Original Investigation

The Effects of Poverty on Childhood Brain Development
The Mediating Effect of Caregiving and Stressful Life Events

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IMPORTANCE The study provides novel data to inform the mechanisms by which poverty negatively impacts childhood brain development.

OBJECTIVE To investigate whether the income-to-needs ratio experienced in early childhood impacts brain development at school age and to explore the mediators of this effect.

DESIGN, SETTING, AND PARTICIPANTS This study was conducted at an academic research unit at the Washington University School of Medicine in St Louis. Data from a prospective longitudinal study of emotion development in preschool children who participated in neuroimaging at school age were used to investigate the effects of poverty on brain development. Children were assessed annually for 3 to 6 years prior to the time of a magnetic resonance imaging scan, during which they were evaluated on psychosocial, behavioral, and other developmental dimensions. Preschoolers included in the study were 3 to 6 years of age and were recruited from primary care and day care sites in the St Louis metropolitan area; they were annually assessed behaviorally for 5 to 10 years. Healthy preschoolers and those with clinical symptoms of depression participated in neuroimaging at school age/early adolescence.

EXPOSURE Household poverty as measured by the income-to-needs ratio.

MAIN OUTCOMES AND MEASURES Brain volumes of children's white matter and cortical gray matter, as well as hippocampus and amygdala volumes, obtained using magnetic resonance imaging. Mediators of interest were caregiver support/hostility measured observationally during the preschool period and stressful life events measured prospectively.

RESULTS Poverty was associated with smaller white and cortical gray matter and hippocampal and amygdala volumes. The effects of poverty on hippocampal volume were mediated by caregiving support/hostility on the left and right, as well as stressful life events on the left.

CONCLUSIONS AND RELEVANCE The finding that exposure to poverty in early childhood materially impacts brain development at school age further underscores the importance of attention to the well-established deleterious effects of poverty on child development. Findings that these effects on the hippocampus are mediated by caregiving and stressful life events suggest that attempts to enhance early caregiving should be a focused public health target for prevention and early intervention. Findings substantiate the behavioral literature on the negative effects of poverty on child development and provide new data confirming that effects extend to brain development. Mechanisms for these effects on the hippocampus are suggested to inform intervention.

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Editorial

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The deleterious effects of poverty on child development have been well established in psychosocial research, with poverty identified as being among the most powerful risk factors for poor developmental outcomes.[1,2] Children exposed to poverty have poorer cognitive outcomes and school performance, and they are at higher risk for antisocial behaviors and mental disorders.[3] Notably, developmental deficits associated with poverty have been detected as early as infancy.[4,5] Despite these established and alarming poor developmental outcomes, to date, there have been little neurobiological data in humans to inform the mechanism(s) of these relationships. This represents a critical gap in the literature and an urgent national and global public health problem based on statistics that more than 1 in 5 children are now living below the poverty line in the United States alone.[6]

The tangible effect of early environmental exposures on brain development has been well established in laboratory animals. Animals exposed to enriched environments high in stimulation have been shown to display increased hippocampal cell proliferation and neurogenesis compared with those reared in relative deprivation.[7] Poverty represents a form of human deprivation that may parallel this animal model, raising the question of whether low levels of stimulation and relative psychosocial neglect associated with poverty have a similar negative effect on human brain development. A few studies have directly investigated the relationship between poverty and childhood brain development. Consistent with animal data, Noble and colleagues[8] detected a smaller hippocampus and amygdala in 5- to 17-year-old children living in poverty. In a large community sample, Hanson et al[9] reported smaller hippocampal gray matter volumes among children from lower-income backgrounds. Lower socioeconomic status was associated with smaller hippocampal gray matter volumes bilaterally in a small sample of healthy 10-year-old children.[10]

These findings suggest that exposure to poverty has deleterious effects on human amygdala and hippocampal development. These brain regions, involved in stress regulation and emotion processing, are known to be sensitive to environmental stimuli. However, what remains unclear, and critical to addressing this public health problem, are the specific factors that mediate this association in humans. Poverty is strongly associated with a number of risk factors implicated in poor developmental outcomes in behavioral studies, such as unsupportive parenting, poor nutrition and education, lack of caregiver education, and high levels of traumatic and stressful life events, making the income-to-needs ratio a good proxy for cumulative developmental stress.[11] These and other associated factors could serve as mechanisms mediating the negative impact of poverty on brain development. It is unclear whether such mediators of risk are also operative at the neurobiological level in humans.

Experimental studies of the neurobiological impact of poverty cannot be conducted in humans for obvious ethical reasons. However, the negative effect of early unsupportive parenting in the form of maternal deprivation and stress on hippocampal and amygdala development has been well established in rodents. Stress paradigms in rodent models have been associated with elevated anxiety and contrasting alterations in neuronal morphology in the hippocampus and amygdala, with dendritic atrophy observed in the hippocampus and increased dendritic arborization in the amygdala.[12,13] Developing rodents deprived of maternal nurturance show decreased hippocampal volume and altered stress reactivity.[14] An epigenetic mechanism for this effect has been elaborated.[15] Importantly, controlled trials that have randomized institutionalized toddlers to early therapeutic foster care vs institutionalization have documented the deleterious effects of early relative deprivation on cognitive outcomes.[16]

A few studies have investigated the effects of early caregiving on amygdala and hippocampal volumes in children. Consistent with animal data, Tottenham et al[17] showed an association between early institutional rearing and larger amygdala volumes. While animal data would suggest that institutional rearing would lead to reduced hippocampal volume, some investigators have suggested that such effects may not become evident in humans until later in life.[18] Consistent with this, decreased hippocampal volumes have been found in numerous studies of adults who experienced high levels of childhood stress/trauma.[19,20] In spite of this hypothesized delayed hippocampal effect, a positive impact of early supportive parenting on hippocampal development has been detected as early as school age.[21]

To investigate the effects of poverty on childhood brain development and to begin to inform the mediating mechanisms of these negative effects, we investigated associations between poverty and total white and total cortical gray matter volume, as well as hippocampus and amygdala volumes, in a sample of children ages 6 to 12 years followed up longitudinally since the preschool period. Based on the behavioral data in humans and the neurobiological data in animals, we hypothesized that an effect of poverty on these brain volume outcomes would be found. We also hypothesized that key variables associated with poverty and known to negatively impact child development outcomes, including caregiving support, caregiver education, and stressful life events, would mediate the association between poverty and brain volumes.

Methods

Participants

A total of 145 right-handed children were recruited from a larger sample enrolled in the 10-year longitudinal Preschool Depression Study (N = 305 at baseline). The larger sample was recruited from metropolitan St Louis day cares and preschools using a screening checklist to include healthy children and to oversample preschoolers with depressive symptoms. Subjects and their caregivers participated in 3 to 6 comprehensive annual diagnostic and developmental assessments prior to the first neuroimaging session (see article by Luby et al[22] for full description). Subjects were screened for standard imaging contraindications. There were no significant differences on demographic variables between the imaging subsample and the original sample. **Table 1** shows the characteristics of the study sample. All study procedures were reviewed and approved by the institutional review board at the Washington University School of

Table 1. Demographics for Current Sample

Characteristic	No. (%)
Average parent education, y	
<High school diploma	10 (7)
High school diploma	11 (8)
Some college	57 (38)
College degree	27 (19)
Some graduate school or graduate/professional degree	40 (28)
Income-to-needs ratio, mean (SD) [range][a]	2.14 (1.27) [0.00 to 4.74]
Family size, mean (SD) [range]	4.27 (1.21) [2 to 8]
Race/ethnicity	
African American	47 (56)
White	81 (32)
Other	17 (12)
Supportive-to-nonsupportive caregiving ratio, mean (SD) [range]	0.67 (0.45) [−0.44 to 1.75]
Children's age, mean (SD) [range], y	9.78 (1.29) [6 to 12]
Female children	73 (51)

[a] Total family income divided by the federal poverty level for a family of that size closest to the year data were collected.

Medicine in St Louis. Written informed consent was obtained from parents, and assent was obtained from children.

Measures

The income-to-needs ratio was operationalized as the total family income divided by the federal poverty level based on family size in the year most proximal to data collection.[23] The value was calculated through baseline Preschool Depression Study data of caregiver-reported total family income and total number of people living in the household.

Psychiatric Diagnostic Status, Stressful Life Events, and Caregivers' Education

Subjects were assessed annually using the Preschool Age Psychiatric Assessment (parent interview, age 3-8 years) and Child and Adolescent Psychiatric Assessment (parent/child interview, age ≥9 years).[24] Both measures also reliably capture experiences of stressful and traumatic life events.[25,26] Life events between baseline and time of scan were used for the current analysis.

Tanner Staging Questionnaire

The Tanner staging questionnaire was used to measure children's pubertal status at the time of the scan.[27,28]

Parental Supportive/Hostile Caregiving

At the second assessment wave (ages 4-7 years), parent-child dyads were observed interacting during the waiting task, a structured task designed to elicit mild dyadic stress.[29] This laboratory task requires the child to wait for 8 minutes before opening a brightly wrapped gift within arm's reach. Children are told that they can open the gift once their caregiver completes questionnaires. Blind raters, trained to reliability, coded the interaction for caregivers' use of both supportive (eg, praising the child for waiting) and hostile (eg, threats about negative consequences) strategies. This task has acceptable psychometric properties and is a well-validated and widely used parenting measure.[29-32] Hostility scores were subtracted from support scores to provide a difference score.

Magnetic Resonance Image Acquisition

Two 3-dimensional T1-weighted magnetization-prepared rapid gradient echo scans were acquired on a Siemens 3.0-T Tim Trio scanner without sedation (sagittal acquisition; repetition time = 2300 milliseconds; echo time = 3.16 milliseconds; inversion time = 1200 milliseconds; flip angle = 8°; 160 slices; 256 × 256 matrix; field of view = 256 mm; 1.0-mm^3 voxels; total time = 12:36 min).

Image Analyses

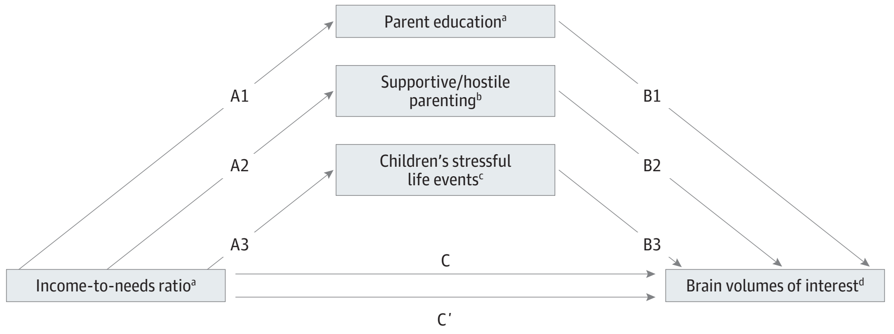
Whole Brain

Total gray and white matter volumes were obtained using FreeSurfer version 5.1. The white and pial FreeSurfer surfaces were visually inspected and were regenerated with manual intervention when necessary. Cortical gray matter volume was defined as the volume between the pial and white matter surfaces. White matter volume was calculated by subtracting the subcortical and ventricular volumes from the volume bounded by the white matter surface.

Amygdala and Hippocampus

The hippocampus was segmented by an automated high-dimensional template-based transformation. The manual template, delineated on 1 subject with typical anatomy, was reviewed by neuroanatomical gold standard experts following boundary definitions.[33,34] The gold template surface, generated from the manual template, included gray and white matter. Subject images, landmarked by an experienced rater blind to subject characteristics, were aligned to the template through an affine transformation followed by a nonlinear large deformation transformation to increase alignment precision. After matching subject-template voxel intensities, a high-dimensional subject-template transformation was generated through large deformation diffeomorphic metric mapping.[35] Results were blindly reviewed (C.B.) for surface quality. The reliability of this process is well established.[34] The amygdala segmentation paralleled the methodology of the hippocampus.

Figure 1. Conceptual Model Testing Multiple Mediators of the Hypothesized Association Between Income-to-Needs Ratio and Variation in Brain Volume



[a] Measured at baseline.

[b] Measured after baseline but before scan.

[c] Between baseline and time of scan.

[d] Time of scan.

Statistical Analyses

Potential Covariates

Pearson correlations and *t* tests were conducted to explore variation in brain volumes related to children's sex, age, pubertal status, history of psychiatric disorders (yes/no), and children's history of psychotropic medication use (yes/no). Covariates were included in the final analyses if significant for that particular region.

Associations Between Income-to-Needs Ratio and Brain Volume

Hierarchical multiple linear regression analyses were conducted to test whether the income-to-needs ratio predicted brain volumes. For all models, covariates were entered at step 1 and the income-to-needs ratio was entered at step 2.

Mediators of the Hypothesized Associations Between Income-to-Needs Ratios and Brain Volumes

Three variables were tested as possible mediators of the relations between baseline income-to-needs ratios and children's brain volumes (**Figure 1**). Mediators were tested by calculating bias-corrected 95% CIs using bootstrapping with 10 000 resamples via the Process procedure for SPSS.[36,37] Given that our data could not establish temporal precedence between caregivers' income-to-needs ratio and highest level of education, we chose to use baseline data for both variables.

Results

eTable 1 in Supplement shows the results of analyses testing potential covariates. Based on these results, sex was included as a covariate in all analyses except those examining right hippocampal volume. For analyses of white matter volume, children's age and pubertal status were also included as covariates. None of the brain volumes differed significantly in relation to children's history of *DSM-IV* Axis I disorder or psychotropic medication exposure. For all analyses examining hippocampus or amygdala volumes, children's total cortical brain volume (total white + total cortical gray) was included as a covariate to assess specificity.

Income-to-Needs Ratio Predicting Total White and Cortical Gray Matter Volumes

White Matter Volume

Children's age, sex, and pubertal status were entered at step 1. The income-to-needs ratio was entered at step 2 and was a positive predictor of white matter volume, accounting for a significant increase in variance (change $F_{1,137} = 8.12$, $P = .005$). The $R^2_{adjusted}$ for each step of the model, as well as the unstandardized regression coefficients (*B*), standard error (SE), and standardized regression coefficients (β), are reported in **Table 2**.

Cortical Gray Matter

Sex was included at step 1 of the model. The income-to-needs ratio was entered at step 2 and was a positive predictor of gray matter volume, accounting for a significant increase in variance (change $F_{1,142} = 21.79$, $P < .001$) (Table 2).

Income-to-Needs Ratio Predicting Left and Right Hippocampus and Amygdala Volumes

Covariates, including whole-brain volume, were entered in step 1. As seen in **Table 3**, for children's left hippocampus volume, including the income-to-needs ratio at step 2 resulted in a significant increase in the amount of variance accounted for (change $F_{1,115} = 5.76$, $P = .02$). The income-to-needs ratio was a positive predictor of children's left hippocampus volumes. For the right hippocampus, the increase in variance accounted for after including the income-to-needs ratio at step 2 only approached significance (change $F_{1,119} = 2.94$, $P = .09$). For children's left amygdala volume, including the income-to-needs ratio at step 2 resulted in a significant increase in the amount of variance accounted for (change $F_{1,120} = 6.28$, $P = .01$). The income-to-needs ratio was a positive predictor of children's left amygdala volumes. For right amygdala volumes, the increase in variance accounted for after including the income-to-needs ratio at step 2 only approached significance (change $F_{1,127} = 2.79$, $P = .09$).

Caregivers' Education, Parenting, and Stressful Life Events as Mediators of the Associations Between Income-to-Needs Ratio and Brain Volumes

The analyses just described established a relationship between the income-to-needs ratio and later brain volumes. We

Table 2. Income-to-Needs Ratio Predicting Total White Matter and Cortical Gray Matter Volumes

Regression Step	$R^2_{adjusted}$	B	SE	β
Total white matter volume				
Step 1	.18[a]			
Sex		35 825.52	8289.96	.33[a]
Age		527.91	380.08	.16
Pubertal status		16 157.45	11 320.94	.15
Step 2	.22[a]			
Sex		33 101.50	8140.35	.31[a]
Age		705.30	373.53	.19[b]
Pubertal status		11 585.00	11 155.72	.11
Income-to-needs ratio		9349.11	3280.85	.22[c]
Total cortical gray matter volume				
Step 1	.11[a]			
Sex		36 014.24	8353.40	.34[a]
Step 2	.22[a]			
Sex		32 716.59	7836.99	.31[a]
Income-to-needs ratio		14 828.42	3176.82	.35[a]

[a] $P < .001$.

[b] $P < .05$.

[c] $P < .01$.

Table 3. Hierarchical Regression: Income-to-Needs Ratio Variable Predicting Hippocampus and Amygdala Volumes

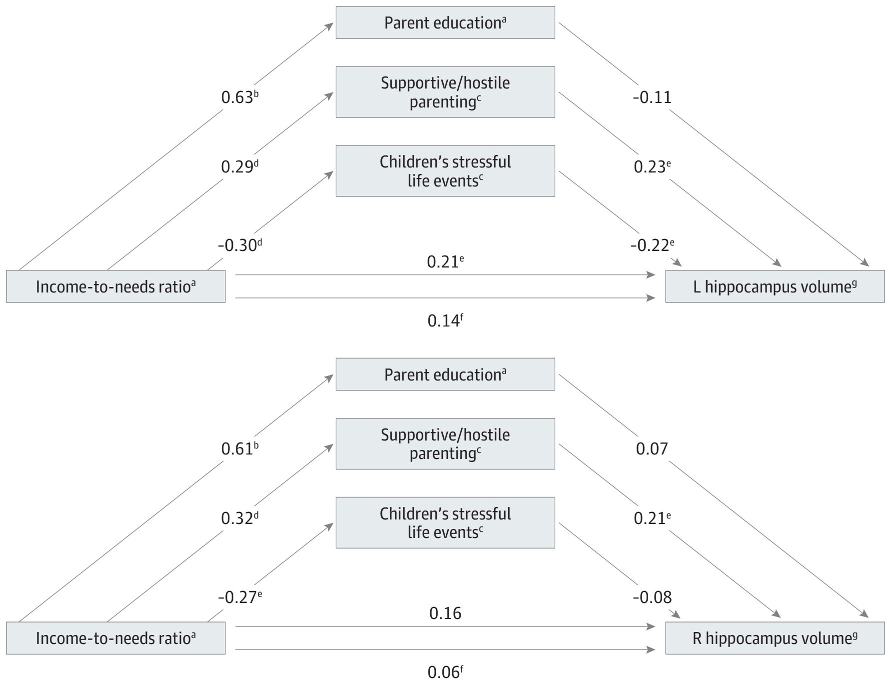
Regression Step	$R^2_{adjusted}$	B	SE	β
Left hippocampus				
Step 1	.15[a]			
Sex		7.40	31.83	.02
Cortical brain volume		.001	.000	.41[a]
Step 2	.19[a]			
Sex		7.19	31.20	.02
Cortical brain volume		.001	.000	.34[a]
Income-to-needs ratio		30.30	12.62	.21[b]
Right hippocampus				
Step 1	.27[c]			
Cortical brain volume		.001	.000	.52[a]
Step 2	.28[c]			
Cortical brain volume		.001	.000	.49[a]
Income-to-needs ratio		20.56	12.41	.14
Left amygdala				
Step 1	.25[a]			
Sex		53.65	26.49	.17[b]
Cortical brain volume		.001	.000	.42[a]
Step 2	.28[a]			
Sex		58.20	25.99	.18[b]
Cortical brain volume		.001	.000	.36[a]
Income-to-needs ratio		25.63	10.23	.20[c]
Right amygdala				
Step 1	.32[a]			
Sex		58.64	26.17	.18[b]
Cortical brain volume		.001	.000	.49[a]
Step 2	.33[a]			
Sex		1.11	26.03	.18[c]
Cortical brain volume		.001	.000	.44[a]
Income-to-needs ratio		17.38	10.41	.13

[a] $P < .001$.

[b] $P < .05$.

[c] $P < .01$.

Figure 2. Caregivers' Education, Supportive/Hostile Parenting, and Children's Experiences of Stressful Life Events as Mediators of the Relation Between Income-to-Needs Ratio and Hippocampus Volumes



Values shown are standardized regression coefficients. The top model is for the left (L) hippocampus volume, while the model at the bottom represents the right (R) hippocampus volume. Both models include whole-brain volume and sex as covariates.

[a] Measured at baseline.

[b] $P < .001$.

[c] Measured after baseline but before scan.

[d] $P < .01$.

[e] $P < .05$.

[f] After adding parents' education, supportive/hostile parenting, and children's stressful life events to the model.

[g] Time of scan.

hypothesized that there would also be indirect (ie, mediated) effects through caregivers' education, observed use of supportive/hostile parenting, and children's experience of stressful life events. Figure 1 provides a conceptual diagram of the meditational analyses conducted. MacKinnon and colleagues[38] suggested that mediation analyses be conducted when there is a relation between a predictor and mediator (paths A1, A2, and A3 in Figure 1), as well as a relation between a mediator and outcome (paths B1, B2, and B3 in Figure 1). To be considered a mediator, the strength of the direct relation between predictor and outcome (path C in Figure 1) will be diminished when the mediator is entered into the analysis (path C' in Figure 1). Covariates included in the meditational analyses were parallel with prior analyses and were only applied to outcome variables. Here we first established the relationship between the predictor (income-to-needs ratio) and the potential mediators (caregiver education, parenting, and life events), and then examined the relationships of the mediators to the outcome (brain volume) and, when significant, whether they reduced the direct effect of income-to-needs ratio on brain volumes.

Income-to-Needs Ratio Predicting Potential Mediators

Regression analyses confirmed that the income-to-needs ratio was significantly associated with caregivers' education (path A1; ranges across all regions: $P < .001$ in all models), predicted caregiving support/hostility assessed 1 year after baseline controlling for caregivers' education (path A2, $P < .001$), and predicted children's experience of stressful life events between baseline and time of scan when covarying for caregivers' education and supportive/hostile parenting (path A3, $P < .001$ in all models).

Mediators of Total White Matter and Cortical Gray Matter Volumes

Paths B1, B2, and B3 from the mediators to white matter and cortical gray matter volume were all nonsignificant (all $P > .05$). Thus, neither caregiving behaviors, education, nor life stress mediated the relationship between the income-to-needs ratio and cortical gray or white matter volume.

Mediators of Hippocampal Volumes

Figure 2 illustrates that 2 of the mediating variables, stressful life events (path B1) and caregiving behaviors (path B3), positively predicted children's left hippocampus volumes. For right hippocampus volume, caregiving behavior (path B3) was the only significant mediator. When mediators were included in the model, the direct paths (ie, path C') from the income-to-needs ratio to the left hippocampus ($P > .51$) and right hippocampus ($P > .55$) volumes were no longer significant, indicating full mediation (Figure 2). In Supplement, eTable 2 shows the mediated effects of the income-to-needs ratio on left and right hippocampus volumes.

Mediators of Amygdala Volumes

Paths B1, B2, and B3 from the mediators to left and right amygdala volumes were all nonsignificant ($P > .14$).

Discussion

These study findings demonstrated that exposure to poverty during early childhood is associated with smaller white matter, cortical gray matter, and hippocampal and amygdala volumes measured at school age/early adolescence. These findings extend the substantial body of behavioral data demonstrating the deleterious effects of poverty on child developmental outcomes into the neurodevelopmental domain and are consistent with prior results.[8,9] Furthermore, these study findings extend the available structural neuroimaging data in children exposed to poverty by informing the mechanism of the effects of poverty on hippocampal volumes. Findings indicated that the effects of poverty on hippocampal volumes were mediated by caregiving support/hostility on both the left and right hippocampus. On the left, stressful life events also emerged as significant mediators. Caregiver education was not a significant mediator. As exposure to poverty is well known to be strongly associated with a variety of negative life experiences, the role that these risk factors appeared to play in the relationship between poverty and alterations in brain development elucidates more specific targets for prevention.

Notably, alterations in brain volume associated with poverty were detected more globally in cortical gray and white matter volume, although mediation in these regions was not identified. The finding that mediation associated with parenting and life stress was selective to the hippocampus suggests regional specificity to these mechanistic relationships. The key role of caregiver nurturance in hippocampal development and its relationship to adaptive stress responses has been well established in animal studies. Consistent findings have been provided from an earlier subgroup of this study sample suggesting that supportive parenting also plays a key role in child hippocampal development independent of income.[21] Thus, the current findings add to and extend the literature underscoring the critical role of nurturance for childhood well-being.[39] The finding that experiences of stressful life events also mediated the relationship between poverty and left hippocampal volume is consistent with the extensive body of animal data that have elucidated the negative effects of early stress on hypothalamic-pituitary-adrenal function and hippocampal volume.[40] Understanding these mechanisms is key to the design of more targeted interventions, providing a feasible alternative to changing psychosocial status itself, a much more challenging goal that vulnerable rapidly developing young children do not have time to await.

Limitations of the current data were that the original study sample was oversampled for preschoolers with symptoms of depression, limiting generalizability. Furthermore, the relationships in the mediation model may be bidirectional. A sample with multiple waves of imaging data starting earlier in development would be necessary to adequately test directionality. Future studies with such designs and more detailed assessments of the correlates of poverty, such as nutrition, parental psychopathology, and genetic factors, are needed to further elucidate the mechanisms of risk.

We believe these findings may be useful to inform preventive interventions for this high-risk population facing a multitude of psychosocial stressors and suggest that caregiving should be a specific target. The importance of early interventions that target caregiving is underscored by studies demonstrating high cost-effectiveness through greatly enhanced long-term outcomes.[41] Furthermore, children who receive more nurturing caregiving may also be protected from exposure to stressful life events, suggesting this central target may have positive ramifications on brain development.[42] Considering these issues, study findings are relevant to the public policy debate on the importance of early preschool programs for young children living in poverty. The finding that the effects of poverty on hippocampal development are mediated through caregiving and stressful life events further underscores the importance of high-quality early childhood caregiving, a task that can be achieved through parenting education and support, as well as through preschool programs that provide high-quality supplementary caregiving and safe haven to vulnerable young children.

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Study concept and design: Luby, Botteron, Barch.
Acquisition of data: Luby, Botteron, Babb, Nishino, Barch.
Analysis and interpretation of data: Luby, Belden, Botteron, Marrus, Harms, Barch.
Drafting of the manuscript: Luby, Belden, Barch.
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