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Original Article

Hippocampal Volume and Memory Performance in Children With Perinatal Stroke

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ABSTRACT

BACKGROUND: Pediatric neurologists and neonatologists often are asked to predict cognitive outcome after perinatal brain injury (including likely memory and learning outcomes). However, relatively few data exist on how accurate predictions can be made. Furthermore, although the consequences of brain injury on hippocampal volume and memory performance have been studied extensively in adults, little work has been done in children. **METHODS:** We measured the volume of the hippocampus in 27 children with perinatal stroke and 19 controls, and measured their performance on standardized verbal and non-verbal memory tests. **RESULTS:** We discovered the following: (1) As a group, children with perinatal stroke had smaller left and right hippocampi compared with control children. (2) Individually, children with perinatal stroke demonstrated 1 of 3 findings: no hippocampal loss, unilateral hippocampal loss, or bilateral hippocampal volume loss compared with control children. (3) Hippocampal volume inversely correlated with memory test performance in the perinatal stroke group, with smaller left and right hippocampal volumes related to poorer verbal and non-verbal memory test performance, respectively. (4) Seizures played a significant role in determining memory deficit and extent of hippocampal volume reduction in patients with perinatal stroke. **CONCLUSIONS:** These findings support the view that, in the developing brain, the left and right hippocampi preferentially support verbal and nonverbal memory respectively, a consistent finding in the adult literature but a subject of debate in the pediatric literature. This is the first work to report that children with focal brain injury incurred from perinatal stroke have volume reduction in the hippocampus and impairments in certain aspects of declarative memory.

Keywords: hippocampus, memory, stroke, pediatrics, epilepsy

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Introduction

Ample evidence demonstrates that adults who sustain damage to the hippocampus and other medial temporal lobe structures incur profound, life-long declarative (ie, episodic and semantic) memory impairment.[1-4] One consistent finding has been that patients with left-sided brain lesions tend to be more impaired at verbal memory tasks, whereas patients with right-sided brain lesions tend to be more impaired at nonverbal memory tasks.[5-13] Similarly, evidence from functional magnetic resonance imaging, positron emission tomography imaging, and behavioral testing of adult patients with epilepsy suggests that the left hippocampus is more involved in verbal memory tasks whereas the right hippocampus is move involved in nonverbal memory tasks.[6,10,12-19] Furthermore, patients with bilateral hippocampal lesions are much more impaired than patients with unilateral hippocampal lesions, such that patients with bilateral lesions may have difficulty holding jobs and managing their own affairs whereas patients with unilateral lesions often learn to function independently with the use of compensatory strategies.[9,20]

In contrast to this extensive literature in adults, comparatively little work has been done to investigate the

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TABLE 1.
Demographics, characteristics, and lesion/neurological information

Patient/Control	Age, y	Sex	Race	IQ	Seizures	Hemiparesis	Lesion Side	Lesion Site	Lesion Severity
Patient									
1	16	M	C	101	No	No	Right	FTPOSW	5
2	14	M	C	121	No	No	Right	FP	5
3	15	F	C	118	No	No	Left	F	2
4	13	M	C	71	Yes	Yes	Right	FTPBW	5
5	7	M	C	83	Yes	Yes	Left	FTPOSGBW	5
6	7	F	C	95	Yes	No	Right	FS	2
7	8	M	C	104	No	Yes	Right	B	2
8	8	M	H	114	No	Yes	Left	F	4
9	10	M	C	89	Yes	No	Right	FSG	3
10	12	F	C	58	Yes	Yes	Right	FTPOSB	5
11	11	F	C	82	No	Yes	Left	M	4
12	8	F	H	100	Yes	No	Left	P	4
13	14	F	C	82	Yes	No	Left	P	4
14	14	F	C	75	No	Yes	Left	T	4
15	7	F	H	63	Yes	Yes	Left	FTPSBW	5
16	14	M	C	99	Yes	Yes	Right	FTP	5
17	12	M	H	86	No	Yes	Left	FPSG	5
18	12	M	C	135	No	No	Left	PS	4
19	8	M	C	68	Yes	Yes	Right	FTPSMBW	5
20	6	F	C	66	Yes	Yes	Left	P	4
21	8	F	C	62	Yes	Yes	Right	FTPOSBW	5
22	9	M	C	89	Yes	No	Left	FP	5
23	9	F	C	86	Yes	Yes	Right	FTPSGBW	5
24	14	F	C	57	No	No	Left	FTP	5
25	13	M	C	112	No	No	Left	FS	4
26	11	F	C	101	No	Yes	Left	TPSW	5
27	12	M	C	67	Yes	Yes	Right	FTPSGBW	5
Control									
1	10	M	H	107	No	No	Normal	None	
2	8	F	C	107	No	No	Normal	None	
3	8	M	C	112	No	No	Normal	None	
4	7	M	C	117	No	No	Normal	None	
5	13	M	AA	90	No	No	Normal	None	
6	8	F	C	113	No	No	Normal	None	
7	12	F	H	120	No	No	Normal	None	
8	10	F	C	113	No	No	Normal	None	
9	7	F	C	131	No	No	Normal	None	
10	13	M	C	133	No	No	Normal	None	
11	10	M	C	122	No	No	Normal	None	
12	8	M	A	135	No	No	Normal	None	
13	8	M	A	135	No	No	Normal	None	
14	7	F	C	128	No	No	Normal	None	
15	9	F	C	106	No	No	Normal	None	
16	9	M	C	113	No	No	Normal	None	
17	14	F	C	107	No	No	Normal	None	
18	8	F	C	121	No	No	Normal	None	
19	7	F	C	110	No	No	Normal	None	

Abbreviations:
A = Asian
AA = African American
B = Broca area
C = Caucasian
F = Frontal
G = Basal ganglia
H = Hispanic
M = Thalamus
O = Occipital
P = Parietal
S = Subcortical
T = Temporal
W = Wernicke area
Severity scores range from 0 to 5 (see Materials and Methods for details).

TABLE 2.
Severity scores for perinatal stroke patients

Severity	Right-sided Lesion	Left-sided Lesion	Total Patients
2	2	1	3
3	1	0	1
4	0	8	8
5	9	6	15
Total patients	12	15	27

Lesion severity was rated by a grading system described previously (Trauner et al,[28] Vargha-Khadem et al[29]) with grades from 1 = minimal ventricular dilation or atrophy to 5 = large porencephaly involving multiple lobes.

neuroanatomical substrates of memory in children. The few previous studies that examine memory in children with perinatal stroke or with localization-related epilepsy have shown conflicting results, with some studies finding that lesion laterality was important in the presence and type of memory deficit whereas others found no difference in memory impairment based on the side of the lesion.[21-26] Notably, in none of the previous studies did authors examine structure-function relationships with hippocampal volume and memory measures.

Studies of memory function in children are vitally important for a variety of reasons. First, such studies offer a unique opportunity to investigate the developing brain. Second, pediatric brain injury is much more common than previously thought; in particular, current estimates suggest that the rate of perinatal stroke is about 1 in 2500 to 1 in 4000 live births.[27] Third, children with memory impairment secondary to brain injury need medical and educational interventions to reach their maximum cognitive and intellectual potential, but again there are insufficient data upon which to base the selection of appropriate treatment modalities. The young brain has remarkable potential for plasticity and functional compensation, but this potential cannot be fully harnessed without a better understanding of the consequences of brain injury during the critical period of development.

As part of a larger study of cognitive function and the role of seizures in children with perinatal stroke, we analyzed hippocampal volume in children with perinatal stroke and correlated hippocampal volume with verbal and nonverbal memory function. We hypothesized that there would be a direct relationship between hippocampal volume and memory function in patients who experienced a perinatal stroke. We also hypothesized that seizures in this population would have an adverse effect on hippocampal volume and memory.

Materials and Methods

Participants

Forty-six children and adolescents participated in the study. Twenty-seven subjects had a single unilateral brain lesion caused by a perinatal stroke (age range 6-16 years, mean 10.7 ± 0.6 years, 14 male and 13 female). Twelve patients had right-hemisphere strokes, and 15 had left hemisphere strokes. Subjects were recruited from pediatric neurology clinics in San Diego County. Perinatal stroke was defined as a single, unilateral brain lesion in an arterial vascular distribution, either identified in the neonatal period with neuroimaging, or identified later in infancy after presentation with a hemiparesis and imaging documentation of an old unilateral infarct (presumed perinatal stroke). Children were excluded if they had bilateral lesions or evidence of more widespread brain damage such as a history of hypoxic-ischemic encephalopathy.

The presence of seizures was determined by review of the medical record and family interview; patients were classified as having seizures if they had a seizure after 28 days of life. A total of 59% of children in the stroke group had hemiparetic cerebral palsy; all had normal function of their nonaffected hand and arm. Exclusionary criteria included a history of hypoxic ischemic encephalopathy, central nervous system infection, in utero drug exposure, significant closed head injury, or any other condition that might have caused brain damage other than from the stroke. Nineteen control subjects (7-14 years [9.3 ± 0.5 years], 9 male and 10 female) were recruited from the community through advertisements and by word of mouth. Complete medical and family histories were obtained for all control children. All control children included in the study had normal developmental and medical histories and were free of learning and behavioral problems. The stroke and control populations were group-matched for socioeconomic status. Demographic information for the children is shown in Table 1. All ages are the age at which the participant underwent the magnetic resonance imaging (MRI) that was used for this study.

Structural MRI

All participants were imaged without sedation in a 3-Tesla GE Signa unit. After scout images, field maps, and alignment scans were performed, 4 whole-brain image series were collected for all participants (3D sagittal T2-weighted, 3D sagittal T1-weighted, diffusion-weighted imaging, fluid-attenuated inversion recovery). Hippocampal measurements were performed on the reconstructed sagittal T1 images (see next paragraph). These T1 images were acquired with a spoiled gradient recall echo pulse sequence with the following scanner settings: TE = 3.1, flip angle = 120, field of view = 25 cm, slice thickness = 1.2 mm, matrix 256 × 256, total 120 images.

A clinical neuroradiologist, who was unaware of the patients' cognitive and clinical status, performed a clinical assessment of each neuroimaging (MRI) study, providing indication of a single unilateral brain lesion as well as documentation of lesion location (ie, designation of cortical, subcortical, and lobar involvement). The severity of the lesion was rated by a grading system described previously with grades from 1 = minimal ventricular dilation or atrophy to 5 = large porencephaly involving multiple lobes.[28,29] Fifteen patients had lesions assigned a severity score of 5 (9 of these patients had a right-sided lesion, 6 of these patients had a left-sided lesion); one of these patients had a lesion described as a "destructive lesion of the left temporal and parietal lobes," and this patient had no remaining left hippocampus. Every other patient in this study had some hippocampal tissue bilaterally. Eight patients had lesions assigned a severity score of 4 (all were left-sided lesions), one patient had a severity score of 3 (right-sided lesion), and 3 patients had a severity score of 2 (2 right-sided lesions, 1 left-sided lesion). No patients in this study were assigned a severity score of 1. Severity scores are summarized in Table 2.[28,29]

Using the AFNI suite of analysis tools,[30] we aligned each patient's MRIs along the anterior commissure to posterior commissure axis, and voxels were linearly resampled to 1 mm × 1 mm × 1 mm. Using methods developed and validated by our group,[31] we measured the left and right hippocampal regions (hippocampus proper, dentate gyrus, and subicular complex) in the sagittal view, beginning laterally at the appearance of hippocampal tissue within the lateral ventricle. The drawing continued medially, observing the separation between the hippocampal region and the amygdala. Measurements were then reevaluated in the coronal view to ensure complete separation between the hippocampus and the posterior aspect of the pulvinar, the separation between the subicular complex and entorhinal cortex, and white matter/gray matter segmentation.

Behavioral testing

Every child was administered the Wechsler Intelligence Scale for Children, Third Edition to assess global cognitive functioning. To assess memory, we administered selected subtests from a broad-based and relatively comprehensive standardized test to assess various aspects of memory. Subjects were administered the Dots and Stories subtests of the Children's Memory Scales (CMS), which measures learning and retrieval

TABLE 3.
IQ scores of patients and controls

	IQ
Controls (n = 19)	117 ± 2.7
All patients (n = 27)	88 ± 4.0
No seizures (n = 12)	100 ± 6.4
Seizures (n = 15)	78 ± 3.7

IQ mean ± SEM. By definition, the mean IQ of the general population is 100.

of nonverbal and verbal material, respectively.[32-35] In the Dot Locations subtest of nonverbal memory, children were presented with a card showing black dots arranged on a grid. The children's task was to re-create the location of the dots on the grid by using plastic chips they could place on a replica of the grid. During each of 3 learning trials, children were shown the target grid for 5 seconds and then were scored based on how many chips they correctly placed on the grid (summed number of correctly placed dots during the three learning trials = Dots–Learning). Children were then shown a distracter grid and were asked to recreate this grid as well (unscored). Children were then asked to reproduce the original target grid, and their performance on the learning trials was added to their performance on this short-delay recall trial to generate a total score (Dots–Total). After 20 minutes, children were given a final opportunity to recreate the original target grid (Dots–Recall). In the Stories subtest of verbal memory, children were presented with a story and then were asked to recount it (Stories–Immediate Recall). After a delay (typically about 20 minutes), children were again asked to recall the story (Stories–Delayed Recall) and then took a recognition memory test for the words and themes of the stories (Stories–Delayed Recognition). This process was repeated so that each child was tested using 2 stories.

Analysis

SPSS for Windows was used for all analyses (SPSS Inc., Chicago, IL). Comparisons of hippocampal volumes between patients and controls, as well as comparisons between scores on CMS subtests, were carried out using 2-tailed *t* tests and reported as significant if $P < 0.05$. Correlations between lesion volume and performance on CMS subtests were performed by the use of linear regression analysis and evaluated with Pearson coefficients that were reported as significant if $P < 0.05$. Mann Whitney U test was also used to compare severity scores (1-5) between the group of patients with seizures and the group of patients without seizures; these results were also reported as significant if $P < 0.05$.

Results

Demographics

Although the focal lesion subjects had a slightly greater mean age than controls, there was no significant difference (control mean 9.31 ± 0.5 years, patient mean 10.7 ± 0.6 years, $P = 0.08$). Full-scale IQ was significantly lower in the focal lesion group compared with controls (Table 3). Patients with right hemisphere lesions (n = 12) were demographically similar to patients with left hemisphere lesions (n = 15). Patients had similar ages (right hemisphere lesion patient mean 10.8 ± 0.8 years, left hemisphere lesion patient mean 10.6 ± 0.8 years, $P = 0.85$), IQs (right hemisphere lesion patients mean 85.0 ± 6, left hemisphere lesion patients mean 91 ± 6, $P = 0.49$), and lesion severity scores (right hemisphere lesion patients mean 4.3 ± 0.4, left hemisphere lesion patients mean 4.3 ± 0.2, $P = 0.87$).

There was no difference between the control and perinatal stroke subjects in socioeconomic status nor on maternal level of education. Patients without seizures were older than patients with seizures (with seizures [n = 15] mean 9.5 ± 0.7 years, without seizures [n = 12] mean 12.2 ± 0.7 years, $P = 0.01$).

TABLE 4.
Volume of the hippocampal region

	Right	Right *P*-value	Left	Left *P*-value
Controls (n = 19)	3797 ± 92		3532 ± 108	
All patients (n = 27)	3109 ± 184	0.005	2922 ± 159	0.006
Left hemisphere lesions (n = 15)	3324 ± 199	0.03	2756 ± 236	0.003
Right hemisphere lesions (n = 12)	2840 ± 325	0.002	3131 ± 197	0.06

Volume in mm^3 ± SEM. *P*-values = 2-tailed *t* test vs controls.

Hippocampal volumes

As a group, patients had smaller hippocampi than controls. All 27 patients and 19 controls were measured. On average, patients with right hemisphere lesions had smaller right hippocampi than controls (control mean 3797 ± 92 mm^3, patient mean 2840 ± 325 mm^3, $P = 0.002$) and patients with left hemisphere lesions had smaller left hippocampi than controls (control mean 3532 ± 108 mm^3, patient mean 2756 ± 236 mm^3, $P = 0.003$) (Table 4). Hippocampal volume was not correlated with age in the range of subjects in this study (control right hippocampal volume vs age R = 0.01, $P = 0.98$; control left hippocampal volume vs age R = 0.24, $P = 0.32$).[36] Similarly, there was no correlation between hippocampal volume and IQ (control right hippocampal volume vs IQ R = −0.12, $P = 0.62$; control left hippocampal volume vs IQ R = −0.19, $P = 0.44$). Further, neither right nor left hippocampal volume was correlated with performance on any subset of the CMS in the control population. Finally, the right hippocampi of the control subjects were somewhat larger than the left hippocampi of the control subjects, which is a well-established finding in MRI measurements of hippocampal volume[37]; for this reason, comparison between the volume of the left and right hippocampi of the patients and controls were not performed.

To investigate the effect of focal (ie, unilateral) brain injury on the contralateral hippocampus, we decided a priori to consider an individual patient's hippocampal volume to be significantly reduced from control if the patient's hippocampal volume was more than 1.5 SD below the control mean. Of the 12 patients with right-sided lesions, 5 had significant unilateral hippocampal volume reduction, 4 had significant bilateral hippocampal volume reduction, and 3 had no significant hippocampal volume reduction. Of the 15 patients with left-sided lesions, 4 had significant unilateral hippocampal volume reduction, 4 had significant bilateral hippocampal volume reduction, and 7 had no significant hippocampal volume reduction. Thus, a subset of the children with right hemisphere lesions and a subset of children with left hemisphere lesions had significantly smaller hippocampi on the side contralateral to the lesion as well as ipsilateral to the lesion. The pattern of volume reduction was not related to the severity score assigned to the brain lesion.

TABLE 5.
Children's Memory Scale performance

Test	Controls, mean ± SEM	All Patients, mean ± SEM	Controls vs All Patients *P*-value	Patients With sz, mean ± SEM	Patients Without Seizures, mean ± SEM	Patients With sz vs Patients Without sz *P*-value	Pt With Lesions in Right Hemisphere, mean ± SEM	Pt With Lesions in Left Hemisphere, mean ± SEM	Right Hemisphere vs Left Hemisphere *P*-value
Stories									
Immediate recall	13.5 ± 0.7	8.4 ± 0.8	<0.001	7.0 ± 0.8	10.1 ± 1.4	0.06	7.8 ± 1.1	8.9 ± 1.2	0.51
Delayed recall	13.9 ± 0.8	7.9 ± 0.8	<0.001	6.2 ± 0.9	10.0 ± 1.2	0.02	7.3 ± 1.1	8.3 ± 1.2	0.56
Delayed recognition	11.5 ± 0.5	8.0 ± 0.8	0.001	7.1 ± 1.1	9.2 ± 0.9	0.17	8.3 ± 1.4	7.9 ± 0.9	0.80
Dots									
Learning	10.9 ± 0.5	8.9 ± 0.8	0.05	7.6 ± 1.1	10.6 ± 0.8	0.05	9.3 ± 1.4	8.7 ± 0.9	0.71
Total	11.8 ± 0.5	9.0 ± 0.7	0.003	7.8 ± 0.9	10.6 ± 0.9	0.04	9.2 ± 1.2	8.9 ± 0.8	0.87
Delayed recall	12.6 ± 0.4	10.0 ± 0.5	<0.001	8.8 ± 0.5	11.4 ± 0.8	0.009	9.7 ± 0.7	10.2 ± 0.7	0.62

Abbreviation:
sz = Seizure
Controls, n = 19 for all tests. All patients, n = 27 (seizures n = 15, no seizures n = 12, right hemisphere lesions n = 12, left hemisphere lesions n = 15), except that one patient did not receive the Delayed Recognition measure of the Stories subtest (patient n = 26, seizures n = 14, right hemisphere lesions n = 11). *P*-value = 2-tailed *t* test.

Behavioral testing

Perinatal stroke subjects as a group had significantly lower IQ scores than did controls (control mean 117 ± 2.7, patient mean 88 ± 4.0, $P < 0.001$). Patients without seizures (mean 100 ± 6.4) had IQ within the range of normal, whereas patients with seizures (mean 78 ± 6.4) had IQ more than 1 standard deviation from the population mean (mean 100 ± SD of 15; Table 3).

All 27 patients and 19 controls participated in all 6 measures of memory tested by the CMS, except that one patient did not receive the Stories–Delayed Recognition test and was excluded from that analysis only. Perinatal stroke subjects as a group were impaired on all 6 measures of the Dots and Stories subtests of the CMS relative to controls (Table 5). Patients with right and left hemisphere lesions were statistically similar on all 6 measures of the Stories and Dot Locations subtests of the CMS. Patients without seizures scored significantly better than patients with seizures on all measures of the Dot Locations subtest and the Delayed Recall measure of the Dot Locations subtest. Patients without seizures scored better than patients with seizures on the Immediate Recall and Delayed Recognition measures of the Stories subtest as well, but the difference in scores did not reach statistical significance (Table 5).

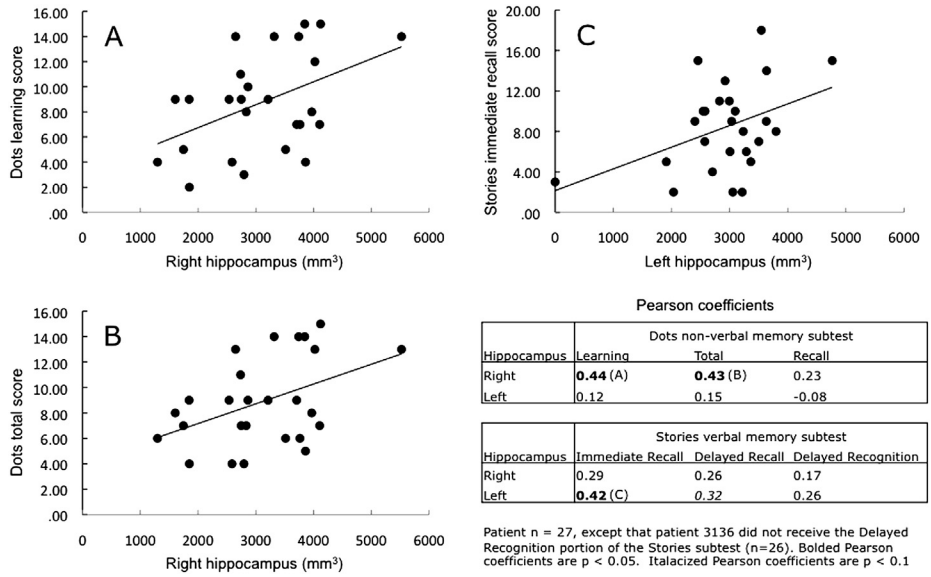
We calculated Pearson coefficients of correlation between hippocampal volume (right and left) and performance on each subtest of the Children's Memory Scale for the patient group (Fig). Statistically significant correlations were: (1) the volume of the right hippocampus vs performance on the Learning measure of the Dots subtest, $R = 0.44$, $P = 0.02$ (Fig A); (2) the volume of the right hippocampus vs performance on the Total measure of the Dots subtest, $R = 0.43$, $P = 0.02$ (Fig B); (3) the volume of the left hippocampus vs performance on the Immediate Recall measure of the Stories subtest, $R = 0.42$, $P = 0.03$ (Fig C). The correlation of the volume of the left hippocampus vs performance on the Delayed Recall measure of the Stories subtest trended toward but did not reach significance ($R = 0.32$, $P = 0.1$). Finally, we calculated all of the Pearson coefficients of correlation analysis again, controlling for IQ. The volume of the left hippocampus vs performance on the Immediate Recall measure of the Stories subtest remained significantly correlated, and the correlation became slightly stronger ($R = 0.49$, $P = 0.01$); similarly, the correlation of the volume of the left hippocampus vs performance on the Delayed Recall measure of the Stories subtest trended even closer to significance ($R = 0.38$, $P = 0.06$). The correlations between the volume of the right hippocampus vs performance on the Learning measure of the Dots subtest ($R = 0.31$) and the volume of the right hippocampus vs performance on the Total measure of the Dots subtest ($R = 0.30$) no longer reached statistical significance ($P > 0.1$).

We calculated Pearson coefficients of correlation between hippocampal volume (right and left) and performance on each subtest of the Children's Memory Scale for the control group. We also calculated Pearson coefficients of correlation between IQ and performance on each subtest of the Children's Memory Scale for the control group. No correlations neared statistical significance ($P > 0.1$ for all comparisons).

Seizures, lesion severity, and hippocampal volume

The group of 15 patients with seizures had significant hippocampal volume reduction relative to controls (right mean 2708 ± 232 mm^3, $P < 0.001$; left mean 2913 ± 96 mm^3, <0.001). As a group, the 12 patients without seizures had no significant volume reduction of the right hippocampus and near-significant hippocampal volume reduction of the left hippocampus (right mean 3609 ± 233 mm^3, $P = 0.39$; left mean 2934 ± 346 mm^3, $P = 0.06$) compared with controls. In part, this was attributable to one patient with a left hippocampal volume of 0 mm^3, as mentioned in the Materials and Methods section; if this patient were excluded from the hippocampal volume analysis then the trend toward statistical significance lessened (left mean 3200 ± 242 mm^3, $P = 0.16$).

Lesion severity was not related to the presence of seizures. Of the patients without seizures, 2 had severity



Pearson coefficients

Hippocampus	Dots non-verbal memory subtest: Learning	Total	Recall
Right	**0.44** (A)	**0.43** (B)	0.23
Left	0.12	0.15	-0.08

Hippocampus	Stories verbal memory subtest: Immediate Recall	Delayed Recall	Delayed Recognition
Right	0.29	0.26	0.17
Left	**0.42** (C)	*0.32*	0.26

Patient n = 27, except that patient 3136 did not receive the Delayed Recognition portion of the Stories subtest (n=26). Bolded Pearson coefficients are $p < 0.05$. Italicized Pearson coefficients are $p < 0.1$

FIGURE.
Figures A through C show correlations between hippocampal volume and memory performance for 3 subtests of the Children's Memory Scale. Patients = 27, except that patient 3136 did not receive the Delayed Recognition portion of the Stories Subtest (n = 26). Bolded Pearson coefficients are $P < 0.05$. Italicized Pearson coefficients are $P < 0.1$.

scores of 2, 5 had severity scores of 4, and 5 had severity scores of 5, whereas of the patients with seizures, one had a severity score of 2, one had a severity score of 3, 3 had a severity score of 4, and 10 had a severity score of 5; this difference is not statistically different (nonparametric Mann-Whitney U test, $P = 0.31$).

Discussion

This is the first study to quantify hippocampal volume loss after unilateral brain injury in the perinatal period, correlate memory impairment with the location and extent of hippocampal volume reduction, and study the role of seizures in both hippocampal volume reduction and memory impairment. We found that stroke in the perinatal period may have variable effects on the hippocampus. It is clear that seizures beyond the neonatal period play an important role in determining the nature and extent of hippocampal volume loss as well as the pattern of memory impairment. The degree of hippocampal volume reduction was correlated with poorer performance on memory tests, with left hippocampal volume reduction related to poorer performance on a verbal memory test and right hippocampal volume reduction related to poorer performance on a nonverbal memory test.

This pattern of memory impairment is congruent with the extensive literature on adult memory, but at odds with a previous study that found disparate patterns of memory impairment after brain injury in children and adults.[21] However, interpretation of that study is complicated for a number of reasons: (1) the study authors combined patients with perinatal strokes and strokes up to 1 year of age and also included a group of pediatric patients with strokes after 1 year of age; (2) the memory test was the California Verbal Learning Test—Children's Version, which tests verbal but not nonverbal memory, making interpretation of a memory deficit as opposed to a language deficit difficult; and (3) the influence of seizures was not considered. Our findings strongly support the view that, as in adults, the left and right hippocampi in children preferentially support verbal and nonverbal memory, respectively.

It is notable that there was a wide range of hippocampal damage after focal stroke. As a group, patients had significant reduction in hippocampal volume bilaterally; some individuals had no significant reduction in hippocampal volume relative to control children, others had unilateral hippocampal volume reduction, whereas others had bilateral hippocampal volume reduction. One likely explanation is that the hippocampus is particularly susceptible to damage in patients with seizures and that patients with seizures are more likely to have hippocampal volume loss (both ipsilateral and contralateral to a brain lesion) than patients without seizures.[18,38-43] Children with seizures show evidence of damage to the hippocampus and other temporal lobe areas, and some investigators have concluded that hippocampal injury is often secondary to a remote seizure focus.[44-46]

In this study, patients with seizures were more likely to have any hippocampal volume reduction (either unilateral or bilateral) than patients who did not have seizures; this was true regardless of the size of the lesion (that is, higher severity scores were not significantly associated with greater hippocampal volume reduction). Using severity score as an indicator of lesion size, we did not find that children with larger lesions were more likely to have seizures than children with smaller lesions. Thus, it appears that a history of seizures, rather than the size of the lesion, is most important in determining whether there will be hippocampal volume reduction after perinatal stroke.

Factors other than seizures also may be related to hippocampal volume reduction after early focal brain injury. For example, network models suggest that damage to one hippocampus especially early in life can result in changes in

synaptic physiology in the contralateral hippocampus.[47] Further work investigating the correlation between hippocampal volume loss and memory performance in children with stroke beyond the perinatal period, as well as children with seizures from causes other than perinatal stroke, is needed to clarify the relationship between stroke, seizure, hippocampal volume loss, and memory performance.

Several interesting trends emerged when our data were analyzed based on the presence or absence of seizures. First, as we have reported elsewhere, individuals with seizures had significantly lower IQ than patients who did not have seizures.[48] In the present study, IQ scores in patients with seizures were more than one standard deviation below the population mean, whereas individuals without seizures had normal IQ. Second, patients with seizures had significantly smaller hippocampi than controls, whereas the hippocampi of patients without seizures were not significantly smaller than controls. Finally, patients with seizures were impaired relative to controls on all 6 measures of the CMS; further, patients with seizures were impaired relative to patients without seizures on 4 of 6 measures of the CMS (and there was a trend toward better performance by the patients without seizures on the other 2 measures).

We recognize that the IQ of our control group was more than one standard deviation greater than the population mean, while the IQ of the patient group was below the population mean. To the extent that subjects with higher IQ may perform better on memory tests generally, this may have caused us to overestimate the magnitude of the memory impairment in the patients relative to the control group due to factors other than IQ. However, performance on the memory tests was not correlated with IQ in the control group in our study. Controlling for IQ within the patient group strengthened some correlations between performance on the memory tests and hippocampal volume while weakening other correlations. Thus, our data suggest that IQ did not have a strong impact on memory performance as measured by the CMS within either the control or the patient group.

This is the first study to show that children with perinatal stroke can exhibit volume reduction in the hippocampus relative to age-matched controls, and that the perinatal stroke children exhibit different patterns of memory impairment (verbal vs nonverbal) correlated with the side of hippocampal volume loss. Specifically, our findings indicate that (1) children who suffer focal brain lesions early in life may demonstrate no hippocampal loss, unilateral hippocampal loss, or bilateral hippocampal volume loss; (2) the degree of hippocampal volume loss is correlated with the degree of impairment on memory tests; (3) damage to the left hippocampus is more likely to result in impairment in verbal memory whereas damage to the right hippocampus is more likely to result in impairment in non-verbal memory; (4) the pattern of memory deficit (verbal or nonverbal) that is found in the context of volume loss in the hippocampus (left, right, or bilateral) in patients with perinatal-onset focal brain damage may be similar to those patterns observed after injury to the hippocampus in adults; (5) seizures play a significant role in determining the presence of memory deficit and extent of hippocampal volume reduction in patients with perinatal-onset focal brain injury; (6) MRI and volumetric analysis of the hippocampus may predict memory impairment after perinatal focal stroke.

The pediatric brain has remarkable capacity for plasticity. Our results caution against dire prognostication about cognitive and memory outcomes after focal stroke in the perinatal period. Based on our findings, it seems likely that seizures may limit the natural postinjury plasticity and prevent full functional recovery. This is critically important because it suggests that aggressive seizure control beyond the perinatal period may improve cognitive and memory outcomes in children who suffer perinatal stroke. Additional work is needed to determine whether optimal seizure control may affect outcomes after perinatal stroke.

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