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Hippocampal Volume in Normal Aging and Traumatic Brain Injury

Erin D. Bigler, Duane D. Blatter, Carol V. Anderson, Sterling C. Johnson, Shawn D. Gale, Ramona O. Hopkins, and Bruce Burnett

PURPOSE: To present a normative database of hippocampal and temporal horn volume and to clarify the relationship between these measures and cognitive outcome in patients with traumatic brain injury. **METHODS:** Ninety-six healthy volunteers and 94 patients with traumatic brain injury were examined with coronal intermediate and T2-weighted MR imaging. Multispectral segmentation and volume analyses were performed. The volumetry of the hippocampus and temporal horn was characterized in the control subjects. Volumetric measures in a group of patients with traumatic brain injury who had received MR imaging 3 months or less after injury were compared with measurements in other patients in the chronic phase of recovery. The relationship between neuropsychological testing and volumetric measures was analyzed with particular emphasis on the correlation between cognitive outcome and hippocampal and temporal horn volumes. **RESULTS:** No significant age group differences were found in the normative group from age 16 to 65. Left and right hippocampal volumes were interrelated and did not differ from each other. This was also true for the temporal horns. Hippocampal and temporal horn volumes were not significantly related. Women had larger hippocampi relative to cranial volume. Comparisons between patients with traumatic brain injury and control subjects showed significant yet modest bilateral atrophic changes in hippocampal and temporal horn enlargement in the patients with brain injury. Hippocampal and temporal horn volumes correlated significantly with each other in the group with traumatic brain injury. Cognitive outcome was modestly related to hippocampal and temporal horn volumes. However, in a specific subgroup whose images were acquired between 71 and 210 days after injury, strong correlations were noted in which temporal horn volume correlated highly with IQ and hippocampal volume correlated with verbal memory function. **CONCLUSION:** Hippocampal and temporal horn volumes appear to be independent variables in healthy control subjects. Traumatic brain injury results in significant hippocampal atrophy and temporal horn enlargement. The hippocampus and temporal horn volumes were inversely correlated in the group with traumatic brain injury, suggesting a differential relationship of these structures in patients with brain injury as compared with control subjects. In the subacute phase, the volume of the temporal horn may be indicative of intellectual outcome and that of the hippocampus appears to be indicative of verbal memory function.

Index terms: Age and aging; Brain, injuries; Brain, volume; Hippocampus

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The role of the hippocampal formation in normal and pathophysiologic states has intrigued neuroscientists and clinicians for decades (1–4). With the advent of magnetic resonance (MR) imaging, in vivo visualization of the hippocampus became possible, with an initial research and clinical focus applied to qualitative descriptions of hippocampal findings (5–7). A variety of imaging quantification techniques became available by the late 1980s, and a flurry of studies focusing on the quantitative analysis of the hippocampal formation have now been published (8–23). Much of this research has been directed toward patients with temporal lobe epilepsy and dementia of the Alzheimer type, with a scattering of studies looking at various neuropsychiatric disorders (13–17, 19, 21, 24–28).

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Because of the crucial role the hippocampus plays in memory and cognition (29), the need to study hippocampal changes associated with a broad spectrum of disorders beyond dementia and epilepsy is apparent (21, 29). A reference normative comparison group may facilitate our understanding of pathologic anatomic changes (30). In this regard, we report our findings in a large group of healthy volunteers, ages 16 to 65 years, with particular emphasis on the relationship between the hippocampus and temporal horn of the lateral ventricle. Hippocampal changes in a group of patients who sustained traumatic brain injury are then described. The temporal horn focus is of particular relevance because of the importance that has been placed on this structure as an indirect index of hippocampal integrity (31–33).

Hippocampal atrophy as a consequence of traumatic brain injury has been documented in animal models (34). In humans, temporal horn dilatation of the lateral ventricular system often accompanies traumatic brain injury, especially when the temporal lobe is the focus of injury (32, 35–37). The temporal lobe is vulnerable to injury because of its position in the middle cranial fossa (31, 35). Previous studies have looked at temporal horn dilatation in traumatic brain injury as related to severity of injury and degree of neuropsychological impairment (32, 37, 38). In an earlier study (32), we noted a significant correlation between the size of the left temporal horn as measured in the axial plane and verbal intellectual function, and a moderate correlation between size and verbal memory. Temporal horn dilatation is often interpreted as an indirect sign of hippocampal atrophy, but the exact relationship between hippocampal atrophy and temporal horn dilatation in traumatic brain injury has not been systematically investigated, to our knowledge.

Two studies are presented here. In study 1, MR-based quantitative normative standards are established for both the temporal horns and the hippocampus. In study 2, the effects of head trauma on the hippocampus and temporal horn, along with the interrelationship of these two structures, are examined in the context of injury chronicity. For comparative purposes, patients in whom quantitative neuroimaging studies were completed before and up to and including 100 days after traumatic brain injury formed the early group, who were compared with those scanned after 100 days (the late group). The reason for the two comparisons is that temporal horn volume may change as a function of time since injury (39). The global functions of memory and intelligence were assessed at particular time points, and the relationship between these functions and the hippocampus and temporal horn is described.

Subjects and Methods

Study 1

Subjects.—Ninety-six healthy control subjects (37 male and 59 female, 16 to 65 years old) were examined. These volunteers were recruited primarily from hospital and university staff and their friends and family. Exclusion criteria included previous head injury causing loss of consciousness; any disease affecting the nervous system, including dementia or psychiatric illness; and a history of alcohol or drug abuse. The imaging and subsequent analyses were performed in compliance with a protocol approved by an institutional review board, and all volunteers gave informed consent.

Imaging.—MR images were acquired on a 1.5-T unit with the use of a quadrature head coil and standard clinical protocol. Sagittal T1-weighted (500/11/2 [repetition time/echo time/excitations]) MR images were acquired and used for localization. Using the midsagittal image as a reference, we acquired coronal intermediate and T2-weighted (3800/21,105/2) fast spin-echo images that extended from the genu to the splenium of the corpus callosum. Interleaved sections were acquired with a section thickness of 3 mm. A 512 × 256 matrix was selected with a 22-cm field of view. Flow compensation, an inferior saturation pulse, and variable bandwidth were used. Axial intermediate and T2-weighted (3000/31,90/1) standard spin-echo images were also acquired with a section thickness of 5 mm and an intersection gap of 2 mm. A 22-cm field of view was used with a 256 × 192 acquisition matrix. This sequence was part of our standard clinical protocol.

Volumetric Image Analysis of Hippocampal and Temporal Horn Volumes.—The coronal intermediate and T2-weighted spin-echo images were processed using Analyze (Biomedical Imaging Resource, Mayo Foundation, Rochester, Minn) running on Sparc 10 workstations. The original 16-bit images were converted to eight-bit images in Analyze file format and then archived permanently on optical disk using a lossless compression algorithm. A multistep volume analysis was then performed using several image processing tools available in Analyze, including multispectral tissue segmentation, region of interest (ROI) pixel counting, and tracing (see Figs 1 and 2). The multispectral tissue segmentation was performed in a manner similar to that described previously (30) (see Fig 2) and was used to classify gray matter, white matter, and cerebrospinal fluid (CSF). On a coronal section, where the hippocampus was clearly distinguishable, the three tissue types were classified. CSF was user-defined by tracing a

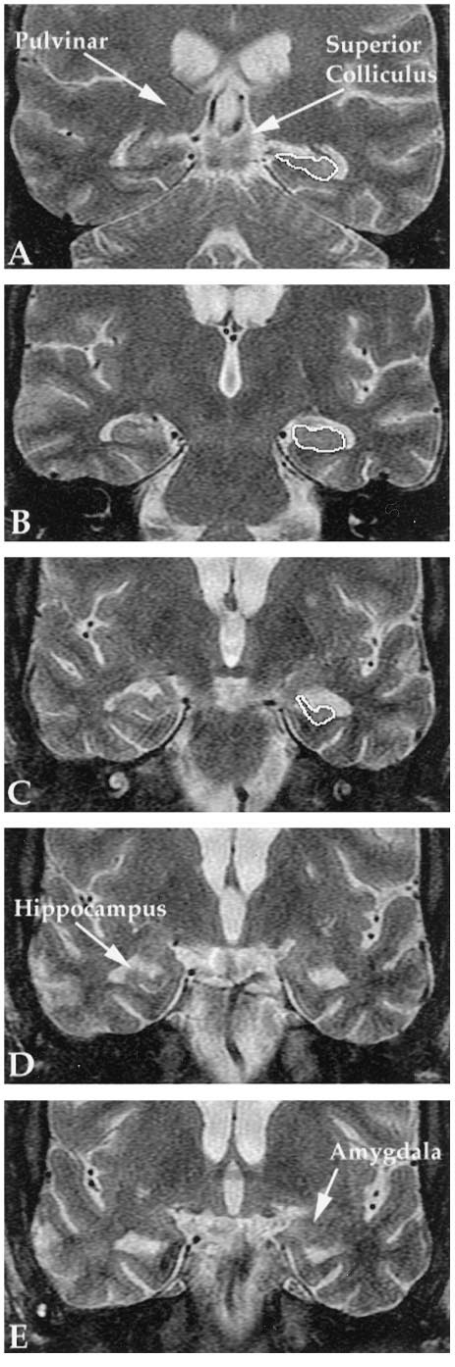

Fig 1. Hippocampal boundaries as defined in a patient with traumatic brain injury. Five T2-weighted coronal MR sections through the hippocampus, progressing from posterior to anterior, are shown. The outline of the left hippocampus is traced. *A* illustrates the establishment of the posterior boundary of the hippocampus. Three of the four criteria are seen: the superior colliculus, the medial pulvinar, and a clear separation of the temporal horn. *B* is a view through the midsection of the hippocampus. *C–E* are successive and progressively more anterior sections through the head of the hippocampus. *D* shows the most anterior section through the hippocampus that was included in the analysis. *E* depicts the globular shape of the amygdala just anterior to the head of the hippocampus.

representative area in the lateral ventricle. Gray matter was defined by pixel intensities represented in the hippocampus, and white matter was defined in the temporal stem (40). Region samples were then plotted in a two-dimensional feature space where the pixel signal intensity on the T2-weighted sequences was the value on the x-axis and the pixel signal intensity in the intermediate-weighted image was the y-axis. A k-nearest neighbor multispectral algorithm was applied to the pixels of the entire section (41). When a feature space map was obtained that accurately represented the three tissue types, with the use of the original spin-echo images as a reference, it was applied to the remaining sections in the study. The classified images were then stored and used for calculating ROI volumes. Unavoidably, with this technique there is always some inherent misclassification. For example, in Figure 2, in which a segmented image is displayed from a subject with traumatic brain injury, there are two separate areas of misclassification consisting of two pixels each in the ventral-medial aspect of the left hippocampus that were classified by the imaging algorithm as CSF rather than brain parenchyma. Since this illustration is from a subject with traumatic brain injury, it is entirely possible that the region may represent an extremely small focus of necrosis, but it is just as possible that this may represent a classification error. Accordingly, some inherent variability is present with this classification and segmentation process. The potential advantage of the multispectral classification approach is less reliance on operator judgment than accompanies pure tracing methods. Although systematic differences of even a single pixel width can alter the accuracy of a measurement (42), it is assumed for the purposes of this study that classification errors were random and that the data were not systematically biased by misclassification. As will be discussed below, interrater reliabilities for this work have been high.

Volumes of the hippocampus and the temporal horn of the lateral ventricle were determined by using the ROI feature of Analyze, which yields a count of gray matter, white matter, and CSF pixels. Because of subject variability, several rules were used to distinguish the anterior and posterior boundaries of the hippocampus. The posterior boundary of the hippocampus was identified when a combination (at least two) of the following four criteria were present when the most posterior section conforming to the criteria was used (always assuming contiguity from section to section from known segmented hippocampal tissue, see Fig 1): presence of superior colliculi; presence of the medial pulvinar nucleus of the thalamus; visibility of the oblong position of the hippocampus at the level of the crura of the fornices, after which contiguity disappears on the next most posterior section; and presence of a distinct separation of the temporal horn from the atria. All tracings began posteriorly where, using the above rules, hippocampal boundaries could be consistently identified. The anterior boundary of the hippocampus is more ambiguous and requires operator decisions. Frequently, the anterior aspect of the hippocampus can be seen to be separate from the amygdala. Along with the boundaries of the temporal

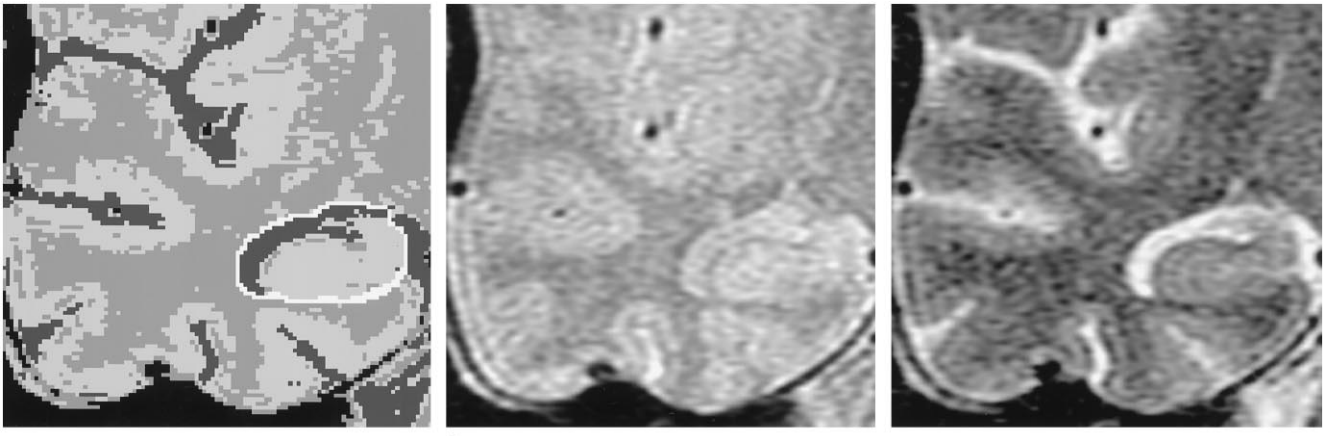

Fig 2. Multispectral segmentation of the left temporal lobe shows the method used to identify gray matter pixels of the hippocampus and CSF pixels of the temporal horn on magnified images.

A, Close-up of segmented image reduced to three tissue types depicting the loosely traced outline of the hippocampus defining the ROI. Once the ROI is identified, the outer boundary of the hippocampus is traced, as depicted in Figure 1. A pixel count is then taken based on gray matter pixels. A similar method is used to obtain temporal horn pixels based on their CSF classification within the ROI.

B, Original intermediate-weighted MR image.

C, T2-weighted MR image.

horn, when clearly identified, the uncal recess separates the pes hippocampus from the overlying amygdala. If neither the uncal recess nor the temporal horn distinctions were present, then the section was not included. Use of this procedure produces a conservative estimate, because the anterior tip of the hippocampus may not have been included in the measurements of some subjects. The temporal horn was defined posteriorly as the most posterior section in which the atria was visibly separate from the temporal horn. The entire temporal horn was included anteriorly.

While the width of the hippocampus is readily identified by the contiguity of the segmentation process, the same is not necessarily true of the temporal horn. The lateral boundary is clear, as it extends to the ventricle wall against the temporal lobe. Medially, the temporal horn extends until it meets the ambient cistern/choroidal fissure. The boundaries here are less distinct. Often, the anterior choroidal artery separates the temporal horn from the cistern and fissure. When present, the anterior choroidal artery served as a medial landmark of the temporal horn. When not present, the temporal horn was traced to the point at which the boundaries of the ambient cistern/choroidal fissure were most readily identified. If the segmented image of the temporal horn CSF was accurate, the ROI application was applied without tracing.

In most cases, because the segmentation step of the process had already identified the interface between CSF and brain, segmented boundaries were used for volume calculation. However, wherever ambiguity over a boundary was encountered, the original spin-echo images were used as a reference, since the software allows the tracing to appear simultaneously on equally registered images. Once the value of each section was determined, total hippocampal volume was calculated by summing the gray matter pixels and then multiplying by the voxel dimension (0.0005539 cm^3). Temporal horn volume was obtained by summing the CSF pixels and multiplying by the voxel dimension. A ventricle-to-brain ratio and head size correction were calculated in the axial plane as described previously (30).

Head size correction using total intracranial volume was done so that hippocampal and temporal horn volumes could be directly compared across subjects and gender. This approach has been established previously for normalizing hippocampal volume (18, 42, 43). The normative data presented by decade are given in both uncorrected (Table 1) and corrected values (Table 2). Correlation statistics were performed with the variability shared by total intracranial volume partialed out.

Because gender differences may be an issue, after combining male and female hippocampal and temporal volumes, these structures were examined separately by gender. There were insufficient subjects to assess gender differences by decade.

Reliability.—An initial rater was trained under the direction of a neuroradiologist, following previously described methods (30). A randomly selected group of 17 MR images was used for intrarater and interrater reliabilities. This group of images was analyzed at two separate times by the initial rater to determine the intrarater reliability. The intrarater reliability coefficient for the hippocampus was 0.92 (combined left and right) and 0.99 (combined left and right) for the temporal horns. An additional rater was similarly trained, and this person analyzed the group of 17 images to determine the interrater reliability, which was 0.87 for the hippocampus and 0.99 for the temporal horns.

Imaging Plane. The irregular and tapering shape of the hippocampus and its obliquity pose several technical difficulties in terms of accurate quantitative image analysis

TABLE 1: Hippocampal and temporal horn volumes by decade, uncorrected for head size

Decade	n	Hippocampus						Temporal Horn					
		L		R		Total		L		R		Total	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
16 to 25	16	2.68	0.33	2.73	0.3	5.41	0.58	0.37	0.22	0.34	0.11	0.70	0.27
26 to 35	15	2.47	0.31	2.58	0.3	5.05	0.56	0.23*	0.09	0.30	0.15	0.53	0.19
36 to 45	18	2.51	0.19	2.56	0.3	5.07	0.43	0.26	0.11	0.31	0.14	0.57	0.23
46 to 55	23	2.38*	0.27	2.41*	0.2	4.80*	0.47	0.24	0.09	0.28	0.13	0.52	0.21
56 to 65	24	2.36*	0.30	2.45*	0.3	4.81*	0.56	0.30	0.14	0.36	0.19	0.66	0.30
	F	3.84		4.19		4.26		2.82		1.02		2.02	
	P	.006		.0037		.0033		.030		.400		.100	

* A significant difference from the 16 to 25 decade using Tukey's studentized range test, $P < .05$.

TABLE 2: Hippocampal and temporal horn volumes by decade, corrected for head size

Decade	n	Hippocampus						Temporal Horn					
		L		R		Total		L		R		Total	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
16 to 25	16	2.63	0.28	2.68	0.25	5.30	0.51	0.36	0.21	0.33	0.11	0.69	0.26
26 to 35	15	2.61	0.32	2.72	0.27	5.33	0.56	0.24	0.10	0.32	0.16	0.56	0.21
36 to 45	18	2.55	0.28	2.58	0.24	5.14	0.48	0.26	0.11	0.32	0.14	0.57	0.22
46 to 55	23	2.54	0.34	2.57	0.33	5.11	0.65	0.26	0.10	0.30	0.13	0.56	0.22
56 to 65	24	2.42	0.22	2.51	0.19	4.93	0.40	0.31	0.14	0.36	0.18	0.67	0.28
	F	1.60		1.97		1.84		2.13		0.68		1.37	
	P	.18		.11		.13		.08		.60		.25	

(8, 44). Accordingly, several researchers have used oblique coronal images for making hippocampal volume estimates (21, 42, 43, 45–47), whereas other investigators have used coronal images (48–50). Preliminary to this normative study, we compared 10 subjects to determine any possible differences between the use of coronal versus oblique coronal MR images for obtaining hippocampal and temporal horn volumes when interleaved identical sections of 3 mm thickness were acquired.

Ten subjects (eight men and two women) who were 27 to 65 years old (mean, 41 years) were examined. Eight were healthy volunteers who were recruited primarily from the hospital staff as part of a normative study at LDS hospital (30) and two were clinical patients seen for carbon monoxide poisoning.

Results were highly comparable between coronal and oblique coronal images for both hippocampus and temporal horn, with all intraclass correlations exceeding 0.90 (see Table 3). Paired *t* tests, which assess the mean difference from zero, showed no significant differences between coronal and oblique coronal images for hippocampal and temporal horn volumes (see Table 3). Pairing each score and finding no difference indicate that not only is there no significant difference in mean hippocampal volume between coronal and oblique coronal images but there was no systematic individual differences between these two techniques. Accordingly, for both studies we used images obtained in the coronal plane.

Statistical Analyses.—Age decades within gender were compared by using analysis of variance (ANOVA). Intercorrelations for volume structures were computed when variance shared with total intracranial volume was partialed. Gender comparisons using *t* tests were also performed.

Study 2

Subjects.—The total sample of persons with traumatic brain injury consisted of 94 subjects (59 male and 35 female). As indicated, these patients were divided into two groups. The early group (n = 45) consisted of patients admitted to the hospital's trauma unit and subsequently transferred to the in-patient rehabilitation unit. All such patients received MR neuroimaging and neuropsychological testing before and up to and including 100 days after injury. The late group (n = 55) included patients in whom neuroimaging and neuropsychological studies were performed more than 100 days after injury. Six of the patients in the late group received MR imaging both before and after 100 days following injury and thus appear in both groups. For consistency with previous research (39), we also analyzed the relationship between neuropsychological function and volumetry during the period of 71 to 210 days after injury. This is an intermediate interval in the recovery process, previously shown to relate possibly more to cognitive outcome (39).

TABLE 3: Hippocampus and temporal horn volumes (in cm^3) as quantified from coronal and oblique coronal MR images

	Mean	SD	*P* Value, *t* test	Correlation
R hippocampus, coronal	2.794	0.222	.792 (NS)	.928*
R hippocampus, oblique coronal	2.787	0.206		
L hippocampus, coronal	2.699	0.202	.536 (NS)	.903*
L hippocampus, oblique coronal	2.719	0.231		
Total hippocampus, coronal	5.493	0.409	.773 (NS)	.994*
Total hippocampus, oblique coronal	5.506	0.424		
R temporal horn, coronal	0.55	0.621	.155 (NS)	.984*
R temporal horn, oblique coronal	0.603	0.618		
L temporal horn, coronal	0.416	0.338	.365 (NS)	.975*
L temporal horn, oblique coronal	0.439	0.342		
Total temporal horn, coronal	0.965	0.947	.212 (NS)	.982*
Total temporal horn, oblique coronal	1.042	0.949		

Note.—NS indicates not significant.

* $P < .001$.

Injury Severity.—The mean initial Glasgow Coma Score (GCS) for the early group was 7.97 (range, 3 to 15); the mean GCS for the late group was 7.12 (range, 3 to 15), a nonsignificant difference. Because severity of injury may play a role in the degree of trauma-induced atrophy of the hippocampus, four arbitrary groups differing in injury severity were compared: very severe (GCS = 3 to 5), severe (GCS = 6 to 8), moderate (GCS = 9 to 12), and mild (GCS = 13 to 15).

All patients met the minimum criteria for brain injury in terms of the traumatic brain injury model systems database definition (51) and generally were in the moderate to severe range of brain injury (GCS $\leq$ 9). The mean age of the entire sample of patients with traumatic brain injury was 27 years (SD = 9), whereas the mean age of the control group, consisting of all cases described for study 1, was 31 years (SD = 8). The difference in age was statistically significant. Because of the direction of the difference (ie, control group older by an average of 4 years), it can be inferred that any differences in brain morphology between the two samples were not age related if the traumatic brain injury values indicate atrophy as compared with the slightly older control subjects. For hippocampal and temporal horn measurements, MR images were obtained and analyzed as previously described for study 1. All other brain structures were analyzed on axial images, as specified in our previous study (30).

Neuropsychological Tests.—The Wechsler Memory Scale–Revised (WMS-R) (52) was administered to a subset of the patients with traumatic brain injury (n = 44) along with the Wechsler Adult Intelligence Scale–Revised (WAIS-R) (n = 56) (53). Both measures were administered as a routine clinical follow-up procedure as standard practice for patients with traumatic brain injury seen at LDS hospital. Imaging for this investigation began before implementation of routine neuropsychological tests for all brain injury subjects. Thus, although there was no selection bias as to which patients received the neuropsychological tests, some patients were scanned before the implementation of the standard neuropsychological protocol and some patients had missing data (ie, all subtests were not administered). Hence, memory and intelligence testing were not available for all subjects who underwent scanning. The WMS-R Verbal Memory Index (VerMI) and Visual Memory Index (VisMI) were used as estimates of general memory functioning. The verbal IQ (VIQ) and performance IQ (PIQ) scores were calculated from the WAIS-R as estimates of general cognitive ability. Average time to neuropsychological testing was 503 days (SD = 708). These neuropsychological measures were compared with hippocampal and temporal horn volumes.

Statistical Analyses.—The findings in the early and late groups were compared with those of control subjects by using ANOVA. Partial correlations, when variance shared with total intracranial volume was removed, were computed within volume measures and between volume measures and cognitive function. For correlations with cognitive function, hippocampal and temporal horn volumes were converted to *z* scores by using the distributions of the normative data by gender group.

Results

Study 1

Tables 1 and 2 summarize the volumetric findings for hippocampal and temporal horn measures over the five decades investigated in this study. Table 4 provides a matrix of partial correlations between the various morphologic measures combined across decades. Although hippocampal volume is modestly negatively correlated with age ($r = -.33$, $P = .001$), statistical analysis (ANOVA) across decades did not yield a significant age effect for either left, right, or total hippocampal volume (see Table 2). This lack of age effect in hippocampal volume is depicted in Figure 3. As presented in Table 4, hippocampal volume did not correlate with temporal horn volume or any other mea-

TABLE 4: Pearson partial correlation matrix combined across decades comparing hippocampus with other morphologic measures and age (n = 96)

	L Horn	R Horn	Total Horn	L Hippocampus	R Hippocampus	Total Hippocampus	Ventricle-to-Brain Ratio
L horn	1	. . .	. . .	. . .	. . .	. . .	. . .
	0						
R horn	0.489	1	. . .	. . .	. . .	. . .	. . .
	0.0001	0					
Total horn	0.855	0.871	1	. . .	. . .	. . .	. . .
	0.0001	0.0001	0				
L hippocampus	0.078	0.083	0.093	1	. . .	. . .	. . .
	0.4552	0.4212	0.3681	0			
R hippocampus	0.187	0.217	0.235	0.823	1	. . .	. . .
	0.0692	0.0344	0.022	0.0001	0		
Total hippocampus	0.135	0.154	0.168	0.960	0.949	1	. . .
	0.1906	0.1373	0.1043	0.0001	0.0001	0	
Ventricle-to-brain ratio	0.295	0.204	0.287	−0.188	−0.176	−0.191	1
	0.0038	0.0477	0.0048	0.0674	0.0888	0.0637	0
Age	−0.025	0.094	0.042	−0.303	−0.320	−0.326	0.368
	0.8075	0.3635	0.6879	0.0029	0.0015	0.0013	0.0002

Note.—For each cell the top number represents the Pearson partial correlation and the bottom number the *P* value.

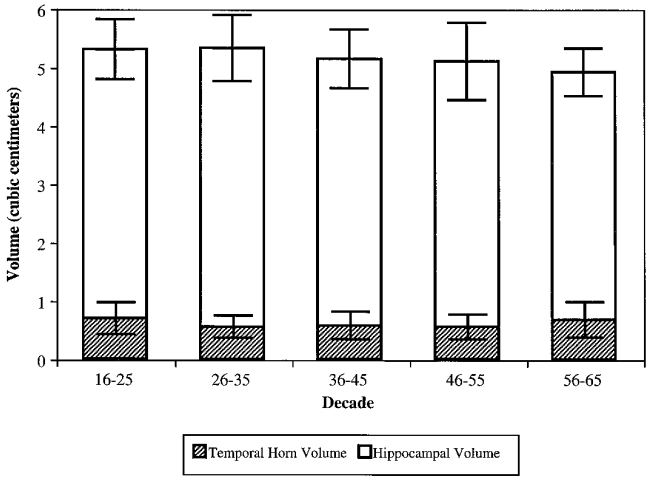

Fig 3. Bar graph compares hippocampal and temporal horn volumes by decade. Although there is a slight trend toward a decrease in hippocampal size with age, it is not significant. *Bars* represent standard deviation.

sure of the ventricular system. Left and right hippocampal volumes did not differ significantly, and were highly interrelated (r = .85, $P \leq$ .001). Temporal horn volume did not significantly change with age (see Table 2 and Fig 3). Left and right temporal horn volumes were significantly interrelated (r = 0.52, $P \leq$ .001).

Gender differences are presented in Table 5. Although males had a larger absolute hippocampal volume than females, when hippocampal volume was corrected for head size, females had a larger hippocampal formation relative to cranial volume. When corrected for head size, temporal horn volume did not show a difference by gender.

Study 2

Hippocampal Volume.—Although there was only a modest decrease (9%), the reduced hippocampal volume in the late group was significantly different from that of control subjects (see Table 6). Reduction in hippocampal size was bilaterally similar as shown by no difference between left and right hippocampi (see Table 6). Hippocampal size was positively correlated with GCS (r = .51, $P \leq$ .0001). As expected, reduction in hippocampal volume appeared to be time dependent following injury, as hippocampal size in the early group did not differ significantly from that of control subjects; however, hippocampal volume was significantly smaller in the late group (see Table 6).

Temporal Horn Volume.—Temporal horn volume increased significantly as a consequence of trauma (see Table 6) in both the early and late groups. The increase was bilateral with no significant difference between left and right. Temporal horn volume was inversely correlated with GCS (r = .34, $P <$ .09) and the greatest increase in temporal horn size occurred in the severe and very severe groups (GCS $\leq$ 8, see Fig. 4). The temporal horn was slightly larger in the early group than the late group.

Relationship of Hippocampal and Temporal Horn Volume to Chronicity of Injury.—The relationship between temporal horn size and hip-

TABLE 5: Comparison of hippocampal and temporal horn volumes by sex

Uncorrected for head size	n	Hippocampus						Temporal Horn					
		L†		R†		Total*		L§		R‡		Total‡	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Female	59	2.39	0.26	2.45	0.24	4.85	0.48	0.26	0.13	0.29	0.14	0.55	0.23
Male	37	2.58	0.32	2.65	0.29	5.23	0.59	0.31	0.15	0.36	0.16	0.67	0.28
Corrected for head size	**n**	**L†**		**R†**		**Total***		**L§**		**R§**		**Total§**	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Female	59	2.6	0.28	2.66	0.25	5.27	0.51	0.28	0.14	0.31	0.14	0.6	0.24
Male	37	2.43	0.28	2.5	0.24	4.92	0.51	0.29	0.13	0.34	0.15	0.63	0.25

* $P \leq .001$.
† $P \leq .01$.
‡ $P \leq .05$.
§ Not significant.

TABLE 6: Mean corrected hippocampal and temporal horn volumes by TBI status

	Control Subjects		Early Group		Late Group		F	*P*
	Mean	SD	Mean	SD	Mean	SD		
Total hippocampus	5.14	0.54	4.91	0.54	4.82*	0.65	6.10	0.0027
L hippocampus	2.54	0.29	2.43	0.27	2.35*	0.35	6.96	0.0012
R hippocampus	2.6	0.26	2.48	0.32	2.47*	0.32	4.35	0.014
Total temporal horn	0.61	0.25	1.36*	1.57	1.08*	0.97	11.38	0.0001
L temporal horn	0.28	0.14	0.58*	0.54	0.56*	0.66	9.98	0.0001
R temporal horn	0.33	0.15	0.78*	1.12	0.53	0.47	7.87	0.0005
n	96		46		57			

Note.—Early group includes patients with traumatic brain injury who received neuroimaging and neuropsychological testing before and up to and including 100 days after injury; late group includes patients in whom neuroimaging and neuropsychological studies were done more than 100 days after injury.

* A significant difference from control group, using Tukey's studentized range test, $P < .05$.

pocampal volume was time dependent following injury. Up to 100 days after injury, the correlation was essentially nonexistent ($r = -.02$). However, more than 100 days after injury, the correlation was negative and significant ($r = -.41$, $P = .002$).

Relationship of Hippocampal and Temporal Horn Volume to Other Morphologic Measures.— Total brain volume and volume-to-brain ratio were compared with hippocampal and temporal horn measures and are given in Table 7. Partial correlations were used for this analysis to control for variability shared with total intracranial volume. Several of the partial correlations were significant between the hippocampus and other brain measures, both before and after 100 days since injury. However, after 100 days many of the correlations were greater in magnitude.

Relationship of Hippocampal and Temporal Horn Volume to Neuropsychological Function.— Partial correlation coefficients, where covariance with total intracranial volume was removed, were computed between clinically obtained cognitive measures (VIQ, PIQ VerMI, and VisMI) and hippocampal and temporal horn volumes (see Table 8). Small but significant correlations were found. The left temporal horn correlated with VIQ. The right horn correlated with PIQ. Left hippocampal volume correlated with PIQ and VerMI. Right hippocampal volume was not significantly correlated with any of the outcome measures.

For patients imaged 71 to 210 days after injury, several significant relationships were found (see Table 9). Left temporal horn volume correlated significantly with VIQ ($r = -.70$, $P = .005$). Right temporal horn volume correlated significantly with PIQ ($r = -.698$, $P = .006$). Both right and left hippocampal volumes correlated with verbal memory function above $r =$

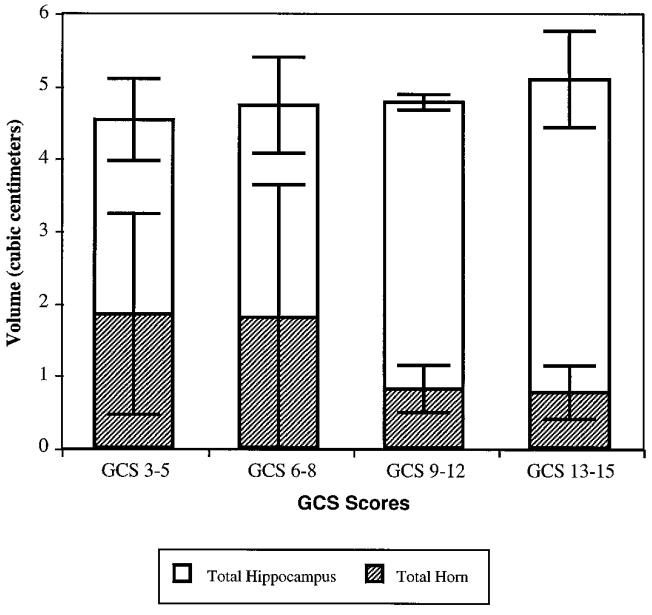

Fig 4. Total hippocampal and temporal horn volumes by severity of injury. Note the significant yet apparently equal increase in temporal horn size when GCS was ≤8. *Bars* represent standard deviation.

.70. However, neither correlated significantly with visual memory.

Discussion

The first objective of any normative study such as this is to demonstrate reliability and validity of the measurement methods used and the generalizability of the findings. Recently there has been considerable discussion concerning various methods of MR-based volume estimates of the hippocampus (8, 18, 42, 54, 55). Obviously, with different imaging parameters and quantification techniques, differences in hippocampal volume would be expected (42, 55). Free et al (18) reported a mean hippocampal volume of 2.75 cm^3 for the left and 2.80 cm^3 for the right hippocampus. Jack et al (43) reported a mean of 2.5 cm^3 for the left and 2.8 cm^3 for the right hippocampus. The normative findings in the current study are consistent with these reports. However, others have reported somewhat larger values (42, 55). Thus, caution needs to be used in generalizing specific values of hippocampal volume from one study to another. Nonetheless, the method reported here provides reliable normative data for hippocampal volume from ages 16 to 65, obtained in the coronal plane, with thin-section acquisition. By using this method we obtained good interrater reliability and consistency between our findings and those of others.

Although there was a modest negative correlation between age and hippocampal volume when corrected for head size, there was no significant difference with age in hippocampal volume from age 16 to 65. Thus, in healthy persons, hippocampal volume remains stable from late adolescence through the mid-seventh decade of life. The other point to be made about the stability of hippocampal volume is that left and right hippocampi remain generally symmetric and stable in size over this five-decade time span. Other studies also have suggested general symmetry of the left and right hippocampi (8, 18, 42, 55–57).

These two points—stability of hippocampal volume over five decades of life and the high symmetry between left and right hippocampi—have considerable clinical importance. Although in the current study there was a slight bias toward the right hippocampus being larger, a finding that has consistently been observed by others (18, 24, 27, 43), the left-right hippocampal correlation was .85. Because of the high similarity between right and left hippocampal volume, deviation from this symmetry may provide significant implications for lateralized abnormality (56). Second, this study provides objective methods for comparing hippocampal volume (either left, right, or total) in any given patient, correcting for head size and age.

Another major finding of this investigation, in normal aging up to age 65, is that temporal horn volume and hippocampal volume are not significantly related. It needs to be stressed that this is a normative sample and other studies have demonstrated a relationship between hippocampal atrophy and temporal horn enlargement in various pathologic states (31, 33) (see also study 2). Nonetheless, in healthy persons, the size of the hippocampus and temporal horn appear to be independent (58). As with the hippocampus, total temporal horn volume does not differ significantly with age. Left and right temporal horn volumes exhibited good symmetry and were significantly interrelated ($r = .52$) but not to the degree that hippocampal volumes are interrelated. The observation that this left-right temporal horn correlation was not as robust as the left-right hippocampal volume interrelationship, and the lack of relationship between hippocampal size and temporal horn volume, further specifies the independence of

TABLE 7: Pearson partial correlations of various intracranial structures by status after injury

	Early Group (n = 45)			
	Age	Hippocampus	Brain Volume	Ventricle-to-Brain Ratio
Hippocampus	−0.286 0.0565	. . .	. . .	. . .
Brain volume	−0.422 0.0039	0.325 0.0296	. . .	. . .
Ventricle-to-brain ratio	0.143 0.3488	−0.178 0.243	−0.680 0.0001	. . .
Temporal horn	−0.061 0.6915	−0.022 0.8841	−0.500 0.0005	0.845 0.0001
	Late Group (n = 55)			
	Age	Hippocampus	Brain Volume	Ventricle-to-Brain Ratio
Hippocampus	−0.277 0.0405	. . .	. . .	. . .
Brain volume	−0.430 0.001	0.536 0.0001	. . .	. . .
Ventricle-to-brain ratio	0.217 0.1108	−0.551 0.0001	−0.729 0.0001	. . .
Temporal horn	0.073 0.5948	−0.408 0.002	−0.381 0.0041	0.741 0.0001

Note.—Partial correlations remove covariance with total intracranial volume; the top number in each cell represents the Pearson partial correlation, the bottom number is the *P* value.

TABLE 8: Partial correlations of hippocampus and temporal horn to memory and intellectual function for the patients with traumatic brain injury in the late group

	VIQ	PIQ	VerMI	VisMI
L temporal horn	−0.293 0.035 53	−0.260 0.063 53	−0.006 0.970 43	−0.102 0.537 40
R temporal horn	−0.269 0.054 53	−0.303 0.029 53	−0.157 0.321 43	−0.288 0.076 40
L hippocampus	0.184 0.192 53	0.318 0.022 53	0.305 0.050 43	0.107 0.516 40
R hippocampus	0.075 0.595 53	0.249 0.075 53	0.198 0.210 43	−0.029 0.863 40

Note.—Partial correlations remove covariance with total intracranial volume; the top number in each cell represents the Pearson partial correlation, the middle number is the *P* value, and the bottom number is the number of observations in the correlation. VIQ indicates verbal IQ; PIQ, performance IQ; VerMI, Wechsler Memory Scale–Revised Verbal Memory Index; and VisMI, Wechsler Memory Scale–Revised Visual Memory Index.

these two structures. One interpretation may be that the temporal horn is much more related to the integrity of the entire temporal lobe than it is a passive, indirect index of hippocampal integrity.

From the normative standpoint, morphologic differences in gender are of interest. Filipek et al (57) provided a detailed morphometric analysis of 10 male and 10 female healthy subjects ranging in age from 17 to 37 years. Their findings demonstrated some degree of sexual dimorphism in the hippocampus. After correcting for head size, they found that the hippocampus in females was larger than that of males. We found the same relationship in this study (see Table 5).

TABLE 9: Partial correlations of hippocampus and temporal horn to memory and intellectual function: 71 to 210 days after injury

	VIQ	PIQ	VerMI	VisMI
L temporal horn	−0.700	−0.484	−0.360	−0.278
	0.005	0.079	0.206	0.359
	15	15	15	14
R temporal horn	−0.364	−0.698	−0.370	−0.523
	0.200	0.006	0.192	0.067
	15	15	15	14
L hippocampus	0.346	0.464	0.703	0.282
	0.225	0.094	0.005	0.351
	15	15	15	14
R hippocampus	0.300	0.348	0.771	0.096
	0.255	0.223	0.001	0.755
	15	15	15	14

Note.—Partial correlations remove covariance with total intracranial volume; the top number in each cell represents the Pearson partial correlation, the middle number is the *P* value, and the bottom number is the number of observations in the correlation. VIQ indicates verbal IQ; PIQ, performance IQ; VerMI, Wechsler Memory Scale–Revised Verbal Memory Index; and VisMI, Wechsler Memory Scale–Revised Visual Memory Index.

In summary, study 1 demonstrates the stability of the hippocampus and temporal horn over five decades of life (16 to 65 years). In the normal, healthy person, hippocampal size does not correlate with size of the temporal horn. The hippocampi and temporal horns have a high degree of symmetry and this symmetry, likewise, is stable over these five decades. The clinical utility of this normative database is evidenced by its use in comparison with pathologic states, such as in patients with traumatic brain injury. We used the normative data from study 1, to examine the effects of traumatic brain injury on hippocampal and temporal horn volume, as well as on neuropsychological outcome (study 2). A discussion of these effects follows.

Results of study 2 describe atrophic changes in the hippocampus detected by MR morphometric analysis. However, these atrophic changes were quite modest and only mildly correlated with temporal horn enlargement. The time sequence of associated changes in the hippocampi and temporal horns is also of interest. Reduction in hippocampal size stabilizes sometime after 100 days following injury. In contrast, the temporal horn initially enlarges to a maximum value somewhere in the first 100 days, then decreases to a stable level (still twice the size of normal) thereafter. Some transient localized CSF change at the temporal horn level is a possibility during the early course of recovery (39).

Although a significant reduction in hippocampal volume with a corresponding increase in temporal horn size occurs as a result of trauma, these alterations in size correlated only modestly with general indexes of memory and intelligence in the late group. However, when looking at a particular time period in recovery (71 to 210 days after injury) we found the temporal horns were highly predictive of intellectual function and the hippocampi were highly related to verbal memory function. Previous research has shown time since injury to be a critical variable in evaluating morphometric relationships with cognitive function (39). The limitation of the sample size in this subgroup precludes definitive conclusions at this point, but these strong relationships suggest two ideas for further study: The hippocampus and temporal horn appear to be highly related to later cognitive function at certain stages following injury; and a particular time frame for predicting outcome may be more advantageous than others. Before or during this time frame (roughly 2.5 to 7 months after injury) a large portion of the degeneration bound to occur after traumatic brain injury will take place (39). Additionally, physiological and environmental compensatory mechanisms probably occur during an extended period beyond this time frame of 71 to 210 days after injury. As the damaged brain adapts to injury beyond this time frame, these data suggest that there are less robust relationships between structure and cognitive function. It also may be that more detailed analysis of the hippocampus in terms of regional differences within the hippocampal formation may provide greater specificity for structure-function relationships (59).

As previously mentioned, the significant correlation between hippocampal and temporal horn volume in patients with traumatic brain injury is modest ($r = -.41$). In contrast, the temporal horn correlation with ventricle-to-brain ratio is particularly robust ($r = .84$ in the early group; $r = .73$ in the late group). Since ventricle-to-brain ratio is thought to be an index of general brain integrity (36, 60, 61), it may be that the stronger correlation between temporal horn and ventricle-to-brain ratio is due to non-hippocampal changes, particularly at the temporal cortical level.

In conclusion, study 1 demonstrates the stability of the hippocampus in healthy control subjects over five decades and that, in the normal brain, temporal horn and hippocampal volumes appear to be independent. However, as indicated in study 2, traumatic brain injury results in a decrease in hippocampal volume and an increase in temporal horn volume. In the pathologic state of cerebral trauma, temporal horn size and hippocampal volume are inversely related. Although hippocampal atrophy may contribute to temporal horn enlargement, temporal horn dilatation is probably more related to temporal lobe rather than hippocampal integrity. In the subacute phase of recovery, these structures may be predictive of long-term cognitive function.

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