Preschool is a sensitive period for the influence of maternal support on the trajectory of hippocampal development

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Building on well-established animal data demonstrating the effects of early maternal support on hippocampal development and adaptive coping, a few longitudinal studies suggest that early caregiver support also impacts human hippocampal development. How caregiving contributes to human hippocampal developmental trajectories, whether there are sensitive periods for these effects, as well as whether related variation in hippocampal development predicts later childhood emotion functioning are of major public health importance. The current study investigated these questions in a longitudinal study of preschoolers assessed annually for behavioral and emotional development, including observed caregiver support. One hundred and twenty-seven children participated in three waves of magnetic resonance brain imaging through school age and early adolescence. Multilevel modeling of the effects of preschool and school-age maternal support on hippocampal volumes across the three waves was conducted. Hippocampal volume increased faster for those with higher levels of preschool maternal support. Subjects with support 1 SD above the mean had a 2.06 times greater increase in total hippocampus volume across the three scans than those with 1 SD below the mean (2.70% vs. 1.31%). No effect of school-age support was found. Individual slopes of hippocampus volume were significantly associated with emotion regulation at scan 3. The findings demonstrate a significant effect of early childhood maternal support on hippocampal volume growth across school age and early adolescence and suggest an early childhood sensitive period for these effects. They also show that this growth trajectory is associated with later emotion functioning.

maternal support | hippocampus | sensitive period | preschool | emotions

A large body of developmental data from studies of rodents has clearly established that the early experience of a highly nurturing caregiver has a powerful effect on hippocampal development in the rat pup, through an epigenetic mechanism (1–4). Building on these findings in animals, an increasing body of data in humans has emerged suggesting that early experiences of support, or conversely of abuse, neglect, or adversity, similarly impact human hippocampal development (5–7). The hippocampus, a region dense with glucocorticoid receptors, plays an integral role in the hypothalamic pituitary axis stress response (8, 9). Related to this role, reductions in hippocampal volume have been implicated in maladaptive stress reactivity and coping, as well as in affective psychopathology (10, 11). Therefore, a greater understanding of the environmental factors, particularly early caregiving experiences, that contribute to healthy hippocampal development in humans is of significant public health importance. Further, it is critical to examine whether variation in hippocampal development related to early caregiving predicts later childhood emotion functioning, as would be expected based on the animal data but not yet established in humans (12).

Although retrospective studies establish a link between childhood trauma and abuse and decreases in hippocampal volume in adults, these findings are limited by the known bias and possible inaccuracy of retrospective accounts of early childhood experiences by adult reporters (13, 14). More recently, some prospective data have become available to inform this issue. Using one wave of scan data from the study sample presented here, we have previously reported a link between higher early childhood maternal support and larger hippocampal volumes measured at school age in nondepressed subjects (15). Another prospective study that followed a small sample of cocaine-exposed infants from birth through adolescence reported decreased hippocampal volumes in adolescents who experienced higher maternal nurturance at age 4 (16). Although this effect was opposite what would be expected from the animal literature, the use of a relatively small sample exposed to drugs in utero may represent a unique developmental trajectory. Alterations in patterns of connectivity between the medial prefrontal cortex and amygdala have been reported in children who experienced early maternal deprivation (17, 18). Notably, another unique prospective study of a small group of children exposed to chronically depressed and less nurturing mothers displayed increases in amygdala volumes but no changes in hippocampus when scanned at age 10 (19). These conflicting findings underscore the need for further investigation of these relationships in larger samples with broader early risk exposures. In addition, there is a need to examine brain outcomes across the trajectory of brain development using multiple scan waves longitudinally. It is possible that disparate findings may reflect the unique risk trajectories of the various study samples, small sample sizes, as well as the limitations of cross-sectional imaging outcomes. As such, the question of whether

Significance

Data from a longitudinal neuroimaging study beginning in the preschool period and including three brain scans through school age and early adolescence were used to investigate the effects of maternal support on the development of the hippocampus. Consistent with animal findings showing that early support enhances hippocampal development and later adaptive coping, findings demonstrated that early childhood maternal support predicted a steeper hippocampal growth trajectory. The data also suggested that early childhood was a sensitive period when the effects of support had a more powerful effect on hippocampal growth. The hippocampal growth trajectory was associated with better emotion regulation in early adolescence. Findings suggest that enhancing early childhood maternal support fosters healthy childhood brain development and emotion functioning.

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the effect of early caregiver support impacts hippocampal development across its growth trajectory is of key interest. The current study aimed to address this question using a longitudinal neuroimaging design across childhood to investigate whether there are effects of support on brain development from school age through early adolescence.

Another key question that has been of interest in the study of the effects of caregiving quality on emotional, cognitive, and related brain development has been whether there are sensitive periods during which these environmental factors may have a particularly powerful effect on developmental outcomes. Such sensitive periods in development, when environmental exposures have a uniquely large and formative effect on neural structure and function, are well-established in visual and sensory-motor systems (20, 21). There has been some emerging evidence for sensitive periods in emotional development as well. This includes data from the Bucharest Early Intervention Project, where institutionalized children randomized to foster care before the age of 2 had superior cognitive and socioemotional outcomes to those randomized at later ages (22). Similarly, Rao et al. (16) report evidence for a sensitive period for the effects of maternal support (although in the opposite direction of that expected from animal studies), with childhood support at age 4 predicting adolescent brain outcomes whereas later childhood support at age 8 did not. If sensitive periods for the effects of supportive caregiving on brain development could be identified, it would have very important early intervention and prevention implications.

To address these questions, we sought to investigate whether experiences of maternal support predicted the trajectory of hippocampal development through school age and early adolescence using a longitudinal neuroimaging study with three waves of structural imaging data. We also tested whether caregiver support during the preschool versus school-age periods had unique effects on hippocampal outcomes. Last, to better interpret the functional significance of any effects found on hippocampal growth trajectories, we examined whether these trajectories predicted emotion reactivity and/or regulation at late school age.

Results

Subjects were 127 children participating in a longitudinal study of preschool depression who met all inclusion/exclusion criteria for magnetic resonance brain imaging at the first of three scan waves at ages 7–13. These children had usable left and/or right hippocampus T1-weighted MRI volume data at one or more scan waves and maternal support data, as well as other data of interest in the trajectory of hippocampal development, including IQ and income-to-needs ratio. Demographic characteristics of the study sample are detailed in Table 1. Multilevel linear models (MLMs) were used to examine the effect of maternal support on hippocampus volume over three scan waves. Two measures of maternal support, one assessed during the preschool period (centered at mean 11.65) and one assessed at school age before the first scan (centered at mean 30.60), were included as independent variables in the models. At the wave where preschool maternal support was assessed, 66% of subjects lived with both maternal and paternal figures in the home. The models included random intercept and slope components with an unstructured covariance matrix between the two. Time was coded as scan number, and covariates were age at scan 1 (centered at mean 10.54 y), quadratic age at scan 1, gender (1 male, 0 female), income-to-needs ratio at scan 1 (centered at mean 1.72), IQ (centered at mean 103.68), and total gray matter volume. Degrees-of-freedom calculations used the method of Kenward and Roger (23), and analyses were conducted using SAS version 9.3.

Maternal Support During Preschool and Developmental Trajectories of Hippocampus Volume During School Age and Early Adolescence. The results of the MLM of total hippocampus volume are shown in Table 2. There was a significant increase in total hippocampus volume over time ($P < 0.0001$). In addition, the main effect of total gray matter volume was significantly positively associated with hippocampus volume ($B = 0.0053$, $SE = 0.0007$, $t = 7.61$, $P < 0.0001$). IQ score was not significantly associated with hippocampus volume. Neither preschool ($P = 0.4629$) nor school-age ($P = 0.4846$) maternal support was significant as a main effect; however, the interaction between preschool maternal support and time was significantly associated with hippocampus volume in a positive direction. That is, total hippocampus volume increased faster for those with higher levels of preschool maternal support. Specifically, subjects with preschool maternal support 1 SD above the mean (19.9) compared with subjects with preschool maternal support 1 SD below the mean (3.3) had a 2.06 times greater increase in total hippocampus volume from scan 1 to 3 (2.70% vs. 1.31%). Fig. 1 shows individually estimated total hippocampus volume slopes as a function of preschool maternal support. Effect size was calculated by taking the correlation of preschool maternal support with subjects' individual slope estimates, and the effect size for this model was 0.22. Fig. S1 shows estimated trajectories of total hippocampus volume by preschool maternal support.

Table 1. Characteristics of the sample (n = 127)

	Mean	SD
Age at scan 1, y	10.54	1.06
Income-to-needs ratio at scan 1	1.72	0.99
Preschool maternal support	11.65	8.30
School-age maternal support	30.60	9.07
IQ score	103.68	15.65
	%	N
Male gender	51.18	65
Internalizing diagnosis through scan 1*	68.50	87
Externalizing diagnosis through scan 1†	52.76	67
Number of scans completed		
One scan	11.81	15
Two scans	29.92	38
Three scans	58.27	74

*Internalizing diagnoses included MDD, generalized anxiety disorder, separation anxiety disorder, and posttraumatic stress disorder.
†Externalizing diagnoses included attention-deficit/hyperactivity disorder, conduct disorder, and oppositional defiant disorder.

In contrast to preschool support, there was no significant change in total hippocampus volume over time as a function of school-age maternal support ($B = –0.0001$, $SE = 0.0011$, $t = –0.10$, $P = 0.9228$). To further evaluate any effect of school-age maternal support, an MLM of total hippocampus volume with school-age, but not preschool, maternal support as an independent variable was conducted. The school-age maternal support by time interaction in that model was still not significant ($B = 0.0012$, $SE = 0.0011$, $t = 1.12$, $P = 0.2647$). Importantly, although preschool and school-age support are correlated at 0.40, there was ample variance in the study sample of children who had high preschool support and low school-age support and vice versa to allow us to test the differential effects of these two variables (*SI Materials and Methods*).

Of note, the significant preschool maternal support by time interaction remained ($B = 0.0034$, $SE = 0.0012$, $t = 2.79$, $P = 0.0067$) when internalizing diagnosis through scan 1 [major depressive disorder (MDD), generalized anxiety disorder, separation anxiety disorder, and/or posttraumatic stress disorder] and externalizing diagnosis through scan 1 (attention-deficit/hyperactivity disorder, conduct disorder, and/or oppositional defiant disorder), and their interactions with time were included as covariates in the MLM.

To further investigate the relationship between maternal support and hippocampus volume, separate MLMs were run for left and right hippocampus volume. Table 3 details the results of

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Table 2. **Multilevel linear model of total hippocampus volume by preschool and school-age maternal support (n = 127)**

	Estimate, cm^3	*SE*	*t*	*P*
Intercept	7.9360	0.0957	82.93	<0.0001
Age	0.1024	0.0528	1.94	0.0546
Age-squared	0.0202	0.0469	0.43	0.6676
Gender, male 1, female 0	0.0568	0.1159	0.49	0.6250
Income-to-needs ratio	0.0285	0.0740	0.39	0.7007
IQ score	0.0070	0.0043	1.63	0.1059
Total gray matter volume*	0.0053	0.0007	7.61	<0.0001
Time[†]	0.0809	0.0106	7.65	<0.0001
Preschool maternal support	0.0058	0.0078	0.74	0.4629
School-age maternal support	0.0059	0.0084	0.70	0.4846
Preschool maternal support × time	0.0035	0.0012	2.83	0.0059
School-age maternal support × time	−0.0001	0.0011	−0.10	0.9228

*Total hippocampus volume was subtracted from total gray matter volume.
[†]Time indicates scan number.

the models by hemisphere. As in the model of total hippocampus volume, the main effects of time and total gray matter volume were significantly associated with left and right hippocampus volume ($P < 0.0001$). Additionally, higher IQ scores were significantly associated with greater right hippocampus volume ($B = 0.0046$, $SE = 0.0023$, $t = 2.02$, $P = 0.0460$). To determine whether verbal or nonverbal IQ had a greater effect on hippocampus volume, additional MLMs were run replacing IQ score with verbal IQ and, separately, nonverbal IQ. Results indicated that verbal IQ was driving the effect, as seen in Tables S1 and S2.

Similar to the total hippocampus volume model, the main effects of preschool and school-age maternal support were nonsignificant, but the interaction of preschool maternal support and time was significantly associated with both left ($B = 0.0019$, $SE = 0.0008$, $t = 2.37$, $P = 0.0203$) and right hippocampus volume ($B = 0.0014$, $SE = 0.0007$, $t = 2.10$, $P = 0.0389$). Specifically, subjects with preschool maternal support 1 SD above the mean (19.9) compared with subjects with preschool maternal support 1 SD below the mean (3.3) had a 2.22 times greater increase in left hippocampus volume from scan 1 to 3 (2.89% vs. 1.30%) and a 1.76 times greater increase in right hippocampus volume from scan 1 to 3 (2.56% vs. 1.46%). Fig. 2 shows individually estimated left and right hippocampus volume slopes as a function of preschool maternal support. Effect sizes were 0.18 for left and 0.17 for right hippocampus. Fig. S2 shows estimated trajectories of left and right hippocampus volume by preschool maternal support.

As with the MLM of total hippocampus volume, the preschool maternal support by time interaction remained significant when internalizing diagnosis through scan 1 and externalizing diagnosis through scan 1, and their interactions with time were included as covariates in the models of left ($B = 0.0019$, $SE = 0.0008$, $t = 2.37$, $P = 0.0206$) and right hippocampus volume ($B = 0.0014$, $SE = 0.0007$, $t = 2.09$, $P = 0.0404$).

Because school-age maternal support was not significantly associated with hippocampus volume trajectory, the MLMs were rerun without this independent variable. Removing school-age maternal support from the model resulted in an increased sample size of $n = 143$ subjects with the same effects found (Tables S3 and S4).

SI Materials and Methods present additional analyses replicating our previous findings (15) at scan 1, only with the larger sample used in the current report (see Tables S5 and S6).

Does the Trajectory of Hippocampal Development Predict Emotion Functioning? Individual-subject intercepts and slopes were generated from the MLM of total hippocampus volume by preschool maternal support and were investigated as potential predictors of the Children's Emotion Management Scale–Sadness (CEMS-S) (24) dysregulation and coping subscales. Individual-subject slopes were significantly associated with CEMS-S dysregulation and coping in a general linear model with individual intercepts and slopes as independent variables ($B = -26.41$, $SE = 12.53$, $t = -2.11$, $P = 0.0374$).

Discussion

These study findings in a group of children observed in interaction with their caregivers during the preschool period and then scanned three times across school age and early adolescence are consistent with the body of animal literature documenting the

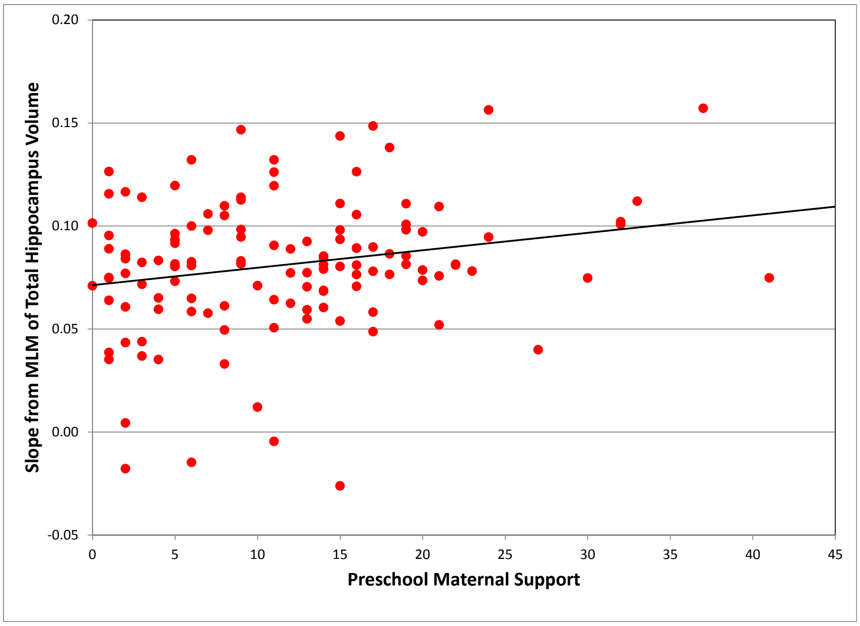

Fig. 1. Individually estimated slopes over time for total hippocampus volume as a function of preschool maternal support (n = 127).

Table 3. Multilevel linear models of left and right hippocampus volume by preschool and school-age maternal support (n = 127)

	Estimate, cm^3	*SE*	*t*	*P*
Left hippocampus volume				
Intercept	3.8856	0.0512	75.85	<0.0001
Age	0.0525	0.0278	1.89	0.0619
Age-squared	0.0020	0.0248	0.08	0.9358
Gender, male 1, female 0	0.0142	0.0619	0.23	0.8195
Income-to-needs ratio	−0.0270	0.0392	−0.69	0.4921
IQ score	0.0022	0.0023	0.97	0.3361
Total gray matter volume*	0.0031	0.0004	7.50	<0.0001
Time†	0.0414	0.0069	6.02	<0.0001
Preschool maternal support	0.0022	0.0043	0.51	0.6119
School-age maternal support	0.0079	0.0045	1.73	0.0854
Preschool maternal support × time	0.0019	0.0008	2.37	0.0203
School-age maternal support × time	−0.0009	0.0007	−1.22	0.2257
Right hippocampus volume				
Intercept	4.0539	0.0505	80.31	<0.0001
Age	0.0485	0.0277	1.75	0.0829
Age-squared	0.0173	0.0247	0.70	0.4842
Gender (male 1, female 0)	0.0272	0.0612	0.44	0.6578
Income-to-needs ratio	0.0472	0.0390	1.21	0.2278
IQ score	0.0046	0.0023	2.02	0.0460
Total gray matter volume*	0.0025	0.0004	6.55	<0.0001
Time†	0.0414	0.0059	7.05	<0.0001
Preschool maternal support	0.0034	0.0041	0.83	0.4102
School-age maternal support	−0.0017	0.0044	−0.37	0.7089
Preschool maternal support × time	0.0014	0.0007	2.10	0.0389
School-age maternal support × time	0.0007	0.0006	1.21	0.2308

*Left/right hippocampus volume was subtracted from total gray matter volume.
†Time indicates scan number.

powerful effects of maternal support on hippocampal development. Study findings confirm and extend earlier cross-sectional findings in the same sample and suggest that failure to find similar effects in smaller samples may be related to type II error, and findings of opposite effects in a cocaine-exposed population may be unique to those exposures. Findings from this longitudinal neuroimaging study extend the literature in three important and previously unidentified ways. First, these results demonstrate that the effect of maternal support extends beyond one outcome measure of hippocampal volume at early school age and has an influence on the trajectory of hippocampal volume growth into later school age and early adolescence. Second, the findings demonstrate

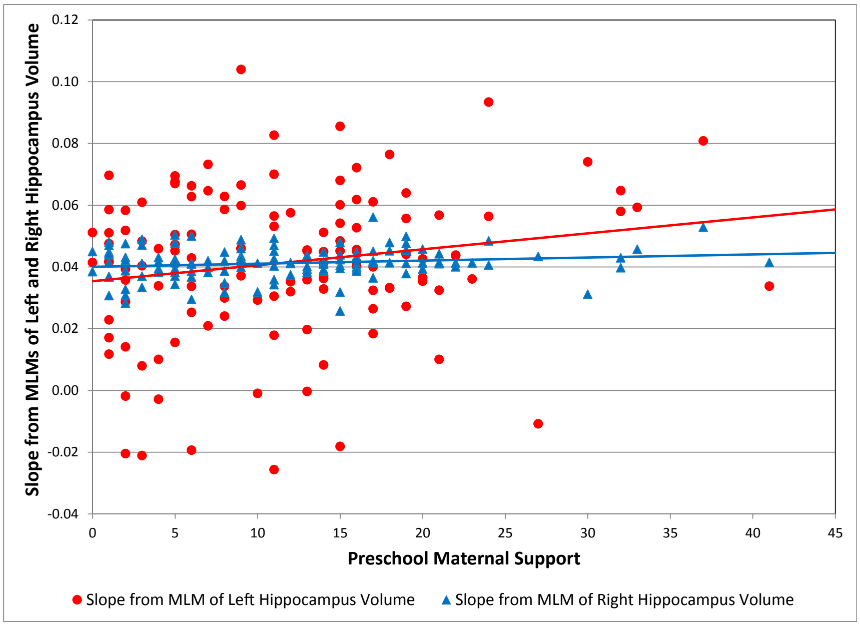

Fig. 2. Individually estimated slopes over time for left and right hippocampus volume as a function of preschool maternal support (n = 127).

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that maternal support measured during the preschool period has a stronger effect on hippocampal volume trajectories compared with support measured at school age, consistent with the hypothesis of a sensitive period for the effects of support on hippocampal development. Third, alterations in the trajectory of hippocampal growth had functional significance for adaptive outcomes, as evidenced by the association between hippocampal volume trajectories and a later measure of emotion regulation.

Consistent with the animal literature, alterations in hippocampal growth trajectories related to early maternal support were associated with more adaptive later emotion regulation (12). The hippocampus is a key brain region known to impact several areas of cognitive and emotion functioning including emotion regulation (10). Therefore, the identification of modifiable environmental exposures that can impact the development of the hippocampus and in turn later emotion functioning is a finding of key public health importance. These findings should inform prevention and early intervention strategies, a number of which have been designed and shown to effectively enhance maternal support (25–27).

These findings are limited by the fact that the study sample was enriched for preschoolers with emotional and behavioral problems. Although the findings held when the effects of these variables were accounted for, this group could have a unique risk trajectory from healthy developing children or children under other risk conditions. Based on this, future investigations of these risk relationships should now be explored in general-population samples. In addition, future studies should further investigate whether the effects found had regional anterior versus posterior subfield specificity in the hippocampus, an issue the current study was unable to address due to the current limitations of FreeSurfer methodology. Although study findings suggest that there is a sensitive period for preschool versus school-age maternal support on the trajectory of hippocampal volume growth, future studies that are specifically designed to more definitively address this question are now needed.

Conclusions

These study findings provide, to our knowledge, the first evidence for the long-term effects of early maternal support on the development of the hippocampus through school age and early adolescence. They also suggest that maternal support during the preschool period may represent a sensitive period when these experiences have a uniquely powerful effect on brain development. The finding that maternal support experienced during the preschool period has a tangible impact on the trajectory of hippocampal development through school age and early adolescence further underscores the importance of public health efforts to enhance maternal support during early childhood, a goal that has proven to be both feasible and cost-effective (28).

Materials and Methods

All study procedures were approved in advance by the Washington University Institutional Review Board and informed consent/assent was obtained from all study subjects (as age-appropriate) and their legal guardians. Subjects were participants in an ongoing 11-y longitudinal neuroimaging study. Behavioral/developmental assessments began when subjects were 3.0- to 5.11-y-old and continued annually over six waves with scanning starting at age 6.11–12.11 and repeated approximately every 18 mo for three waves of neuroimaging; $n = 127$ subjects who completed at least one scan (out of three), had maternal support data available at both preschool and school age (before the first scan), and had a valid IQ score were included in the primary analysis.

Maternal Preschool and School-Age Support Defined. Maternal support in the present study was conceptualized as the degree to which mothers view and approach their children with positive regard overall as well as their efforts to be emotionally and developmentally aware of their children's emotional well-being. Furthermore, caregiver support includes their ability to facilitate their children's sense of autonomy by supporting and validating their child's intent to lead and strategize to solve problems. More specifically, support was coded during an interval when parents expressed predominantly positive emotions during the mildly stressful task, when they remained calm, and when they were reassuring when reacting to the child's emotional expressions elicited by the parent–child interaction task. Supportive behaviors included acknowledging the child's accomplishments on the task or behaviors related to the parent–child interaction. Support includes verbally encouraging the child with positive emotional regard (e.g., "You're really good at this" or "You got another one right"). Another example of support occurs when a child becomes visibly upset/anxious and the parent changes their proximity to the child so that they are closer and the caregiver may rub the child's back to help him/her regulate.

Preschool Maternal Support. Preschool maternal support was measured at the second annual study wave when subjects aged 3.11–6.11 and their caregivers engaged in a mildly stressful task in the laboratory. This task, known as "the waiting task," required the child to wait for 8 min before opening a brightly wrapped gift sitting within arm's reach while the parent completed questionnaires. This paradigm was designed to evoke mild stress for both parent and child. Staff trained to acceptable interrater reliability coded the interaction for supportive caregiving strategies the parent used to help regulate the child's impulse and desire to open the gift before the appropriate amount of time had elapsed. Each instance of specific types of supportive caregiving strategies used by the parent was counted as 1 unit and summed to give an overall preschool maternal support score. Thus, each parent's supportive caregiving score represents the total number of supportive behaviors they were observed using over the course of the 8-min task. Prior findings suggest that caregiving support behaviors coded during this task have good psychometric properties (29, 30). Specifically, Cronbach's alpha for the combined supportive behaviors coded was alpha = 0.86.

School-Age Maternal Support. Subjects and their caregivers completed a different developmentally appropriate mildly stressful task, "the puzzle task," at the third annual study wave (child age 4.11–7.11) and again at their fifth annual assessment wave ~4–5 y later (child age 8.3–12.6). In this task, a puzzle of the United States is placed between the parent and child under a cardboard box. The child is asked to attempt to put together a puzzle within an enclosed box so that they cannot see the pieces but are instructed only by the parent, who can see. Children are told that they cannot look and puzzle pieces are given to the parent, who can clearly see the puzzle board and where the child's hands are. Parents are told to give the child instructions on how to place each piece, and both are told to finish the puzzle in 5 min to earn a prize. The examiner then sets a timer and tells the pair to begin. The 5-min task was separated into 30-s segments during which coders trained to adequate interrater reliability provided ratings for the frequency of parents' supportive caregiving behaviors observed during the task. Maternal support data coded from the puzzle task were only included in these analyses if the child completed the task after age 6.0 and before their first scan. In instances where the subject had two ratings of maternal support from the puzzle task, school-age maternal support was calculated as the mean of the two values. Out of the $n = 127$ subjects included in this analysis, $n = 120$ (94%) had the same caregiver at preschool and school-age assessments of support.

Income-to-Needs Ratio. An income-to-needs ratio was calculated as the total family income at the first scan divided by the federal poverty level based on family size for the year of data collection.

IQ Score. Subjects were assessed with either the Kaufman Brief Intelligence Test (KBIT) (31) or the Wechsler Abbreviated Scale of Intelligence (WASI) (32) (depending upon age at study wave) to determine verbal and nonverbal intelligence.

Children's Emotion Management Scale–Sadness. The CEM-S measures is a parent report of the child's sadness. The 11 items are on a Likert scale of hardly ever (1), sometimes (2), and often (3) and are summed to create inhibition, dysregulation, and coping subscales. The coping subscale was reverse-scored and added to the dysregulation subscale to create an overall measure of dysregulation and coping.

Imaging and Hippocampal Quantification. Two 3D T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) scans were acquired sagittally on a Siemens 3.0T Tim Trio using a 12-channel head coil [repetition time (TR) 2,300 ms, echo time (TE) 3.16 ms, inversion time (TI) 1,200 ms, flip angle 8°, 160 slices, 256×256 matrix, field of view 256 mm, 1.0-mm^3 voxels, 6:18 min per scan]. The two MPRAGE scans were assessed visually, and the best one was selected for further processing by blinded raters. The selected MPRAGE for each wave was processed using the longitudinal stream in the FreeSurfer software package, version 5.3 (surfer.nmr.mgh.harvard.edu) (33). Several processing steps, such as skull stripping, Talairach transformations, and atlas registration, as well as spherical surface maps and parcellations were initialized with common information from an unbiased within-patient template. This longitudinal stream reduces the bias that would otherwise be present in selecting a single scan result as baseline, and significantly increases reliability and statistical power (34). The white and pial surfaces generated by FreeSurfer were visually inspected and, when necessary, appropriate edits were performed and the surfaces were regenerated. For ~10% of scans, poor scan quality required discarding them from further analysis (n = 15, 11, and 7 at the three waves, respectively). In those cases, all data were generated from within-subject templates using the remaining scans. Hippocampal and total gray matter volumes (sum of cortical, subcortical, and cerebellar gray matter) for the left and right hemispheres were obtained from the "Hippocampus" and "TotalGrayVol" measures, respectively, in Freesurfer's "aseg.stats" report.

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