

Maternal support in early childhood predicts larger hippocampal volumes at school age

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Early maternal support has been shown to promote specific gene expression, neurogenesis, adaptive stress responses, and larger hippocampal volumes in developing animals. In humans, a relationship between psychosocial factors in early childhood and later amygdala volumes based on prospective data has been demonstrated, providing a key link between early experience and brain development. Although much retrospective data suggests a link between early psychosocial factors and hippocampal volumes in humans, to date there has been no prospective data to inform this potentially important public health issue. In a longitudinal study of depressed and healthy preschool children who underwent neuroimaging at school age, we investigated whether early maternal support predicted later hippocampal volumes. Maternal support observed in early childhood was strongly predictive of hippocampal volume measured at school age. The positive effect of maternal support on hippocampal volumes was greater in nondepressed children. These findings provide prospective evidence in humans of the positive effect of early supportive parenting on healthy hippocampal development, a brain region key to memory and stress modulation.

depression | parental support | nurturance | neurodevelopment

The suggestion that environmental enrichment early in life results in enhanced brain development was first proposed and investigated by Hebb in the late 1940s and was empirically validated in rodents 20 y later (1). These findings provided some of the first quantitative evidence supporting the tangible role of environmental experience on structural brain development. More recent research has extended these findings by investigating the biological mechanisms by which psychosocial factors influence neuronal development. Of critical importance to the study of risk for psychopathology, animal models have elucidated the mechanisms by which maternal nurturance, a uniquely powerful form of early enrichment, promotes adaptive programming of the hypothalamic–pituitary–adrenal axis stress response and hippocampal development (2, 3). Improvements in the capacity for stress modulation have been shown to be related to epigenetic modifications whereby methylation of multiple genes results in changes in gene expression for glucocorticoid and mineralocorticoid receptors (4, 5). These changes are associated with increases in dendritic branching and neurogenesis and related increases in hippocampal volumes (6–9). Consistent with this phenomenon and conversely, the stress of early maternal deprivation has been shown to have negative effects on this cascade (10, 11). A similar relationship between early nurturance and stress modulation has also been reported in nonhuman primates (12, 13). This work has shown that early nurturance in nonhuman animals facilitates the offspring's enduring capacity for adaptive stress modulation, a phenomenon with potentially powerful public health implications if also operational in humans.

Building on these animal findings, there has been a surge of interest in the effects of early experience on brain development in humans (14). Numerous studies have documented a relationship between key early environmental factors and later cognitive

and socio-emotional outcomes. Studies of Romanian orphans, using the naturalistic stress of institutional care, have shown that enhanced early caregiving through placement in therapeutic foster care had a robust and positive impact on cognitive, social, and emotional outcomes (15, 16). Differential patterns of DNA methylation in children raised in institutions compared with those raised by their biological parents have recently been provided, suggesting that the epigenetic phenomenon known in animals might also be operative in human development (17). Prospective evidence of the impact of early nurturance on structural brain development has been provided in a few studies to date. Tottenham et al. (18) reported that institutionalized orphans who experienced environmental enrichment in the form of earlier adoption displayed smaller amygdala volumes (an anatomical variation associated with better emotion regulation), but they did not find a relationship with hippocampal volumes. Lupien et al. (19) also reported larger amygdala but no change in hippocampal volumes in a sample of children exposed since birth to maternal depression, the latter a condition known to be associated with decreased parenting sensitivity and responsiveness (20). In another small study group, larger right amygdala volumes were found in institutionalized children compared with noninstitutionalized control subjects (21). Additionally, a study of a small group of premature infants demonstrated that early environmental enhancement in the neonatal intensive care unit was associated with positive changes in brain structure, evidenced by higher relative anisotropy in several specific white matter tracts (22). Rao et al. (23) found a relationship between increased early higher-quality parental care and smaller hippocampal volumes in a sample of children exposed to cocaine in utero, findings in the opposite direction of that expected from the animal data. These studies, although suggestive, have not yet provided findings in humans analogous to the animal literature and are limited by the use of populations also exposed to multiple perinatal and postnatal stressors and traumas known to impact brain development.

An increasing body of retrospective data also suggests a relationship between early nurturance, or the lack of nurturance based on the experience of trauma, and later stress reactivity and hippocampal volumes in a variety of human populations, including those with depression (24, 25). Importantly, numerous studies have reported that major depressive disorder (MDD) is associated with smaller hippocampal volumes in adults (26, 27). The findings in children and adolescents are less consistent than in adults, with some investigators reporting no hippocampal volume differences (28, 29) and others reporting decreased

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Table 1. Characteristics of the sample, part 1

Characteristic	Preschool depression severity score 4–9 (<i>n</i> = 41)		Preschool depression severity score 0–3 (<i>n</i> = 51)		χ^2	<i>P</i>
	%	<i>n</i>	%	<i>N</i>		
Sex					0.46	0.499
Female	56.1	23	49.0	25		
Male	43.9	18	51.0	26		
Age (y)					FE	0.560
6	2.4	1 (1 M, 0 F)	0.0	0 (0 M, 0 F)		
7	4.9	2 (0 M, 2 F)	7.8	4 (1 M, 3 F)		
8	9.8	4 (1 M, 3 F)	13.7	7 (5 M, 2 F)		
9	34.1	14 (4 M, 10 F)	39.2	20 (9 M, 11 F)		
10	24.4	10 (6 M, 4 F)	27.5	14 (10 M, 4 F)		
11	19.5	8 (5 M, 3 F)	11.8	6 (1 M, 5 F)		
12	4.9	2 (1 M, 1 F)	0.0	0 (0 M, 0 F)		
Parental education					2.87	0.412
High school diploma	14.6	6	7.8	4		
Some college	41.5	17	33.3	17		
4-y college degree	17.1	7	29.4	15		
Graduate education	26.8	11	29.4	15		
Psychotropic medication use					1.74	0.187
Yes	29.3	12	17.6	9		
No	70.7	29	82.4	42		
Maternal history of depression					0.80	0.370
Yes	42.5	17	33.3	17		
No	57.5	23	66.7	34		
Maternal prenatal tobacco use					1.05	0.307
Yes	27.8	10	18.2	8		
No	72.2	26	81.8	36		
Maternal prenatal alcohol use					4.31	0.038
Yes	36.1	13	15.9	7		
No	63.9	23	84.1	37		

F, female; FE, Fisher's exact test; M, male.

predictor of greater hippocampal volume in nondepressed children. These findings suggest that early maternal support exerts a positive influence on hippocampal development in children without depression but not in depressed children, in whom the negative effects of this risk condition seem to impede the potential benefits of maternal support. As such, our findings did not support the hypothesis that the influence of maternal support on hippocampal volume would be found among children with depression. Instead, these results suggest that either

depression has an effect on hippocampal volumes that is not mediated by maternal support or that an examination of maternal support before the onset of depression is needed to adequately test this risk hypothesis. Our sample of depressed children all had very-early-onset depression that was present before our assessment of maternal support. Other limitations to the design include the fact that maternal support was measured only in early and not later in childhood and that earlier experiences of nurturing before age 3 y, shown to be important to

Table 2. Characteristics of the sample, part 2

Characteristic	Preschool depression severity score 4–9 (<i>n</i> = 41)		Preschool depression severity score 0–3 (<i>n</i> = 51)		<i>t</i>	<i>P</i>
	Mean	SD	Mean	SD		
Maternal support	12.17	9.13	12.12	8.91	0.03	0.978
Preschool depression severity	5.12	1.25	1.41	1.04	15.53	<0.001
Internalizing dimensional score	6.66	3.21	3.10	1.97	6.23	<0.001
Externalizing dimensional score	10.12	7.39	4.25	4.38	4.49	<0.001
No. of traumatic life events	2.78	1.76	1.57	1.37	3.67	<0.001
IQ score	104.1	14.1	108.2	15.9	1.30	0.197
Birth weight (kg)	3.24	0.55	3.34	0.63	0.86	0.392
Gestational age (wk)	38.82	2.09	39.06	2.38	0.50	0.620
Days in NICU	0.31	0.98	3.50	14.92	1.35	0.185
Hippocampus volume, right (mm ³)	1,720	169	1,789	212	1.66	0.101
Hippocampus volume, left (mm ³)	1,715	136	1,781	195	1.79	0.078

IQ, intelligence quotient; NICU, neonatal intensive care unit.

Table 3. Repeated-measures mixed models of hippocampal volume

Model	Estimate	F	df	P
Model 1				
Left brain hemisphere	-3.20	0.06	1, 75	0.811
Female sex	-78.87	5.76	1, 87	0.019
Preschool depression severity	7.68	0.39	1, 87	0.533
Maternal support	13.38	18.58	1, 87	<0.001
Preschool depression severity × maternal support	-1.59	4.07	1, 87	0.047
Model 2				
Left brain hemisphere	-5.40	0.09	1, 74	0.761
Female sex	-78.82	5.75	1, 87	0.019
Preschool depression severity	7.63	0.39	1, 87	0.536
Maternal support	13.37	18.55	1, 87	<0.001
Preschool depression severity × maternal support	-1.61	4.02	1, 87	0.048
Preschool depression severity × maternal support × left brain hemisphere	0.06	0.04	1, 74	0.848
Model 3				
Left brain hemisphere	0.74	0.00	1, 74	0.954
Female sex	-75.57	4.62	1, 80	0.035
Psychiatric medication use	-49.08	1.26	1, 80	0.265
Internalizing dimensional score	11.24	1.87	1, 80	0.175
Externalizing dimensional score	-4.01	1.42	1, 80	0.237
Number of traumatic life events	-11.17	0.86	1, 80	0.357
Maternal history of depression	28.95	0.59	1, 80	0.446
Preschool depression severity	11.30	0.44	1, 80	0.511
Maternal support	14.25	18.09	1, 80	<0.001
Preschool depression severity × maternal support	-1.92	5.09	1, 80	0.027

developmental outcomes, were not prospectively studied. Prospective research in high-risk samples before the onset of depression may be needed to specifically assess whether hippocampal volume mediates a relationship between poor early nurturance and subsequent risk for depression.

The experience of a nurturing caregiver early in life has proven to be one of the most essential prerequisites for healthy development and adaptive functioning in mammals (37). The current data provide evidence that the well-established significant impact of positive parenting on enhancing and maintaining hippocampal neuroplasticity, likely through epigenetic mechanisms enhancing neurogenesis, as suggested by the work of Naumova et al. (17), may also be operative in humans. Further, it was notable that this effect remained robust even after controlling for other factors known to impact hippocampal volume, such as stressful life events and maternal history of depression. Importantly, although 96.7% of caregivers in this study

sample were mothers, we expect that this effect pertains to the primary caregiver (the provider of nurturance) whether it be mother, father, grandparent, or other.

Whether maternal support early in childhood is more or less powerful than at later periods of development is of interest and remains unclear from these data. However, sensitive periods for the importance of maternal support have been suggested by early adoption studies (15). However, given the central role of the caregiver in the life of the young child, this developmental period would seem to be an optimal time for enhancing the early maternal-child relationship. On the basis of these data, one cannot rule out that the relationship between maternal support and hippocampal volume in offspring is based on genetic factors, that supportive caregivers could have larger hippocampal volumes and then have biological children with larger volumes. However, there is no evidence in the literature of a relationship between hippocampal volume and supportive care giving in adults. The

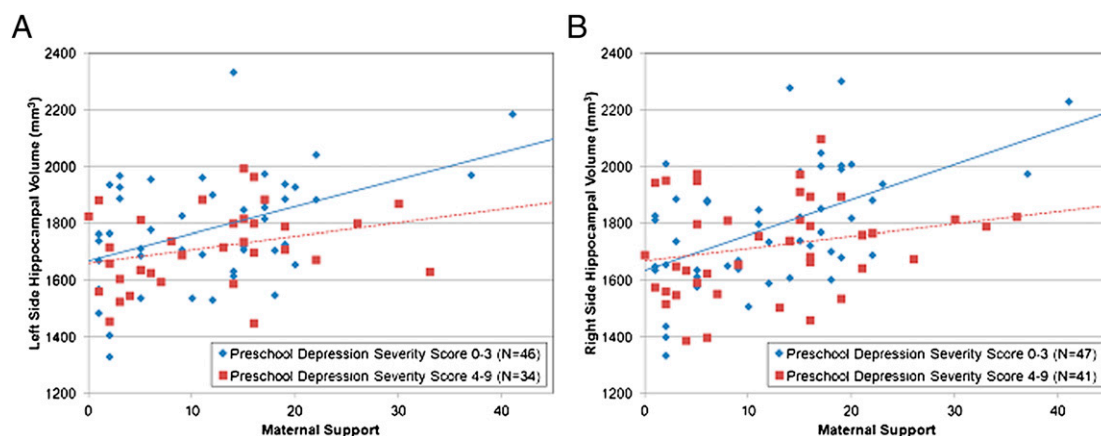


Fig. 1. (A) Left side hippocampal volume by preschool depression severity and maternal support. (B) Right side hippocampal volume by preschool depression severity and maternal support.

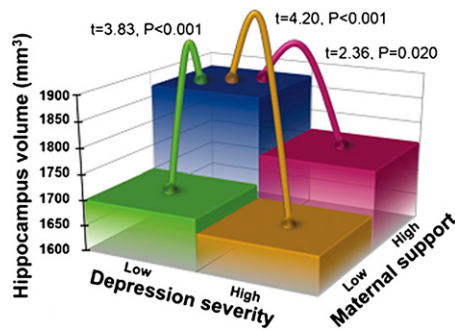


Fig. 2. Hippocampus volume by preschool depression severity and maternal support.

available data also suggest that heritability of hippocampal volumes is moderate and lower than many other brain regions (38). Furthermore, numerous studies have demonstrated that the hippocampus is sensitive to environmental and psychosocial influences in both animals and humans, making a purely genetic mechanism less likely (9, 39). Despite these assurances, longitudinal scan data, including scans at the preschool period, would be necessary to clarify the role of genetic factors, a conclusion underscored by previous research showing that smaller hippocampal volumes increased the risk for development of stress-related psychopathology, suggesting that complex interactive processes could be at play (35).

These data extend the current literature, establishing the crucial role of the caregiver in early childhood for healthy social and emotional development by demonstrating that the early experience of supportive caregiving also positively impacts structural development of the hippocampus, at least in children without early-onset depression. Notably, the relationships between maternal support and hippocampal volumes remained highly significant when comorbid internalizing and externalizing symptoms were controlled in the analysis. The importance of this effect is underscored by the fact that the hippocampus is a brain region central to memory, emotion regulation, and stress modulation, all areas key to healthy social adaptation. We believe these findings have potentially profound public health implications and suggest that greater public health emphasis on early parenting could be a very fruitful social investment. The finding that early parenting support, a modifiable psychosocial factor, is directly related to healthy development of a key brain region known to impact cognitive functioning and emotion regulation opens an exciting opportunity to impact the development of children in a powerful and positive fashion. This finding, when replicated, would strongly suggest enhancement of public policies and programs that provide support and parenting education to caregivers early in development.

Materials and Methods

Participants. The study sample was originally recruited between the ages of 3 and 6 y from daycare centers and preschools in the St. Louis metropolitan area using a screening checklist to oversample children with symptoms of depression (40). Healthy preschoolers and those with other psychiatric disorders were included as comparison groups for the original study sample ascertainment. Preschoolers with neurological or chronic medical problems or those with significant developmental delays were excluded. Informed consent (or assent) was obtained from all study subjects, who were fully informed about the nature and consequences of the study procedures before participation. Children and their caregivers were assessed at four to six annual waves before the time of scanning.

Measures. At each annual wave, parents were interviewed about their child using the Preschool Age Psychiatric Assessment (PAPA), an age-appropriate diagnostic interview addressing the child's psychiatric symptoms and stressful

life events with established reliability (41). The PAPA was used to derive depression severity scores by summing all symptoms of depression, a variable previously shown to be a sensitive measure of the severity of illness (42). Further details on training and administration of the PAPA in the study sample can be found in Luby et al. (40).

At the second annual wave, when subjects were between the ages of 4 and 7 y, parent and child were also observed interacting in a mildly stressful challenging task in the laboratory, "the waiting task," during which maternal support was measured. The waiting task is a parent-child interaction paradigm designed to elicit mild stress for both members of the dyad (43). The task requires the child to wait for 8 min before opening a brightly wrapped gift, which is sitting within arm's reach. Concurrently the child's primary caregiver completes questionnaires. The supportive and/or nonsupportive care giving strategies that the parent uses to help regulate the child's impulse and desire to open the gift immediately are coded by staff trained to reliability. Each display of specific types of supportive strategies by the caregiver is counted as 1 unit. Several research groups have previously reported acceptable psychometric properties for the task, and it is a well-validated approach to measuring parenting strategy during which maternal support and responsiveness was evaluated (43, 44).

Maternal history of depression was measured using the Family Interview for Genetic Studies (45), a widely used and well-validated measure of family history of psychiatric disorders. Detailed methods of training and administration are described by Luby et al. (40).

Structural Imaging Methods. Parents of either healthy or depressed study subjects who were participants in a longitudinal study of preschool-onset depression were screened by phone to determine whether any exclusion criteria for MRI scanning were present. Exclusion criteria included (i) contraindications for MRI scanning; (ii) head injury with loss of consciousness >5 min; (iii) stroke, seizure disorder, or other chronic neurological or medical illness with known neurological impact; (iv) diagnosis of a pervasive developmental disorder; and (v) treatment for lead poisoning.

All MR scans were performed on a Siemens 3.0-T Tim Trio dedicated research scanner. Subjects were scanned without sedation in a semi-standardized position. Two 3D T1-weighted magnetization prepared rapid gradient echo research-tailored MR scans (1-mm isotropic voxels) were acquired sagittally (repetition time 2,400 ms, echo time 3.16 ms, inversion time 1,200 ms, flip angle 8°, slab 160 mm, 160 partitions, 256 × 256 matrix, field of view 256, total scanning time 12:36). Images were coregistered and averaged to increase signal to noise ratio (46), then 16-bit image data were linearly interpolated to 0.5-mm³ voxels and converted to 8-bit using ANALYZE (47).

Hippocampal volumes were derived from a well-established template-based automated segmentation using high-dimensional transformation methods (48–50). Briefly, hippocampal segmentations and volumes were derived from an atlas- or template-based automated segmentation using a high-dimensional transformation after placement of standardized landmarks by an experienced rater (C.B.) (51) and preliminary transformations using these landmarks. Hippocampus boundary definitions were standardized as detailed in previous reports (48, 52). As specified by these definitions, a template segmentation was created by hand (C.B.) and based on one subject with typical anatomy and reviewed by neuroanatomical gold standard experts (K.N.B. and Mohktar Gado). This gold standard hippocampal segmentation was converted to a 3D tessellated surface. Using the landmarks, the target (subject) images were oriented to the template image by initially applying a rigid landmark transformation algorithm, followed by a more precise target to template nonlinear, large deformation landmark matching algorithm (LDL). Voxel intensities in each target image were scaled to more closely match those of the template image. A high-dimensional transformation, large deformation diffeomorphic metric mapping (51), was then used to generate a transformed template surface. After inverting the LDL algorithm described above, the transformed template surface represented the target (subject) hippocampus. The reliability of this process is equivalent or superior to manual outlining by experts (52). All segmentation results were blindly reviewed for accuracy (C.B.), and inadequately defined hippocampi were not included in analyses. Hippocampal volumes included all hippocampal gray matter and white matter contained within the segmented structure.

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