NEW RESEARCH

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Preschool Depression and Hippocampal Volume: The Moderating Role of Family Income

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Objective: Depression and low socioeconomic status have both been associated with hippocampal volume alterations. Whether these factors interact to predict neurobehavioral outcomes has not been adequately studied. The authors investigated family income as a moderator of the relationship between depression and hippocampal volume in a longitudinal sample.

Method: Longitudinal behavioral data, beginning at preschool age, and behavioral and neuroimaging data from school age to adolescence were used to assess the impact of preschool only and total preschool to adolescent depression symptoms on hippocampal volumes using family income as a moderator (N = 176).

Results: Depression severity during the preschool period interacted with family income to predict hippocampal volumes at the intercept (ie, age 13 years; B = −0.078, p = .003). Interaction decomposition revealed that only individuals with relatively high family income exhibited smaller hippocampal volume with increasing depression severity (B = −0.146, p = .005). Family income was associated with hippocampus volumes only in individuals with low to moderate preschool depression severity (B = 0.289, p = .007 and B = 0.169, p = .030, respectively).

Conclusion: Preschool depression severity interacts with family income to predict hippocampal volume across development, such that the effects of early depression are evident only in those with higher income. These findings suggest that hippocampal volume may not be an effective marker of risk for depression at different levels of socioeconomic status, and emphasizes the importance of the environmental context when assessing risk markers for depression. Future research should explore how socioeconomic stress may eclipse the effects of depression on hippocampal development, setting alternative neurodevelopmental risk trajectories.

Key words: preschool depression; hippocampus; poverty; structural MRI

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Poverty is a common experience for children in the United States and is associated with poor long-term physical and behavioral outcomes.[1] Similarly, major depressive disorder (MDD) is experienced by many youth and is associated with impaired productivity and poor physical health in adulthood.[2,3] Approximately 17.5% of children and youth in the United States live below the federal poverty line, with 40% living in low-income families (ie, with family incomes ≤2 times the poverty line),[4] and the lifetime prevalence of depression is estimated to be as high as 24% in adolescence.[5] Adolescence is not the first developmental period in which the impacts of poverty and MDD can be observed, however. Family poverty has been associated with alterations in brain structure evident as early as infancy.[6] Furthermore, depression symptoms have been validated in children as young as 3 years of age,[7,8] with increased risk for later childhood and adolescent depression associated with the early onset of symptoms.[9-11] Importantly, both poverty and MDD have been associated with similar neurobiological outcomes, particularly in the development of the hippocampus. Decreased hippocampal volume has been associated with experiencing poverty in early life and is one of the most replicated neural markers of MDD in adolescents and adults.[12-14] Despite this overlap, little research has investigated the relations of poverty and MDD to hippocampus development in an integrative manner, a crucial step toward investigating whether risk markers for MDD differ across the socioeconomic gradient. This study aims to begin this integrative research by prospectively modeling the combined effects of family income and depression symptoms during early childhood on hippocampus volume measured 5 times from late childhood through adolescence.

Research focused specifically on family income or parental education (ie, socioeconomic status) in childhood has consistently reported associations with alterations in

childhood brain development. For example, total brain volume has been shown to be positively related to socioeconomic status in children and adolescents, including significant associations with total gray matter, white matter, and total cortical volume.[14] The same pattern of results has been reported in adolescent cortical gray matter when using family income as the predictor of interest.[15] In each of these studies, regions positively related to family socioeconomic status were also associated with performance on IQ or achievement tests.[14,15] Hippocampus-specific relationships with family income in childhood have also been reported by several groups, including positive associations between family income and hippocampus volume[13,16] and a parental education–based measure of socioeconomic status and hippocampal volume.[14] Finally, in a study that included both children and adults, hippocampal volume was positively associated with socioeconomic status in 8- to 12-year-old children but not adults, suggesting important effects of developmental timing.[17]

Similarly, altered hippocampal volumes are among the most well-replicated neural correlates of MDD in all periods of development, a finding also confirmed in meta-analyses.[12,18] Whereas decreased total cortical gray matter, cortical thinning, and smaller volumes in a diverse group of cortical and subcortical regions have been associated with MDD in early childhood,[19,20] the hippocampus has been a frequent focus of the literature based on the diathesis–stress model of depression.[21,22] Although the results of some studies suggest specific associations between MDD and reduced hippocampal volumes, others suggest that reduced hippocampal volume is a transdiagnostic marker that is also found in patients with obsessive compulsive disorder, schizophrenia, posttraumatic stress disorder, and bipolar disorder.[23-25] The issue of specificity aside, a better understanding of the associations between MDD and the hippocampus and their potential interactions with other risk factors is an important next step in developmental psychopathology research.

More specifically, further unpacking the associations between MDD and hippocampal volume requires consideration of environmental influences such as poverty and the stressors associated with experiencing impoverished environments. Researchers have argued that reductions in hippocampal volume may occur as a result of experiences of stress in childhood, which affect the structure of the hippocampus via stress hormone feedback from dysregulated stress systems (eg, the hypothalamic–pituitary–adrenal axis).[13,16,26,27] These differences in hippocampal volume associated with early stress may also be associated with the development of MDD in some individuals, particularly if they reflect dysregulation of stress responsivity systems thought to be important in MDD.[27-30] Alternatively, reduced hippocampal volume in individuals with depression might indicate neurotoxic effects of experiences of chronic MDD. Some evidence suggests that smaller hippocampal volumes are present in adults with recurrent depressive episodes compared to adults with only a first depressive episode.[31,32] This prior research suggests that both stress- and depression-related factors contribute to variation in hippocampal volume.

Limited research has assessed both stress and MDD within the same analytic framework to better understand their roles in hippocampal development. As reviewed above, 1 form of early stress known to relate to hippocampal volume is poverty, which has been associated with greater exposure to trauma, neglect, and chronic stress in childhood.[33] Supporting a role for poverty-related stress in the development of depression, meta-analytic research has reported increased risk for MDD as a function of low income-to-needs ratio (INR), whereas other research has associated specific poverty-related stressors with increased risk for MDD.[34,35] Recent work has also suggested that the predictive validity of early-onset depression differs on the basis of INR.[36] Because of the strong association between INR and hippocampal volume, and the possibility that INR is associated with MDD risk, statistically controlling for INR in investigations of MDD and the hippocampus is common. However, using INR as a covariate is not sufficient to fully understand the associations among stress, depression, and hippocampal volume. For example, one study found that MDD moderated the link between INR and hippocampal volume before (with lower INR associated with lower hippocampal volume), but not after, the onset of MDD in adolescence.[37] This study supports the notion that examining interactions between INR and MDD may elucidate links among MDD, poverty, and the development of the hippocampus. Further supporting an interaction approach, the mechanisms by which poverty and associated stressful life events affect the hippocampus (eg, increased exposure to stress hormones) are highly similar to those implicated in stress-sensitization theories of depression, which highlight interactions among stress-responsive systems, brain structure, and experiences of depression.[38-40]

Although INR is strongly associated with hippocampal volume, hypothesized to affect brain structure via stress-related mechanisms, its interaction with MDD is an important next step for developmental psychopathology research. Despite preliminary evidence from a single study on the interaction of MDD and INR in relationship to hippocampal volume in adolescence, how these factors interact to affect hippocampal volume from early childhood through adolescence remains unknown. It may be that low

family INR and greater depressive symptoms interact additively, resulting in smaller hippocampal volumes and increased subsequent risk for MDD. Alternatively, INR and MDD might interact in such a way that the impact of 1 factor on hippocampal volumes reduces relations to the other factor. For example, it is possible that poverty affects hippocampal volume via stress-related remodeling of subcortical structures in ways that override additional influences of depression, or that severe depression relations to hippocampal volume override additional influences of family income via neurotoxic effects of depression. Importantly, investigating these relationships is important to better understand specific developmental trajectories of risk depending upon INR and MDD symptoms via either stress-sensitization or neurotoxic mechanisms, with implications for more precise prevention and intervention efforts.

In this study, we extended the previous literature and examined whether family income moderated the association between MDD and hippocampal volume trajectory. Using 5 waves of imaging data across development in a sample ascertained in the preschool period and oversampled for depression, we tested the interaction between INR in early childhood and MDD severity as a predictor of hippocampal volume. The analysis was completed using MDD severity data from the preschool period only, and then with MDD severity data spanning the length of the study, to evaluate the possibility of timing effects in experiences of depressive symptoms on hippocampal development (given the previous finding of timing effects).[41] We then tested the specificity of the associations to depression, using aggregated externalizing and internalizing symptoms as alternative predictors. Finally, we completed a set of specificity analyses to determine whether subcortical structures other than the hippocampus were associated with MDD severity across the socioeconomic gradient.

METHOD

Participants

The current study sample comprised 176 youth who were part of the larger Preschool Depression Study (PDS). The PDS includes 5 waves of brain imaging as part of a 17-year longitudinal study beginning when participants were 3 to 5 years of age. Participants were oversampled for depression using the Preschool Feelings Checklist[42] and those with developmental and/or neurological disorders were excluded. Inclusion criteria for the analysis reported here included complete data for baseline INR and having usable imaging data from at least one of the 5 scan waves (the participants section in Supplement 1, available online, provides additional details on recruitment and inclusion criteria). Demographic information for the participants included in this study can be found in Table 1. Participants and their caregivers provided informed consent and assent. All methods were approved by the Institutional Review Board at Washington University (IRB #201502094).

Preschool Income-to-Needs Ratio

Family income at baseline was measured using income-to-needs ratio (INR), defined as the total family income at time 1 (T1) divided by the federal poverty level based on family size.[43]

Preschool and Overall Depression Assessment

Participants and their primary caregivers completed up to 10 in-person assessments with trained staff from the Early Emotional Development Program over the course of the study. Participants were between the ages of 3.0 and 5.11 years at T1 and ranged from 15.3 to 21.7 years at the most recent assessment (T10/scan wave 5). The Preschool-Age Psychiatric Assessment (PAPA), Child and Adolescent Psychiatric Assessment (CAPA) and Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) were used to assess depression symptoms as age appropriate (detailed in Preschool and Overall Depression Assessment in Supplement 1, available online).

Externalizing and Internalizing Assessment

Aggregated externalizing and internalizing symptoms were also assessed using parent-report from the PAPA. The externalizing dimensional score was calculated at each wave as the number of PAPA attention-deficit/hyperactivity, oppositional defiant, and conduct disorder symptoms endorsed, and the internalizing dimensional score was calculated at each wave as the number of PAPA generalized anxiety, separation anxiety, and posttraumatic stress disorder symptoms endorsed. These scores were then averaged across waves in participants 3.0 to 5.11 years of age to create mean preschool externalizing and internalizing dimensional scores.

Structural Imaging Acquisition

Structural magnetic resonance imaging (MRI) data were acquired on a 3.0T Siemens Trio whole-body scanner during scan waves 1 to 3 and a 3.0T Siemens Prisma during scan waves 4 and 5. Specific acquisition parameters and how the data were integrated between the 2 scanner platforms are detailed in the supplemental methods section of Supplement 1, available online. Task-based and resting-state scans were also completed during the scanning sessions but are not considered here.

TABLE 1 Subject Characteristics

	Total n	%	n
Female sex	176	48.3	85
Race	176		
White		51.7	91
Black or African American		37.5	66
American Indian or Alaska Native		0.0	0
Asian		1.1	2
Native Hawaiian or Other Pacific Islander		0.0	0
Other		9.7	17
	Total n	**Mean**	**SD**
T1 income-to-needs ratio	176	2.01	1.11
T1 age	147	4.52	0.78
Scan 1 age	176	10.30	1.29
Scan 2 age	173	11.77	1.20
Scan 3 age	162	13.03	1.27
Scan 4 age	146	16.34	1.12
Scan 5 age	142	18.61	1.23
Mean preschool MDD severity	147	2.40	1.63
Mean preschool–adolescent MDD severity	176	2.16	1.37
S1 hippocampus volume (cm^3)	157	8.16	0.78
S2 hippocampus volume (cm^3)	146	8.14	0.80
S3 hippocampus volume (cm^3)	132	8.18	0.83
S4 hippocampus volume (cm^3)	124	8.70	0.97
S5 hippocampus volume (cm^3)	110	8.89	0.91
Intracranial volume (cm^3)	176	1555.21	153.14

Structural Imaging Processing

MRI data from scan waves 1 to 3 had been previously processed as detailed in a prior publication,[41] and data from scan waves 4 and 5 were downsampled to match the 1.0-mm isotropic voxels of the previous waves. The FreeSurfer Longitudinal processing stream was used to process all acceptable MRI scans for each participant (v 5.3 http://surfer.nmr.mgh.harvard.edu).[44] Further details are provided in the supplemental methods section of Supplement 1, available online. Hippocampus volumes were obtained using FreeSurfer's "aseg.stats" report, as were intracranial volume and the regions used for specificity analyses, including putamen, amygdala, nucleus accumbens, caudate, and thalamus. Region volumes from each hemisphere were summed to create a single, bilateral volume measure for each structure. FreeSurfer output was visually inspected to ensure high-quality segmentations.

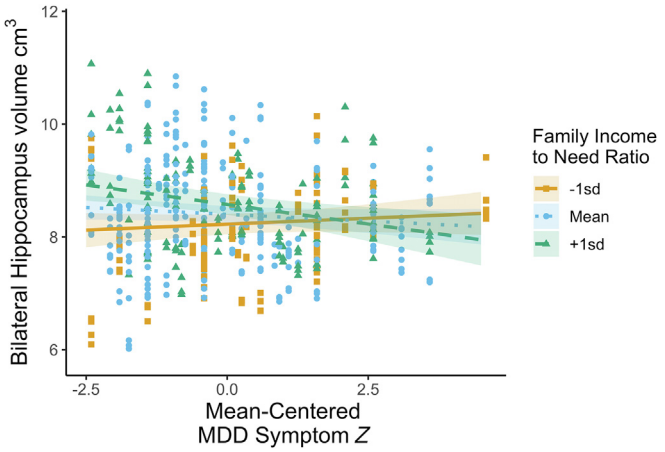
Statistical Analysis

Hippocampus volume across scan waves 1 to 5 (S1–S5) were investigated using multilevel models (MLMs) in SAS version 9.4. Hippocampus volume (in cubic centimeters) was the dependent variable, and the mean MDD severity score was the independent variable. Two different measures of MDD severity were investigated: (1) MDD severity during preschool, and 2) MDD severity across all waves of the PDS study (participants ranging in age between 3.0 and 21.7 years). Baseline INR was examined as a potential moderator of the relationship between MDD severity and hippocampus volume. The MLMs of hippocampus volume included random intercept and slope components and assumed an unstructured covariance structure. The time variable was age at scan, centered at the median age of 13 years. Intracranial volume and sex were covariates, and the sex by age interaction was included in the model to account for differing hippocampus volume by sex. In addition, the interactions between MDD severity and age, baseline INR and age, and MDD severity, baseline INR, and age were included in all models. All models treated MDD severity and baseline family INR as continuous predictors. Grouping was used for visualization purposes only in Figure 1. A small difference in sample size exists between the model investigating preschool MDD severity (N = 147) and the model investigating preschool–adolescent MDD severity (N = 176) due to data availability in the preschool period. All participants with MDD severity data from the developmental period of interest who also had usable hippocampal and baseline INR data were included in these models. Because of the a priori nature of the statistical tests, they were not corrected for multiple comparisons. Details on the symptoms included and additional model information are provided in the statistical analyses section of Supplement 1, available online. Post hoc specificity analyses were completed using alternative subcortical structural volumes as the outcome variable (putamen, amygdala, nucleus accumbens, caudate, and thalamus), alternative covariate specifications, and alternative treatment of the baseline family INR data. Further details of these specificity analyses are provided in the additional specificity analysis section of Supplement 1, available online.

RESULTS

Participant characteristics are detailed in Table 1. There were 176 children with at least 1 scan with usable data and baseline INR available. Of these, 147 children had at least 1 assessment at age 3.0 to 5.11 years and therefore have a mean preschool MDD severity score. All participants have a mean preschool–adolescent MDD severity score. Of the 176 participants, 4 had 1 usable scan, 21 had 2 usable scans, 43 had 3 usable scans, 46 had 4 usable scans, and 62 had 5 usable scans.

FIGURE 1 Bilateral Hippocampus Volume as a Function of Major Depressive Disorder (MDD) Symptoms and Family Income-to-Needs Ratio (INR)



Note: Estimated trajectories from a multilevel model of hippocampus volume at scans 1 to 5 by preschool MDD severity and family INR. Separate lines for −1, 0, and +1 SD from the sample INR mean are for visualization purposes only. All analyses treated MDD severity and family INR as continuous variables. Model predictions presented are from a conditional interaction and represent predicted hippocampal volumes at 13 years of age, which is the median age of the sample. Please note color figures are available online.

Table 2 details the results of the MLMs of S1 to S5 hippocampus volume by preschool MDD severity and mean preschool−adolescent MDD severity. The interaction between baseline INR and preschool MDD severity was significantly associated with hippocampus volume at the intercept (median age, 13 years). In contrast, there was a main effect of greater baseline INR predicting greater hippocampal volume in the preschool−adolescent MDD severity model, but there was no significant main effect of preschool−adolescent MDD severity and no further moderation by baseline INR (Table 2). To determine whether the null finding in the model with preschool−adolescent MDD severity could be explained by decreased MDD severity after the preschool period, a paired t test of mean MDD severity during preschool vs after preschool was conducted, but no significant difference was found (during preschool: 2.40 ± 1.63 vs after preschool: 2.37 ± 1.45, $t = 0.19$, $p = .85$).

To decompose the interactive effect of baseline INR and preschool MDD severity on S1 to S5 hippocampus volume, youth were grouped into 3 income groups and additional MLMs were conducted separately in each subgroup. The low-income group consisted of youth with baseline INR <1.46 (less than mean –0.5 SD); the moderate-income group consisted of youth with baseline INR ≥1.46 and <2.57 (mean –0.5 SD to mean +0.5 SD); and the high-income group consisted of youth with baseline INR ≥2.57 (greater than mean +0.5 SD). The mean ±0.5 SD cutoff was chosen to result in a similar number of participants in each subgroup. These MLMs of S1 to S5 hippocampus volume included preschool MDD severity as the independent variable, with age as the time variable and intracranial volume and sex as covariates. Again, a sex by age interaction was included, along with the preschool MDD severity by age interaction. As detailed in Table 3, preschool MDD severity was significantly associated with hippocampus volume only in the highest-income group, with greater severity associated with smaller volume (Figure 1 and Figure S1 in Supplement 1, available online). Preschool−adolescent MDD severity was not significantly associated with hippocampus volume in separate MLMs in the 3 income subgroups (detailed in Table S1 in Supplement 1, available online).

To further clarify the source of the interaction between baseline INR and preschool MDD severity, participants were also divided into low, moderate, and high preschool MDD severity groups, and additional MLMs of hippocampus volume by baseline INR were conducted separately in each subgroup. The low-severity group consisted of youth with preschool MDD severity <1.58 (less than mean –0.5 SD); the moderate-severity group consisted of youth with preschool MDD severity ≥1.58 and <3.21 (mean –0.5 SD to mean +0.5 SD); and the high-severity group consisted of youth with preschool MDD severity ≥3.21 (greater than mean + 0.5 SD). As with income, the mean ±0.5 SD cutoff was chosen to result in a similar number of participants in each subgroup. These MLMs of S1 to S5 hippocampus volume included independent variable baseline INR with age as the time variable, intracranial volume and sex as covariates, and sex by age and baseline INR by age interactions. As detailed in Table 4, baseline INR was significantly associated with hippocampus volume in the low and moderate preschool MDD severity groups, but not in the high preschool MDD severity group.

Specificity analyses showed that the interaction between preschool MDD severity and INR as predictors of hippocampus volume were specific to MDD (as compared to externalizing and internalizing symptoms) and to the hippocampus (putamen, amygdala, nucleus accumbens, caudate, and thalamus volumes were used in specificity analyses; more detail can be found in Supplement 1, available online). Additional specificity analysis results, including alternative covariate specifications and alternative treatment of the family INR data can be found in the supplemental results presented in Tables S2 to S6 in Supplement 1, available online.

TABLE 2 Multilevel Models of Hippocampus Volume at Scans 1 to 5 by Mean Preschool Major Depressive Disorder (MDD) Severity and Mean Preschool–Adolescent MDD Severity With T1 Income-to-Needs Ratio (INR) as a Moderator

Model 1: preschool MDD severity (n = 147)	**Estimate**	**SE**	***t***	***p***
Intercept	8.3384	0.0740	112.71	<.0001
Intracranial volume (cm^3)	0.0025	0.0004	6.35	<.0001
Female sex	−0.0855	0.1118	−0.76	.4457
T1 INR	0.1444	0.0464	3.11	.0022
Preschool MDD severity	−0.0489	0.0320	−1.53	.1289
Age	0.1122	0.0050	22.50	<.0001
Female sex × age	−0.0511	0.0072	−7.14	<.0001
T1 INR × age	0.0060	0.0031	1.95	.0532
Preschool MDD severity × age	0.0018	0.0023	0.77	.4435
Preschool MDD severity × INR	−0.0776	0.0260	−2.98	.0034
Preschool MDD severity × INR × age	0.0005	0.0019	0.24	.8099
Model 2: preschool–adolescent MDD severity (n = 176)	**Estimate**	**SE**	***t***	***p***
Intercept	8.3367	0.0719	115.93	<.0001
Intracranial volume (cm^3)	0.0030	0.0004	8.34	<.0001
Female sex	−0.0558	0.1081	−0.52	.6068
T1 INR	0.1288	0.0465	2.77	.0063
Preschool–adolescent MDD severity	−0.0051	0.0362	−0.14	.8879
Age	0.1072	0.0050	21.49	<.0001
Female sex × age	−0.0422	0.0071	−5.95	<.0001
T1 INR × age	0.0075	0.0033	2.29	.0235
Preschool–adolescent MDD severity × age	0.0045	0.0027	1.67	.0984
Preschool–adolescent MDD severity × INR	−0.0259	0.0326	−0.80	.4275
Preschool–adolescent MDD severity × INR × age	0.0000	0.0024	0.02	.9875

DISCUSSION

The goal of the current study was to evaluate whether early-life INR moderated the well-replicated association between MDD and smaller hippocampal volumes. Our results, generated from a study oversampled for preschool depression, indicate that early-life INR moderated the relationship between MDD severity and hippocampal volume across multiple scanning waves, but only in the context of MDD severity experienced during the preschool period. Preschool–adolescent MDD severity, assessed from early childhood to late adolescence, did not interact with baseline INR to predict hippocampal volume across 5 waves of MRI data. In addition to the specificity of the preschool period, the effects were also specific to MDD: externalizing and internalizing symptoms did not relate to hippocampal volume. Associations were also specific to the hippocampus compared to other selected subcortical regions.

Our results are consistent with prior literature reporting smaller hippocampal volumes in individuals with MDD. Previous meta-analytic research has reported smaller hippocampal volumes in the context of MDD,[18] and theoretical research has long implicated stress-mediated reductions in hippocampal volume in depression.[28,45] The novel finding of this study, however, is that the relationship between MDD severity and smaller hippocampal volume was moderated by family income. The importance of understanding heterogenous developmental trajectories as a function of socioeconomic status is receiving increased attention in developmental science[46,47] and is an important step toward a more precise and contextually appropriate approach to prevention and intervention. Nonetheless, very few prior studies have investigated the moderating role of family INR in the association between MDD and hippocampal volume. Like 1 other study,[37] our results include a significant moderating relationship, this time between income and MDD severity, suggesting that: (1) hippocampal development is related to early childhood depression only at higher levels of early-life income; and (2) early-life income levels are related to hippocampal volumes only at lower levels of preschool depression. This finding supports the notion that high early-life INR and severe preschool MDD symptoms reduce the influence of the other on hippocampal volume without evidence of additive effects. Furthermore, this pattern of results suggests that smaller hippocampal volume is not a specific developmental marker of MDD for individuals at all levels of income. Alternatively, the association between early-life INR and hippocampal volume

TABLE 3 Multilevel Models of Hippocampus Volume at Scans 1 to 5 by Mean Preschool Major Depressive Disorder (MDD) Severity by Income Group

Model 1: INR < 1.46 (n = 54)	**Estimate**	**SE**	***t***	***p***
Intercept	8.1606	0.1107	73.71	<.0001
Intracranial volume (cm^3)	0.0031	0.0006	5.21	<.0001
Female sex	−0.1642	0.1679	−0.98	.3327
Preschool MDD severity	0.0473	0.0442	1.07	.2898
Age	0.1077	0.0082	13.19	<.0001
Female sex × age	−0.0626	0.0127	−4.95	<.0001
Preschool MDD severity × age	0.0010	0.0038	0.27	.7865
Model 2: 1.46 < INR < 2.57 (n = 31)	**Estimate**	**SE**	***t***	***p***
Intercept	8.4458	0.1866	45.26	<.0001
Intracranial volume (cm^3)	0.0029	0.0013	2.29	.0302
Female sex	0.0180	0.2829	0.06	.9497
Mean preschool MDD severity	−0.0707	0.0968	−0.73	.4716
Age	0.1001	0.0104	9.66	<.0001
Female sex × age	−0.0276	0.0136	−2.03	.0537
Preschool MDD severity × age	−0.0065	0.0054	−1.22	.2358
Model 3: INR > 2.57 (n = 62)	**Estimate**	**SE**	***t***	***p***
Intercept	8.5180	0.1199	71.05	<.0001
Intracranial volume (cm^3)	0.0022	0.0006	3.71	.0005
Female sex	−0.1298	0.1759	−0.74	.4634
Preschool MDD severity	−0.1464	0.0504	−2.91	.0051
Age	0.1236	0.0076	16.31	<.0001
Female sex × age	−0.0547	0.0109	−5.00	<.0001
Preschool MDD severity × age	0.0041	0.0035	1.15	.2563

Note: *INR = income-to-needs ratio.*

also seems to be eliminated in children with the most severe preschool MDD, suggesting that severe MDD eclipses the ability to detect additional relationships to the stress of low early-life INR.

Based on our results, the developmental timing of MDD symptoms also influences the relationships between MDD severity, early-life INR, and hippocampal volume. Sensitive periods have long been a focus of the field and are returning to the fore, particularly in developmental psychopathology research.[48] Here, MDD severity during the preschool period specifically, but not mean MDD severity across development (from age 3 to 21 years), interacted with baseline INR to predict hippocampal volumes. This is consistent with previous work in this sample showing that maternal support during the preschool period has the most powerful influence on later hippocampal trajectories compared to later developmental periods.[41] Furthermore, theoretical work has suggested that stress in early childhood may begin a developmental cascade via hippocampal alterations that leads to depressive outcomes later in life.[49] It may be that MDD is a particularly impactful experience during early childhood, a period of enhanced plasticity, leading to altered hippocampal volume throughout development.

Taken together, decomposing the interaction of MDD and early-life INR suggests that there are heterogeneous risk trajectories related to hippocampal development based on family income, and that more severe depressive symptoms arising during the preschool period can eclipse effects of income on hippocampal volume. The fact that developmental timing, MDD symptom severity, and family income must all be considered to fully interpret these results further emphasizes the importance of considering INR, a traditional covariate, as a moderator in diverse samples instead. These findings also have important clinical implications in terms of how clinicians might determine different levels of risk in children facing either poverty or depression, or both.

Another important aspect of these results is the specificity of MDD and hippocampal volumes. Neither general externalizing nor internalizing symptoms during the preschool period showed the same pattern of association as MDD symptoms with baseline INR and the hippocampus. Additional specificity analyses in other subcortical regions

TABLE 4 Multilevel Models of Hippocampus Volume at Scans 1 to 5 by T1 Income-to-Needs Ratio (INR) by Major Depressive Disorder (MDD) Severity Group

Model 1: MDD severity < 1.58 (n = 54)	**Estimate**	**SE**	***t***	***p***
Intercept	8.4341	0.1577	53.50	<.0001
Intracranial volume (cm^3)	0.0027	0.0008	3.53	.0009
Female sex	−0.1464	0.2250	−0.65	.5183
T1 INR	0.2888	0.1024	2.82	.0069
Age	0.1129	0.0116	9.76	<.0001
Female sex × age	−0.0545	0.0150	−3.65	.0009
T1 INR × age	0.0030	0.0071	0.42	.6747
Model 2: 1.58 < MDD severity < 3.21 (n = 52)	**Estimate**	**SE**	***t***	***p***
Intercept	8.4384	0.1211	69.66	<.0001
Intracranial volume (cm^3)	0.0028	0.0007	3.94	.0003
Female sex	−0.0872	0.1767	−0.49	.6238
T1 INR	0.1689	0.0753	2.24	.0295
Age	0.1042	0.0078	13.28	<.0001
Female sex × age	−0.0419	0.0112	−3.74	.0005
T1 INR × age	0.0069	0.0050	1.39	.1696
Model 3: MDD severity > 3.21 (n = 41)	**Estimate**	**SE**	***t***	***p***
Intercept	8.1463	0.1083	75.21	<.0001
Intracranial volume (cm^3)	0.0022	0.0006	3.78	.0006
Female sex	−0.0502	0.1740	−0.29	.7748
T1 INR ratio	−0.0458	0.0626	−0.73	.4694
Age	0.1229	0.0078	15.73	<.0001
Female sex × age	−0.0634	0.0122	−5.21	<.0001
T1 INR × age	0.0052	0.0049	1.06	.2969

also suggested specific effects of MDD and baseline INR on the hippocampus. This specificity may be due to an accumulation of convergent factors. Previous research has identified a combined contribution of genetic risk and early-life stress as predictors of smaller hippocampal volume,[50] whereas stress sensitization and stress autonomous theories of depression suggest that stressful experiences are crucial to first-episode and/or recurrent depression.[28] These factors, in combination with the high degree of stress sensitivity in the hippocampus due to stress hormone receptor density,[51] direct actions of corticotropin-releasing hormone on hippocampal dendrites,[52] and human neuroimaging associating MDD with hippocampal volume,[12,18,53] provide a strong theoretical foundation for interpreting specific effects of MDD on hippocampal volumes.

Finally, it is important to acknowledge that the intersection of race and socioeconomic status in the United States must be considered whenever research addresses the role of poverty in the development of psychopathology. Poverty rates among Black youth in the United States are 3 times greater than those of White youth,[54] an inequality created by institutionalized racism targeting people of color that is rooted in historical events and current structural barriers.[55] Importantly, the intersection of racism and poverty can have a negative impact on each domain of the social determinants of health for children, including safe housing (eg, redlining, mass incarceration, property devaluation), quality education (eg, school defunding), and access to safe recreational facilities (eg, poor park quality).[56] In this study, we investigated only the influence of income on the well-established relationship between depression and hippocampal volume. However, it must be emphasized that the pattern of results identified here may be, in part, influenced by race and experiences of racism among participants of color and their families, an unmeasured variable in this study. Taken together, these issues at the intersection of race and poverty underline the importance of ensuring that efforts to identify developmental risk include explicit examination of socioeconomic and demographic variables to ensure equitable screening and prevention efforts for all youth.

This study contributes to a growing literature emphasizing the importance of family income during childhood in predicting unique neurodevelopmental trajectories, extending prior work to focus specifically on depression and hippocampal development. However, the results should be interpreted in the context of several limitations. The initial

recruitment of this sample was designed to enrich the sample for preschool depression, limiting generalizability of the results, possibly increasing the likelihood of genetic predisposition for decreased hippocampal volume, and making it difficult to test a plausible alternative model in which MDD symptoms mediate the effects of early-life INR on hippocampal volume. The timing of the MRI scans also complicates interpretation, in that brain imaging took place after the initial measurement of MDD severity. This does not allow the current study to draw conclusions about the chronicity of hippocampal changes in relation to MDD onset, and it necessitates further study beginning at earlier ages of the developmental timing effects observed here. Furthermore, the timing of the MRI assessments precludes us from eliminating the possibility of reverse causation: that lower preschool-age hippocampal volume may lead to increased preschool MDD severity and persist into preadolescence, when hippocampal volume was first assessed. We note, however, that moderation of the association between preschool MDD and hippocampal volume by early-life family income retains its importance in understanding the pathophysiology of depression even in this alternative interpretation of our results. To fully address the possibility of reverse causality, or to make causal claims of any kind, future research using experimental designs (eg, assignment to cash transfer programs) is needed. A scanner upgrade also took place during this longitudinal study, but all imaging data within each wave were acquired on the same scanner, and all participants transitioned to the upgraded scanner at scan 4, mitigating the effects of this upgrade on our results. The upgrade does, nevertheless, preclude interpretation of normative trajectories of hippocampal development in the context of MDD severity. Finally, despite the strong predictive power of INR, it is only a proxy for the environmental experiences associated with socioeconomic status. Future research should attempt to replicate these effects and to extend the current findings by emphasizing environmental factors associated with differences in family income (eg, home and neighborhood environment, caregiver availability, systemic discrimination, etc) in an effort to achieve improved mechanistic specificity.

In this study, we identified a moderating role for early-life INR in the relationship between MDD severity during the preschool period and later hippocampal volume trajectories. These results further emphasize the important roles of early depression, along with environmental factors and particularly the central role of socioeconomic status, in influencing the development of the hippocampus, a key brain region subserving cognitive and emotional functioning. Study findings show that family income in early childhood is positively associated with hippocampal volume, in the context of mild or moderate depression symptoms. However, when depression is severe during the preschool period, higher family income is no longer associated with larger hippocampal volume. We believe that these results suggest that hippocampal volume is not an equally valid biomarker for depression risk at different levels of socioeconomic status. Future research focused on charting the developmental trajectories of psychopathology risk across levels of socioeconomic status will be important for improved understanding of the contributions of early-life experience and basic resource availability in childhood to brain development and related risk of mental illness.

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