context (e.g., low- vs. high-threat environments) but may also be associated with pre-existing diatheses that render individuals vulnerable to the development of depression symptoms.

How different environmental experiences in early adolescence alter the association between hippocampus volume and later depression symptoms in the baseline endorsing group, however, is less clear based on the prior literature. Stress-related theories of depression development emphasize the role of stressful life events as precipitating factors in depression onset (Monroe and Harkness, 2005). Additional literature has also demonstrated associations between life stress, socioeconomic status, and hippocampal volume (Chaney et al., 2014; Hanson et al., 2011; Hodel et al., 2015; McDermott et al., 2019; McLaughlin et al., 2019). Yet, the biological manifestation of depression, and thus early neurodevelopmental risk markers, may differ between high and low stress contexts. These possibilities warrant further developmental work

and suggest that consideration of the current environmental context is crucial when assessing the validity of risk markers for depression.

Despite the significant effects observed for psychosocial threat, this study did not replicate the prior finding that family income moderates the association between depression symptoms and hippocampus volume. There are a number of factors that may have contributed to the different pattern of results observed in this study. The prior research spanned a larger developmental age range, including assessment of family income during the preschool period. Observing effects of early family income is consistent with the large effects of very early experience on later neural and behavioral outcomes observed in prior research (Bick and Nelson, 2016; Luby et al., 2020; Pechtel and Pizzagalli, 2011). It is possible that if the assessment of family income in the ABCD study had occurred during early sensitive periods for the development of hippocampal volume that a different pattern of results would emerge. Further, the imaging data in our prior study were collected when participants were between ten- and eighteen-years-old, which may have allowed for greater variation in hippocampal volume associated with depression risk or family income across the adolescent period. Finally, it is important to note that the prior sample was enriched for depression in early childhood, in contrast to the non-enriched sample used here. Despite differences in the sample composition and patterns of results, the findings of the current study provide additional support for a growing literature emphasizing the importance of considering more specific environmental effects in place of, or in conjunction with,socioeconomic status when developing new markers of risk for psychopathology (DeJoseph et al., 2022; Herzberg, 2022; Neckerman et al., 2016; Noble et al., 2015). Taking such an approach improves the interpretability of results, reducing the need to speculate about what aspects of socioeconomic status, as measured by family income or caregiver education, might drive a particular result. Taking person-centered dimensional approaches to individual experiences in future research will facilitate investigation of more proximal mechanisms through which neurobiological development can confer risk or protection from psychopathology.

Demonstrating the utility of more specific methods for assessing environmental effects in studies of psychopathology risk, only psychosocial threat moderated the prospective link between hippocampus volume and depression symptoms in this study. It is possible that baseline family income does not index a sufficiently proximal mechanism to affect the role of hippocampus volume as a marker of risk for future depression symptoms in the large ABCD sample. Recent theoretical work supports this notion, drawing a distinction between “exposures” and “experiences” in which family income is characterized as exposures that may or may not give rise to particular experiences (e.g., limited access to mental health care; McLaughlin et al., 2021). In this framework, it may not be surprising that our effects were specific to psychosocial threat, which was operationalized using a method better equipped to assess individual experiences as opposed to exposures. Conversely, neither caregiver social support nor material and economic deprivation were significant moderators of the relationship between baseline hippocampus volume and depression symptoms at the two-year follow-up. Unlike family income, however, caregiver social support was assessed using youth experiences and has a clearer mechanistic path by which it might promote adaptive behavioral development, as high-quality caregiving has long been associated with adaptive outcomes (Fraley et al., 2012; Gee and Cohodes, 2021; Vandell et al., 2010). Similarly, material and economic deprivation was assessed using items that included reports of experiences that may be associated with being exposed to low income environments (e.g., being evicted for not paying rent or a mortgage in the last 12 months). As such, it is not immediately clear why psychosocial threat, but not caregiver support or material and economic deprivation, was associated with future depression symptoms. One possibility is that the impact of caregiver social support on behavioral outcomes may wane during the adolescent period as youth begin to orient their attention toward peer relationships (Foulkes and Blakemore, 2016; Lam et al., 2014; Nelson et al., 2016). Alternatively, it may be that the effects of material and economic deprivation or caregiver social support are most important in the high threat environments that, in our analyses, may have already rendered small hippocampus volume a non-specific marker of risk for future depression symptoms. Whether healthy peer relationships are an important environmental moderator of depression risk and whether material and economic devprivation or caregiver social support are more or less impactful in promoting adaptive development as a function of environmental threat exposure are important avenues for future research.

This study was characterized by a number of strengths in comparison to the prior research. Our primary outcome models were pre-registered based on the results of previous research, enhancing the identified effects with *a priori* theoretical justification and interpretation. The strengths of this study were also, in part, due to the large sample size and richness of the ABCD study allowing replication and extension of our previously published work. For example, this study established prospective relationships between hippocampus volume in low threat environments and depression symptoms two years later, even when controlling for initial levels of depression symptom endorsement. We were also able to generate and use person-specific factor scores of environmental experience known to reduce demographic bias in the reporting of psychosocial threat (DeJoseph et al., 2022). This adjustment is crucial for several reasons, including minimizing bias in the inferences drawn, enhancing individual variation, increasing the specificity of our results, and providing a tractable target for intervention in early adolescence. We also observed consistency across reporters, with the pattern of results holding when both parent-reported depression symptoms and youth-reported internalizing symptoms were used as the outcome of interest.

Despite these strengths, the study is also characterized by a number of limitations which should be considered when interpreting the results. The ABCD study sample is largely urban and, on average, largely comprised of relatively well-resourced youth and their families. An even lower income sample, like that in our previous research, may have revealed larger effects of material and economic deprivation or have benefitted from a larger degree of variance across the dimensions of experience. Similarly, we were only able to assess dimensions of experience effectively assessed in the ABCD data set. It is possible that additional dimensions of experience, such as environmental unpredictability, play an important role in the determinants of depression risk that we were unable to address. Further, the internal consistency of the Family Conflict subscale of the Family Environment Scale and CRPBI scores used in this study were in the questionable range using standard interpretation of Cronbach’s alpha values ($\alpha = 0.68$ and $\alpha = 0.66$, respectively for youth report in our sample). While the use of demographically-adjusted MNLFA scores improves our measurement of the environmental experiences of youth in the ABCD study, the internal consistency of the data used to generate these scores is a limitation of the current analyses. In an exploratory analysis, we also assessed parent-reported psychosocial threat, but were only able to use the raw sum scores from the Family Environment Scale as MNLFA-adjusted scores were unavailable. As a result, while our results suggest specific effects of youth perceptions of threat in their environment, it may also be the case that demographically adjusted parent-reports of the construct would also interact with hippocampus volume to predict later depression symptoms. Future research continuing to increase the specificity of the assessment of youth- and parent-reported dimensions of experience may continue to improve our understanding of depression risk in adolescence. This study also focused specifically on replicating and extending effects that were limited to hippocampus volume. As a result, future research that extends these effects to additional measures of brain structure and function may provide additional understanding of the pathophysiology of depression risk in early adolescence. Finally, given the specific focus of this study, there is not yet a clear alternative risk marker for youth in high threat environments, where hippocampal

volume was not shown to be a specific marker of risk for depression symptoms. Identifying such an alternative is crucial for the development of more equitable markers of risk during the adolescent period.

In this study, we identified psychosocial threat as a significant moderator of the association between hippocampus volume and depression symptoms two years later in early adolescence. We did not, however, replicate our previous research in a different sample that had indicated family income during the preschool period played a similar moderating role in determining depression risk from preschool through late adolescence. Despite this, these results emphasize the importance of considering individual dimensions of experience when seeking valid and specific risk markers for psychopathology. While it remains common to study income-to-needs ratio or caregiver education as proxy measures of socioeconomic status, we believe that our results make a strong case for increasing the specificity of environmental experience assessment in future research. In particular, identifying specific environmental experiences that may increase risk for the development of psychopathology is an important first step toward the development of improved prevention and intervention efforts during the early adolescent period. As such, producing a more nuanced understanding of the environmental and neurobiological factors contributing to the development of psychopathology holds great promise for promoting the wellbeing of all youth.

CRediT authorship contribution statement

Barch Deanna M.: Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **DeJoseph Meriah L.:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Luby Joan:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Herzberg Max P.:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The ABCD data repository grows and changes over time. The ABCD data used in this report came from DOI 10.15154/1519007.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dcn.2024.101359.

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