Volume of focal brain lesions and hippocampal formation in relation to memory function after closed head injury in children

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Abstract

Objectives—(1) A study of verbal learning and memory in children who had sustained a closed head injury (CHI) at least 3 months earlier. (2) To relate memory function to focal brain lesion and hippocampal formation volumes using morphometric analysis of MRI.

Methods—A group of 245 children who had been admitted to hospital for CHI graded by the Glasgow coma scale (GCS), including 161 patients with severe and 84 with mild CHI completed the California verbal learning test (CVLT) and underwent MRI which was analysed for focal brain lesion volume independently of memory test data. Brain MRI with 1.5 mm coronal slices obtained in subsets of 25 patients with severe and 25 patients with mild CHI were analysed for hippocampal formation volume. Interoperator reliability in morphometry was satisfactory.

Results—Severity of CHI and age at study significantly affected memory performance. Regression analysis showed that bifrontal, left frontal, and right frontal lesion volumes incremented prediction of various learning and memory indices after entering the GCS score and age into the model. Extrafrontal lesion volume did not contribute to predicting memory performance.

Conclusions—Prefrontal lesions contribute to residual impairment of learning and memory after severe CHI in children. Although effects of CHI on hippocampal formation volume might be difficult to demonstrate in non-fatal paediatric CHI, further investigation using functional brain imaging could potentially demonstrate hippocampal dysfunction.

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Keywords: head injury; magnetic resonance imaging; verbal learning and memory; frontal lobe; hippocampus

Previous research on the neurobehavioural sequelae of closed head injury (CHI) in children has shown that learning and memory are impaired as a function of injury severity and age. Children with severe head injury show substantial impairment of memory¹ and other cognitive functions.² Although two studies have reported that the effects of CHI severity on cognition are most notable in children younger than 10 years,^{3 4} Levin *et al*⁵ found that adolescents initially exhibited a more marked impair-

ment of verbal learning and memory after severe CHI relative to the outcome in children.

In adults, there is wide agreement that declarative memory—such as the capacity for acquisition and recall of word lists—mainly depends on an intact hippocampal system.^{6 7} Neuropsychological studies of patients with mesial temporal lobe lesions and animal models have demonstrated convincingly that declarative memory depends on the integrity of the hippocampal formation and its surrounding tissue—that is, perirhinal and parahippocampal cortex.⁸ Neuropathological studies have disclosed that hippocampal lesions are generally present after fatal CHI in adults and children.^{9 10} Although hippocampal damage after CHI has been traditionally attributed to decreased cerebral perfusion secondary to raised intracranial pressure (ICP), Kotapka *et al*¹¹ reported that hippocampal lesions were present in 12 of 14 fatal cases of CHI in adults whose measured ICP was less than 20 mm Hg. The hippocampal lesions in these cases were typically bilateral and situated in the CA 1 subfield, a distribution similar to the findings in a non-impact primate model of acceleration head injury.⁹ Magnetic resonance imaging has further corroborated the important role of the hippocampal formation in declarative memory. In a study¹² that compared MRI volumetry and memory in adults with head injury, memory impairment was related to the degree of hippocampal atrophy, particularly in the left hippocampus. However, Bigler *et al*¹³ found that a significant reduction in volume relative to normal controls was confined to the left hippocampus of adults with head injury who underwent MRI more than 3 months (mean interval was about 2 years) after injury.

In view of the demands on children's verbal learning and memory imposed by their school curriculum, elucidating the determinants of recovery after CHI is clinically relevant. Initial MRI studies in children with head injury showed that verbal memory was related to frontal lobe lesion size.^{4 13} Another MRI volumetric study of severe CHI in children documented tissue loss in the prefrontal region, even in the absence of abnormal signal areas.¹⁴ In the absence of comprehensive studies on the relation between MRI volumetry and verbal learning and memory in children with head injury, we explored the relations between various aspects of verbal learning and memory and both focal brain lesions and hippocampal volume disclosed by MRI after paediatric head injury.

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Table 1 Demographic and clinical features of severely and mildly head injured children in the study

	Severe CHI (n=161)	Mild CHI (n=84)	p Value
Age at test (y) (mean (SD))	11.1 (3.6) (age range 5.5–17.6)	10.8 (3.4) (age range 5.8–16.1)	0.5
Age at injury (y) (mean (SD))	8.2 (3.7)	8.8 (3.8)	0.2
Injury-study interval (y) (mean (SD))	2.9 (3.3)	1.9 (2.4)	0.02
Parental education (y) (mean (SD))	13.7 (2.2)	14.2 (2.3)	0.1
GCS score (mean (SD))	5.7 (1.7)	14.6 (90.7)	<0.0001
Sex (n (%)):			0.8
Boys	101 (62)	51 (61)	
Girls (n (%))	60 (38)	33 (39)	
External cause of injury (n (%)):			
MVA	73 (45.34)	28 (33.30)	
MVA:pedestrian	55 (34.16)	7 (8.33)	
Fall	9 (5.59)	25 (29.76)	
Recreation	10 (6.21)	11 (13.10)	
Hit by falling object	5 (3.11)	3 (3.57)	
Bicycle	2 (1.24)	7 (8.33)	
Assault	1 (0.62)	1 (1.19)	
Other	6 (3.73)	2 (2.38)	

MVA=motor vehicle accident; GCS=Glasgow coma score.

Methods

SUBJECTS

Our sample included 245 children who had been admitted to hospital after having sustained a CHI at least 3 months before memory testing (table 1). The full range of CHI severity was represented in the sample provided that the child recovered consciousness and could cooperate. Severe CHI was defined as an injury producing a lowest post-resuscitation GCS score of 8 or less at any time during the initial hospital stay, whereas a mild CHI was defined as an injury resulting in a period of unconsciousness of 20 minutes or less, a lowest GCS score of 13 to 15, normal neurological findings, normal MRI findings, and no severe extracranial injury. According to these definitions, 84 children had sustained a mild CHI and 161 children had sustained a severe CHI. Age at test, age at injury, parental education, and sex distribution did not differ significantly between the two severity groups (table 1). Although the mean postinjury interval was longer in the patients with severe CHI, the mild CHI group was studied after a mean postinjury interval longer than 1 year. Relatively high velocity injuries involving motor vehicles predominated in the severe CHI group, whereas falls were more common in the mild CHI group (table 1).

MEASUREMENT OF FRONTAL AND EXTRAFRONTAL LESION SIZE

MRI acquisition

A 0.5 T Toshiba system (Toshiba American Medical Systems, South San Francisco, CA, USA) was used to obtain T1 weighted (repetition time (TR), 600/30 ms), 5 mm midsagittal images for 62 patients studied from March 1990 to August 1991. Coronal T1 weighted (TR, 300/20 ms) and T2 weighted (TR, 3000/30/120 ms), unenhanced images were also obtained using a 7.5 mm slice thickness and a 1.5 mm gap. Beginning in August 1991, patients (n=183) were imaged using either a 1.5 T Picker (Picker International, Highland Heights, Ohio) or a 1.5 GE (General Electric, Milwaukee, WI, USA) magnet to obtain 5 mm three dimensional Fourier transformation T1 weighted sagittal and coronal images (26/10/30

TR/TE/flip angle). In addition, 5 mm T2 weighted (TR, 2817/20/80 ms) coronal images were done with no gap. All of the MRI scans were reviewed by a neuroradiologist. The findings were entered on a coding form that specified the location of each focal area of abnormal intensity and atrophy, including specific gyri of the frontal lobes.

Volumetric analysis

All intracranial lesions were measured using a Jandel planimeter (Jandel Scientific, San Rafael, CA, USA) connected to a microcomputer. The area of each lesion was measured on successive slices and summed to obtain a total volume using IMG, a program with a manual outlining procedure.¹⁵ None of the 84 patients with mild CHI was included in the focal lesion study because the selection criteria for this group included normal MRI findings.

Interobserver reliability

The MR images of 11 patients with CHI were analysed independently by two observers. The mean age of the patients was 8.4 years (SD 0.98), their mean post-resuscitation GCS score was 8.2 (SD 6.1), and the mean interval from injury to MRI was 749.8 days (SD 197.6). A total of 14 focal brain lesions (one patient had three lesions) were measured by each observer using Sun Sparc LX 20 platforms. After the lesions were identified by a neuroradiologist, each operator outlined the area of abnormal signal and measured the area (number of 0.859x0.859 mm pixels) on consecutive, interleaved 3 mm T2 coronal slices. The Pearson correlation coefficient between the number of pixels measured by each observer was 0.9998 and the mean percentage difference in the number of pixels measured by each observer was 2.9 (SD 2.9).

HIPPOCAMPAL VOLUME MEASUREMENT

MRI acquisition

For hippocampal volume analysis, a GE Signa 1.5 T system (General Electric, Milwaukee, WI, USA) was used to obtain T1 weighted 1.5 mm coronal images for 50 more recently studied patients (25 children with mild CHI and 25 with severe CHI). The images were displayed on a 256x128 matrix, with a field of view of 22 cm and a pixel size of 0.74 mm. The images were acquired with no gap. All MR scans were reviewed by a neuroradiologist independent of the cognitive data.

Method of volume measurement

The most anterior slice containing the hippocampal formation was identified by the appearance of either the shallow hippocampal sulcus (for example, digitation) between the amygdala and the hippocampus, or the presence of the white matter of the alveus. When neither the digitation nor the alveus could be clearly discerned, a line was drawn from the superior border of the temporal horn horizontally to the ambient cistern, to dissociate the amygdala dorsally from the hippocampus ventrally. Medially this line cut the uncus. The most posterior slice of the hippocampal formation was

Table 2 Description of California verbal learning test measures included in this study

Memory aspect	Variable name	Description
Immediate free recall	Correct Monday	Total number of the 15 list A words recalled on learning trials 1 to 5.
Learning characteristic	Cluster Monday	Total number of list A words recalled immediately after a word from the same semantic category on learning trials 1 to 5.
Recall errors	Perseverations Monday Intrusions Monday	Total number of repeated responses on learning trials 1 to 5. Total number of non-target items reported on learning trials 1 to 5.
Susceptibility to interference	Correct Tuesday	Number of words recalled immediately after presentation of list B (15 words).
Short delay (5 min) recall	Short delay free recall Short delay cued recall	Total number of list A words recalled immediately after presentation of list B. Total number of list A words recalled immediately after presentation of list B when semantic categories were provided.
Long delay (20 min) recall	Long delay free recall Long delay cued recall	Total number of list A words recalled after a 20 minute delay. Total number of list A words recalled after a 20 minute delay when semantic categories were provided.
Recognition	Correct recognitions	Number of list A words correctly identified among a list of words including distractor items.

that clearly showing the crus of the fornix emerging from the hippocampal formation. On the most posterior slice, the gyrus fasciolaris, the fasciola cinerea, and the isthmus were excluded from the measurements.

On each coronal slice, the hippocampal formation was outlined by drawing a line along the superior aspect of the parahippocampal gyrus white matter ventrally, until reaching the ambient cistern medially, thus including the subiculum. From this point, the line curved dorsally following the choroidal fissure or superior aspect of the entorhinal cortex and then, laterally, immediately, above the alveus and fimbria. Laterally, the line followed the temporal horn. Using a semiautomated program, the hippocampal area was calculated for each successive slice and then summed to obtain the hippocampal volume. This measurement was performed for the left and right hemispheres separately.

Interobserver reliability

The observers were blind to severity of injury and neuropsychological test results. After an initial training period, two observers (GD and JB) measured hippocampal volumes in 10 randomly selected cases (five children with mild CHI and five with severe CHI). Interrater reliability (intraclass correlation coefficient) was $r=0.95$ for both the left and right hippocampal volumes.

A *t* test comparing the hippocampal volumes measured by the two operators was not significant ($p=0.2$), showing that the two operators did not disagree in a systematic way. Analysis of the remaining 40 cases was performed by GD. The measures of hippocampal volume were corrected for brain size. To do this, the intracranial area was measured on a midsagittal MR slice in each of the 50 cases. The intracranial area measured on a midsagittal plane is known to be a useful correction factor to normalise hippocampal volumes for interindividual differences in brain size.¹⁶ The previously computed measures of hippocampal volume were then divided by the obtained intracranial midsagittal area.

ASSESSMENT OF VERBAL LEARNING AND MEMORY

The California verbal learning test-children's version (CVLT)¹⁷ was employed to assess declarative memory, including the use of memory strategies to recall 15 nouns which were exemplars of three categories. The standard procedure for administration was followed. The CVLT variables included in the analysis are listed in table 2. In regard to our selection of a verbal test, the literature indicates that neuropsychological impairments after severe head injury are usually generalised regardless of whether the test material is verbal or non-verbal.¹⁸ Although cases with unilateral haematomas or contusions could possibly have material specific memory problems, this would be unusual. Additionally, plasticity mechanisms might apply to the patients in whom lateralised lesions contribute to the memory deficits, but this mechanism is unlikely to have a major role in diffuse injury. Consequently, we selected the CVLT, a task which has developmental norms.

STATISTICAL ANALYSIS

To elucidate the contribution of focal lesions to verbal learning and memory, hierarchical multiple regression analyses were used to determine whether lesion size could significantly improve the prediction of cognitive test scores obtained by using severity of injury and age at testing alone. Separate regression analyses were performed for left, right, and bilateral frontal and extrafrontal lesion size. In the analyses of hippocampal volume, 25 children with mild and 25 with severe head injury were compared. The relation between hippocampal volume and memory was also examined by using a multiple regression model.

Results

VERBAL LEARNING AND MEMORY PERFORMANCE

As reflected in table 3, performance on most verbal learning and memory variables was significantly affected by severity of injury and age at test, but no interaction of age with CHI severity was found. Compared with the mild

Table 3 Verbal learning and memory performance in the groups of children with severe or mild head injury (CHI) and the effects of severity of injury and age at test

	Severe CHI (n=161)		Mild CHI (n=84)		Severity of injury (p Value)	Age at test (p Value)
	Mean	(SD)	Mean	SD		
Correct Monday	40.8	14.3	50.6	10.9	0.0001	0.0001
Cluster Monday	12.3	7.7	18.5	9.8	0.0001	0.0001
Perseverations Monday	4.1	4.2	6.0	6.0	0.004	0.71
Intrusions Monday	2.9	5.3	1.9	2.8	0.13	0.0001
Correct Tuesday	5.0	2.3	5.6	1.9	0.03	0.004
Correct short delay free recall	7.4	3.8	10.1	3.3	0.0001	0.0001
Correct short delay cued recall	8.1	3.5	10.6	3.1	0.0001	0.0001
Correct long delay free recall	8.1	3.9	10.5	3.1	0.0001	0.0001
Correct long delay cued recall	8.4	3.9	10.9	3.2	0.0001	0.0001
Correct recognitions	13.0	2.7	13.7	1.8	0.03	0.0001

CHI group, the severely injured children had difficulty in learning and delayed recall for the Monday and Tuesday word lists, they produced fewer clusters, and recognised fewer words. By contrast, the children with severe head injury had fewer perseverative errors (repetition of words on the five learning trials of the Monday list) than the mild CHI group. With the exception of the number of perseverations, age at testing was significantly related to verbal learning and memory variables, as older children exhibited better performance.

FRONTAL AND EXTRAFRONTAL LESION ANALYSIS

Because normal MRI findings were used to select our mild CHI group, an analysis of lesion size was confined to the severe CHI group. Bifrontal (n=97, mean total lesion size=6.92, (SD 19.79)), left frontal (n=72, mean=4.11, (SD 7.65)), right frontal (n=71, mean=5.28,

(SD 17.09)), bilateral extrafrontal (n=84, mean=7.40, (SD 16.08)), left extrafrontal (n=44, mean=3.05, (SD 7.10)), and right extrafrontal lesion size (n=61, mean=7.99, (SD 17.85)) were analysed separately. Among extrafrontal lobe lesions, the most common locations were temporal lobe (n=70, 25.2%), parietal lobe (n=62, 22.3%), corpus callosum (n=56, 20.1%), basal ganglia (n=22, 7.9%), cerebellar hemisphere (n=17, 6.1%), occipital lobe (n=16, 5.8%), and others (n=35, 12.6%). Multiple lesions in the same patient were possible. To explore the contribution of focal lesion size, hierarchical multiple regressions were used to determine whether lesion size could significantly improve the prediction of each verbal learning and memory variable obtained by using severity of injury and age at testing alone. As illustrated in the figure, when bifrontal lesion size was entered into the regression equation after GCS score and age at test, it significantly improved prediction of recall of the Monday list, short delay free and cued recall, and the long delay free recall. A statistical trend was found for long delay cued recall. When entering left frontal lesion size into the regression equation, prediction of the Monday list and the short delay cued recall improved significantly, and a trend was found for short delay free recall. When right frontal lesion size was entered into the regression equation, prediction of short delay free recall and long delay free recall improved significantly, and a statistical trend was found for the Monday list, short delay cued recall, and long

Summary of the results of hierarchical multiple regression that evaluated the incremental contributions of bilateral frontal (top left), bilateral extrafrontal (top right), left frontal (middle left), left extrafrontal (middle right), right frontal (bottom left), and right extrafrontal (bottom right) lesions to predicting the verbal learning and memory test scores after entering the severity of injury and age at testing alone. Closed bars indicate R^2 when entering GCS score and age at testing into the regression equation; hatched bars indicate incremental R^2 when additionally entering lesion size into the regression equation. CORR MON=correct words on Monday list; CORR TUES=correct words on Tuesday list; CORR S=correct words on short delay free recall; CORR SC=correct words on short delay cued recall; PERS=perseverations on Monday list recall; INTR=intrusions on Monday list recall; CORR L=correct word on long delay free recall; CORR LC=correct word on long delay cued recall; RECOG=correct recognitions; CLTER=clusters on Monday list recall.

Table 4 Demographic and clinical features and hippocampal volume (HV), corrected for brain size, of the subsets of children with severe or mild head injury used for the HV analysis

	Severe CHI (n=25)		Mild CHI (n=25)		p Value
	Mean	(SD)	Mean	(SD)	
Age at test (y)	11.90	(3.64)	12.31	(2.91)	0.67
	(age range 5.9–17.0)		(age range 6.1–15.9)		
Age at injury (y) (mean (SD))	10.61	(3.18)	10.92	(3.10)	0.73
Injury-study interval (y) (mean (SD))	1.40	(1.39)	1.30	(1.39)	0.81
Parental education (y) (mean (SD))	13.72	(2.46)	14.54	(2.72)	0.27
GCS score	5.40	(1.87)	14.44	(0.71)	0.0001
Sex (n (%)):					
Boys	15	(60)	17	(68)	0.56
Girls	10	(40)	8	(32)	
Left HV (mean (SD))†	21.95	(3.66)	22.28	(2.40)	0.7
Right HV (mean (SD))†	21.36	(5.37)	23.38	(2.17)	0.09

GCS=Glasgow coma score. †Ratio obtained by dividing hippocampal volume by intracranial area to control for intersubject variation in brain size.

Table 5 Summary of regression analyses: predicting memory performance with severity of injury (GCS score), left HV and right HV

	Left HV (p Value)	Right HV (p Value)	Severity of injury (p Value)
Correct Monday	0.25	0.39	0.001
Cluster Monday	0.66	0.84	0.01
Perseverations Monday	0.71	0.88	0.57
Intrusions Monday	0.67	0.86	0.42
Correct Tuesday	0.55	0.37	0.05
Correct short delay free recall	0.19	0.17	0.001
Correct short delay cued recall	0.94	0.77	0.01
Correct long delay free recall	0.08	0.14	0.001
Correct long delay cued recall	0.74	0.94	0.01
Correct recognitions	0.01	0.16	0.001

delay cued recall. Further regression analyses were used to determine the improvement of prediction when entering bilateral extrafrontal, and left and right extrafrontal lesion size, but none reached a significant level.

HIPPOCAMPAL VOLUME ANALYSIS

In a subset of 50 children with head injury (25 severe CHI and 25 mild CHI) whose MRIs were performed using 1.5 mm slices, hippocampal volume was measured. As shown in table 4, the groups did not differ in age at injury, age at test, parental education, or sex.

There were no significant differences in the hippocampal volume of the mild and severe CHI groups (table 4). Attempts to predict memory performance in this group of 50 cases by entering left hippocampal volume, right hippocampal volume, and GCS score into the regression equations disclosed that the GCS score proved significant in eight out of 10 memory variables. Only a single significant variable (correct recognitions) was found for left hippocampal volume, and right hippocampal volume did not show any significant results (table 5).

Discussion

Consistent with previous research on neurobehavioural outcome of paediatric head injury,^{4 19} severity of injury and age at time of examination were found to affect verbal learning and memory. In a regression analysis, we evaluated whether lesion size (left frontal, right frontal, bifrontal, left extrafrontal, right extrafrontal, bilateral extrafrontal) measured from MRI at least 3 months after injury increased the infor-

mation obtained from GCS score and age at time of examination in accounting for individual differences in verbal learning and memory. Left, right, and bilateral frontal lesion size incremented prediction of various memory indices, whereas extrafrontal lesion size proved not significant. The adverse effect of bilateral frontal lesion size on verbal learning and memory was stronger than the separate effects of left or right frontal lesion size. These findings emphasise the importance of prefrontal injury for verbal learning and memory in children with head injury.

In adult patients with CHI, hippocampal atrophy has been demonstrated on MRI^{12 20} performed 3 months after injury. Using 3 mm coronal slices (compared with 1.5 mm in our study), Bigler *et al*¹² found that the reduction in volume relative to normal controls was confined to the left hippocampus. Apart from age differences between the patients of Bigler *et al*. and our paediatric patients, it is also possible that alcohol misuse was contributory to the findings in the adults (screening for alcohol misuse was not mentioned, but this comorbidity is common in patients with trauma). Differences in the software used to measure volumes and possibly variation in the anatomical landmarks could have also potentially contributed to the disparate findings. Hippocampal damage has also been found in fatal paediatric head injury.¹⁰ However, we found only a trend toward a smaller right hippocampal volume measured from MRI in the children with severe head injury that was not confirmed for the left hippocampal volume. Although the lack of consistent volumetric differences in the hippocampal formation of children with mild or severe head injury does not imply that this structure is unaffected by paediatric head injury, our study highlights the vulnerability of the frontal lobes in paediatric head injury and the potentially adverse effects of frontal lobe damage on learning and memory in children with head injury.

The most puzzling result of this study concerns the weak relation between hippocampal volume and verbal learning and memory. At first glance, this outcome seems difficult to understand, because the role of the hippocampus in memory processes, particularly declarative memory, has been demonstrated in various human and non-human primate studies.⁸ The memory impairment found in patients with hippocampal damage contrasts with the generally normal scores on commonly used memory tests in patients with frontal lobe damage.^{1 21}

However, various reports have highlighted the role of frontal lobes in memory processing. Frontal lobe lesions have been found to impair free recall of word lists similar to those used in this study.²¹ In another experiment, patients with frontal lobe damage were compared with patients with brain lesions outside the frontal lobe.²² Under the free recall condition 1 day after learning a list of 16 words, patients with frontal lobe lesion exhibited a drastically impaired performance. These findings and other studies²³ suggest that the frontal lobes contribute to memory processing by providing

useful organisational strategies. Frontal lobe lesions might also impair subtle aspects of memory function such as judgment of item recency, item frequency, and temporal order. This hypothesis has been corroborated by recent functional imaging results. In a PET study, human subjects were investigated during free recall of a list of words studied before scanning.²⁴ The results demonstrate the involvement of the left ventrolateral frontal cortex during recall of verbal information from long term memory. In another PET study of age effects during mnemonic processing, younger but not older persons showed significant blood flow increases in the anterior frontal lobes during attempted retrieval of previously studied words.²⁵ In accord with our findings, these results demonstrate the importance of the frontal lobes in specific aspects of mnemonic performance. For instance, frontal lobe damage might impair performance on memory tasks requiring strategic encoding and information retrieval. Fuster²⁶ has also shown in infrahuman primate experiments that the dorso-lateral prefrontal cortex is involved in maintaining information over a delay period. However, the pattern of memory deficit after severe CHI as detected in this study was found to be generalised, most likely due to diffuse axonal injury, multiple ischaemic lesions, and secondary injury due to excitotoxicity.¹⁸

An alternative explanation concerns differential maturation processes of neuronal structures contributing to memory, such as maturation of medial temporal structures that are essential for declarative memory versus maturation of neocortical areas that are served by these structures and are thought to be the repositories of long term memory.²⁷ Although the emergence of recognition memory during infancy in human and non-human primates has been interpreted as evidence for early maturation of the hippocampus,²⁸ other behavioural and anatomical findings indicate that hippocampal development might be more protracted. Firstly, the standard delayed non-matching to sample task, which requires recognition memory in addition to other abilities (for example, quick visual encoding), is mastered much later than elementary recognition memory.²⁸ Secondly, postnatal development of synaptic connections between granule cells and their postsynaptic target neurons reflects variable rates of maturation in the human hippocampus. Seress and Mrzljak²⁹ found that the granule cell layer in the human dentate gyrus was relatively mature at birth with elaborate axonal connections to the hilar region and CA3 area of Ammon's horn. However, these investigators also found that the proximal dendrites of mossy cells had a simple spine structure at birth which increased in number and complexity between 2.5 and 5 years of age. In general, postnatal development of synaptic connections in the hippocampal formation seems to be more rapid in the monkey than in humans.³⁰ Consistent with this view, myelination in a key relay zone of the hippocampal formation in humans continues throughout adolescence.³¹ Chugani *et al*³² studied recovery from temporal

lobectomy in epileptic children by PET. They found that peak cerebral metabolism declined after the age of 9 years, a finding they interpreted as reflecting reduced plasticity. However, our results suggest that prefrontal functioning is also relevant to memory performance as measured by CVLT. Huttenlocher *et al*³³ report prefrontal maturation continuing until mid-adolescence and being more prolonged than in other cortical regions. However, diffuse axonal injury and multiple ischaemic injury associated with severe CHI are quite different mechanisms than focal cortical lesions in vascular insult which have been the basis for the concept of greater plasticity in young children compared with adults. Levin *et al*³⁴ found that the most frequent site of lesion in children on late MRI was the frontal lobe white matter. This finding supports our view that disruption of white matter maturation might have adverse effects on cognitive development which do not recover to normal levels, especially when the severely injured child's performance is compared with peers of similar age over time. Finally, quantitative MRI of healthy children has documented marked heterogeneity in the growth of hippocampal volumes between 4 and 18 years.³⁵ Significant increase in hippocampal volume was confined to the right side in females, whereas the change in males was non-significant. By contrast, the only significant age related, volumetric change of mesial temporal lobe in males was an increase in the left amygdala. Taken together with the variable rates of functional maturation of subregions of prefrontal cortex in non-human primates,³⁶ an explanation of our findings based entirely on differences in maturation between the prefrontal and hippocampal formation seems unlikely.

Methodological limitations of this study could have also contributed to our marginal finding of hippocampal formation damage in children after severe CHI. The subset of children who had 1.5 mm slices provided less statistical power to detect severity group differences than the analysis of lesion size, which was based on the total severe CHI group. However, we also recognise that thinner slices would have been more sensitive to subtle hippocampal atrophy than the 1.5 mm slice thickness used in the present study. As the investigational MRI protocol in the present study was designed to provide broad anatomical coverage, it was not feasible to use much thinner slices to image the temporal lobes. Differences in statistical power also apply to the relatively few extrafrontal lesions, which we identified compared to prefrontal lesions. Because our total patient groups were recruited from consecutive admissions to neurosurgical services, we interpret the preponderance of prefrontal lesions as representative of severe CHI. Consistent with the major role of diffuse axonal injury in human and experimental CHI,³⁷⁻⁴⁰ Levin *et al*³⁴ reported that the frontal lobe white matter was the most frequent lesion site in their MRI study of paediatric CHI. An implication of this neuropathological and imaging evidence for frontal white matter injury is that post-traumatic

memory deficit could be due in part to prefrontal-hippocampal disconnection effects.

Utilisation of functional MRI could potentially elucidate residual hippocampal formation dysfunction that is not apparent from volumetric analysis.⁴¹ Although the present study was confined to a verbal learning and memory test, the explicit memory deficit resulting from CHI is not typically material-specific. Future studies could utilise functional MRI to assess deficient hippocampal activation as a residual deficit after paediatric CHI.

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