Developmental amnesia associated with early hypoxic–ischaemic injury

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Summary
We recently reported on three young patients with severe impairments of episodic memory resulting from brain injury sustained early in life. These findings have led us to hypothesize that such impairments might be a previously unrecognized consequence of perinatal hypoxic–ischaemic injury. Neuropsychological and quantitative magnetic resonance investigations were carried out on five young patients, all of whom had suffered hypoxic–ischaemic episodes at or shortly after birth. All five patients showed severe impairments of episodic memory (memory for events), with relative preservation of semantic memory (memory for facts). However, none had any of the major neurological deficits that are typically associated with hypoxic–ischaemic injury, and all attended mainstream schools. Quantitative magnetic resonance investigations revealed severe bilateral hippocampal atrophy in all cases.

Keywords: episodic memory; perinatal; hypoxic–ischaemic injury; hippocampus; magnetic resonance imaging

Abbreviations: Cho = choline-containing compounds; Cr = creatine + phosphocreatine; MQ = memory quotient; MRS = magnetic resonance spectroscopy; NAA = N-acetylaspartate; PIQ = performance IQ; VIQ = verbal IQ

Introduction
Hypoxic–ischaemic brain injury is recognized as a major cause of neurological morbidity, both in premature and in full-term infants (Volpe, 1995). The long-term deficits, which vary according to the extent of injury, can include severe mental retardation, seizures and cerebral palsy. The dominant opinion in recent years has been that cognitive impairments do not occur as isolated sequelae to hypoxic–ischaemic insult, but are invariably associated with definite neurological signs, most often with cerebral palsy, and that in the absence of such neurological deficits the attribution of purely cognitive impairments to hypoxic–ischaemic injury is not warranted (Brown et al., 1974; Volpe, 1995; Perlman, 1997). In this paper, however, we report on five young patients whose impairments do not appear to conform to this widely held view. These patients show pronounced memory problems that we attribute to hippocampal damage sustained at or shortly after birth probably as a result of hypoxic–ischaemic episodes, yet none of them has any of the major neurological deficits that are typically associated with hypoxic–ischaemic injury.

The hippocampus is one of the brain regions that is particularly vulnerable to hypoxic–ischaemic damage (Zola-Morgan et al., 1986; Hodges et al., 1996, and references therein), and it plays a critical role in memory function (Squire and Knowlton, 1995; Tulving, 1995). The occurrence of memory deficits following injury due to hypoxic–ischaemic episodes is therefore to be expected. However, little information is available on selective memory problems following hypoxic–ischaemic insults, in part because pathology of the hippocampus has traditionally been
demonstrated on analysis of surgical specimens following temporal lobectomy, or on post-mortem examination. Such examinations have naturally involved the most severely injured cases, typically with pathology that extended far beyond the hippocampus, and with correspondingly profound neurological and cognitive deficits that would encompass many domains of brain function. This precluded the establishment of correlations between focal brain damage and selective cognitive impairments, including those relating specifically to the hippocampus and memory function.

The establishment of such correlations has been made possible by the development of MRI techniques that enable us to detect and measure hippocampal damage non-invasively, and, moreover, to do this in children who show the complete spectrum of disabilities from minor to severe. For example, we recently reported on three young patients with severe memory impairments, all of whom showed bilateral hippocampal pathology on MRI (Vargha-Khadem et al., 1997).Remarkably, despite their inability to recall the episodes of everyday life, such as remembering where their belongings are located, or remembering messages, visitors, etc., all three patients had attended a mainstream school and had attained levels of speech and language competence, literacy and factual knowledge that are within the low-average to average range. These patients thus appeared to have a profound impairment of episodic memory (memory for events) but relatively preserved semantic memory (memory for facts). The question arose as to whether such an impairment may be a previously unrecognized consequence of hypoxic–ischaemic brain injury sustained perinatally. The findings described here on three new patients, together with two of those reported previously (Vargha-Khadem et al., 1997), suggest that this may indeed be the case.

Patients and methods

Patients

The patients were all referred for neuropsychological investigation because of problems with memory function. Their age at initial referral to us ranged from 8 to 14 years. We report here on five children selected from a consecutive series of 17 children who have shown a broadly similar pattern of memory function, the selection criterion being that all of these five children suffered hypoxic–ischaemic episodes at or shortly after birth.

Case 1 (Beth in Vargha-Khadem et al., 1997) was born to a mother with insulin-dependent diabetes mellitus following pregnancy complicated by polyhydramnios. Labour was induced at 37 weeks. Birth weight was 5060 g. Delivery was difficult following slow progression of labour and foetal distress with cardiac deceleration down to 80 beats per min. Shoulder dystocia resulted in injury to the right brachial plexus. There was no heartbeat at birth, and she was immediately intubated and underwent cardiac massage and intracardiac administration of adrenalin before being resuscitated after 7–8 min. The Apgar score was 0 at birth and 5 min after birth, and 8 at 10 min. Two hours after resuscitation, she had a generalized seizure, and such attacks recurred sporadically for 3 days despite treatment with anticonvulsants. She was initially floppy, with absent Moro and grasp reflexes. Within 2 weeks, however, she had made a good recovery, although the brachial plexus injury resulted in permanent impairment of the right arm and hand due to partial loss of the nerve function deriving from the fifth and sixth cervical nerve roots. Development was normal, except for poor motor skills, possibly related to mandatory dominant use of the left hand, and no other neurological problems were evident after the neonatal period.

Case 2 was delivered at 42 weeks following a normal pregnancy. His birth weight was 5200 g. Delivery was difficult, with shoulder dystocia. There was no heartbeat at birth and he was apnoeic for 10 min, requiring external cardiac massage and intracardiac injection of adrenalin. His heartbeat was regular at 20 min, but he had gasping respiration until then. Blood pH was 7.14 with a base excess of −18.9 mEq on day 1. Breathing became regular at 25 min. He was ventilated for 2 days, and had recurrent neonatal convulsions during the first days before being discharged home at 2 weeks. Development was normal, and he attends mainstream school with some difficulties. There were no problems until the age of 6 years, when he had some brief vacant episodes, and at age 7 years he had three generalized tonic or tonic–clonic seizures.

Case 3, a non-identical twin, was born with the umbilical cord around his neck. He was not ventilated in the neonatal period. Labour was said to be delayed and he was said to have lacked oxygen for 20 min. He was placed in a special care unit for 2.5 weeks, and three major seizures were reported in the first 36 h of life. Development was apparently normal, but there was a tremor of the hands, especially on writing, pale optic discs (6/6 vision bilaterally) and mild inco-ordination.

Case 4 (Jon in Vargha-Khadem et al., 1997) was delivered prematurely at 26 weeks of gestation, following a twin pregnancy. His co-twin died from apnoeic attack at age 3 days. The surviving twin weighed 940 g at birth and suffered from breathing problems that required intubation at 15 min, but spontaneous breathing was established 30 min later. Blood pH at birth was 7.28. He did well, despite some brief apnoeic attacks, until the age of 3 weeks, when more severe and repeated attacks required intubation and positive pressure ventilation for 1 week. He was suspected to have enterocolitis and had stormy periods with multiple episodes of severe apnoea, again necessitating intubation and positive pressure ventilation, and he was transferred to an intensive care unit for the next 3 weeks. Thereafter, he improved steadily. He walked alone at 16 months and spoke short sentences by 2 years. At 3 years 10 months, he had an unconfirmed convulsive episode in association with a cold and cough. He was always somewhat clumsy, but developed with no other motor abnormalities.
Case 5 was born at 33 weeks of gestation. During pregnancy, his mother had high blood pressure and pre-eclampsia. Congenital heart disease (ventricular septal defect) was noted a few days after birth. At 11 weeks, he was placed in an intensive care unit because of pneumonia with several respiratory arrests that required assisted ventilation for 4 days; seizures were reported. He was hospitalized five further times during his first year because of multiple respiratory arrests and dyspnoeic attacks. His development was mildly delayed; he walked at 18 months, could say sentences of three or four words by 2 years 2 months, and was clumsy. He had seizures with a temporo-occipital spike focus from age 7–8 years.

Magnetic resonance techniques
MRI and magnetic resonance spectroscopy (MRS) studies were carried out on a 1.5 T Siemens system. Structural MRI investigations included 3D data acquisition with the T1-weighted magnetization prepared rapid acquisition gradient echo sequence (Mugler and Brookeman, 1990): TR (repetition time) 10 ms; TE (echo time) 4 ms; TI (inversion time) 200 ms; flip angle 12°; matrix size 256 × 256; field of view 250 mm; partition thickness 1.25 mm; 128 sagittal partitions in the third dimension; acquisition time 8.3 min. For the measurements of hippocampal volume, the data sets were reformatted into 1-mm-thick contiguous slices in a tilted coronal plane perpendicular to the long axis of the hippocampus. Cross-sectional areas were measured along the entire length of the hippocampi, using every third slice as described previously (Van Paesschen et al., 1997). The volumes were calculated by summation of the cross-sectional areas and multiplying by the distance between the measured slices. A correction was then made for intracranial volume, and the hippocampal volumes are presented here in this corrected form.

The 3D MRI data sets were also analysed using voxel-based morphometry, implemented in SPM96 software (Wellcome Department of Cognitive Neurology, London, UK) running in MATLAB (Mathworks Inc., Sherborn, Mass., USA), according to a procedure similar to that described by Wright and colleagues (Wright et al., 1995). Briefly, each data set was spatially normalized to a template image which conformed to a standard space (Talairach and Tournoux, 1988), then partitioned to produce a segmented grey matter image which was finally smoothed using a 4-mm full-width half-maximum isotropic Gaussian kernel. The smoothed grey matter images of the patients (n = 5) were compared with those of controls (n = 8; mean age 13 years 6 months) using ANCOVA (analysis of covariance) with the global amount of grey matter as a covariate. This technique generates data sets which can be thought of as images representing the local volume, or regional density, of grey matter. The comparisons between the two groups of imaging data are derived for the whole brain, and they are characterized in terms of uncorrected P values, or in terms of F values that are corrected for multiple comparisons, using distributional approximations from the theory of random Gaussian fields. The P values are derived both for differences in grey matter density on a voxel-by-voxel basis, and also for the spatial extent of clusters of affected voxels.

Hippocampal water T2 values were obtained from T2 maps constructed from a 16-echo sequence, as previously described (Jackson et al., 1993; Van Paesschen et al., 1997). The cross-section from which the hippocampal T2 values were taken was oriented in a tilted coronal plane along the anterior border of the brainstem perpendicular to and at the level of the body of the hippocampus. T2 values were measured by placing a region of interest in the largest possible circular area within the hippocampus while avoiding boundaries at which partial volume effects with cerebrospinal fluid may occur.

For the assessment of more diffuse temporal lobe pathology, 1H MRS data were obtained from 2 × 2 × 2 cm cubes centred on the medial portions of the right and left temporal lobes, using a 90–180–180 spin-echo technique (TR 1600 ms; TE 135 ms), as described previously (Connelly et al., 1994; Cross et al., 1996). Signal intensities at 2.0 p.p.m. [primarily N-acetylaspartate (NAA)], 3.0 p.p.m. [creatinine + phosphocreatine (Cr)] and 3.2 p.p.m. [choline-containing compounds (Cho)] were measured from the peak areas by integration, and corrected for differences in radio frequency coil-loading among the different individuals. The data are presented in the form of the signal intensity ratio NAA/(Cho + Cr) which provides a simple index of spectral abnormality, values below 0.72 (the lower limit of the 95% reference range) being indicative of neuron loss or damage and/or astrocytosis (Connelly et al., 1994; Cross et al., 1996). The positioning and volume of the selected regions were such that the hippocampi in the patient group made only a minor contribution to the observed signal intensities.

Neuropsychological tests
Neuropsychological evaluation provided measures of the following: intelligence (Wechsler Intelligence Scale for Children—Third Edition, 1992); immediate and delayed memory [Wechsler Memory Scale (Wechsler, 1945), adapted for children]; auditory verbal learning [Children’s Auditory Verbal Learning Test (Talley, 1993)]; memory for complex design [Rey-Osterrith Complex Figure (Rey, 1964)]; working memory [digit span and Corsi block span, which is a spatial analogue of digit span (see Isaacs and Vargha-Khadem, 1989)]; memory for everyday events and episodes [Rivermead Behavioural Memory Test (Wilson et al., 1985)]; a parental rating of everyday memory (Sunderland et al., 1983); and reading, reading comprehension and spelling [WORD (Wechsler Objective Reading Dimensions) test (Rust et al., 1993)].

Informed consent was obtained for all of the patients, and the study was approved by the Great Ormond Street Hospital
Table 1 Results of neuropsychological tests

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Mean ± SD</th>
<th>Normal subjects (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at testing (years)</td>
<td>12.8</td>
<td>11.7</td>
<td>11.6</td>
<td>16.3</td>
<td>12.3</td>
<td>12.9 ± 1.9</td>
</tr>
<tr>
<td>VIQ</td>
<td>82</td>
<td>84</td>
<td>87</td>
<td>109</td>
<td>89</td>
<td>90.2 ± 10.8</td>
</tr>
<tr>
<td>PIQ</td>
<td>61</td>
<td>74</td>
<td>78</td>
<td>109</td>
<td>85</td>
<td>81.4 ± 17.7</td>
</tr>
<tr>
<td>MQ</td>
<td>83</td>
<td>83</td>
<td>79</td>
<td>93</td>
<td>81</td>
<td>83.8 ± 5.4</td>
</tr>
</tbody>
</table>

Digit span
- Forward: 6, 7, 6, 8, 7
  - Mean: 6.8 ± 0.8 | Normal: 6.4 ± 1.2
- Backward: 5, 5, 6, 6, 3
  - Mean: 4.7 ± 1.3 | Normal: 4.2 ± 1.5

Block span
- Forward: 4, 7, 6, 7, 7
  - Mean: 6.2 ± 1.3 | Normal: 5.6 ± 0.9*
- Backward: 6, 5, 4, 8, 6
  - Mean: 5.8 ± 1.5 | Normal: 5.5 ± 1.0*

Literacy (WORD) subtests
- Basic reading (standard score)
  - Actual score: 85, 97, 99, 102, 105
  - IQ predicted score: 83, 86, 89, 106, 92
  - Mean: 97.6 ± 7.7 | Normal: 100 ± 15†

- Spelling (standard score)
  - Actual score: 77, 96, 88, 84, 118
  - IQ predicted score: 85, 88, 90, 105, 93
  - Mean: 92.6 ± 15.8 | Normal: 100 ± 15†

- Reading comprehension (standard score)
  - Actual score: 84, 87, 74, 97, 87
  - IQ predicted score: 81, 85, 87, 107, 91
  - Mean: 85.8 ± 8.2 | Normal: 100 ± 15†

VIQ subtests
- Information
  - Actual score: 9, 7, 8, 10, 9
  - IQ predicted score: 8.6 ± 1.1 | Normal: 10 ± 3†
- Vocabulary
  - Actual score: 7, 7, 8, 11, 9
  - IQ predicted score: 8.4 ± 1.7 | Normal: 10 ± 3†
- Comprehension
  - Actual score: 7, 8, 9, 14, 8
  - IQ predicted score: 9.2 ± 2.8 | Normal: 10 ± 3†

The measurements are of intelligence quotients (VIQ and PIQ), MQ, digit span and block span, tests of literacy, and selected verbal IQ subtests. All scores are standard scores (mean = 100 ± 15) except for digit and block spans, which are the actual span lengths in terms of digits or blocks recalled in sequence, and subtest scores, which are standardized scaled scores (mean = 10 ± 3). * Isaacs and Vargha-Khadem, 1989; † normative data.

Results

Despite the fact that all five children had suffered hypoxic–ischaemic episodes at or shortly after birth, none showed hard neurological signs (motor milestones were passed at normal ages), although in four of them there were signs of clumsiness and mild inco-ordination. However, all of the children had problems with memory function. We begin by describing the results of neuropsychological tests, carried out between 11 and 16 years of age (Table 1), which provide a number of quantitative measures of the children’s cognitive function, and we then discuss the neuroimaging findings.

The neuropsychological data for the five patients agree well with those described in our initial report of amnesia in childhood (Vargha-Khadem et al., 1997). Mean verbal IQ (VIQ), performance IQ (PIQ) and memory quotient (MQ) scores were 90.2, 81.4 and 83.8, respectively (Table 1). In one of the patients (case 4), there is a VIQ – MQ difference of 16 points, a discrepancy that is characteristic of amnesia in adults, but in the other four cases the comparison between VIQ scores and MQ scores (which are largely a measure of verbal memory) gives little hint of any specific memory problems. On tests of verbal (digit span) and spatial (block span) immediate memory, the patients performed normally. In addition, they have learned to read and spell and to understand text at levels that correspond to their VIQ scores, as indicated by their performance on tests of literacy. Moreover, they all performed within the normal range on the vocabulary, information and comprehension subtests of the VIQ scale. Thus their semantic memory, as manifested in their acquisition of factual knowledge, appears relatively intact.

To evaluate the relationship between VIQ and MQ in more detail, we compared the patients’ performance on the Wechsler Memory Scale with that of a group of normal children ranging in age from 12 to 14 years. For 11 normal children with VIQs in the range 79–92, we found that their MQ values were on average 12 points higher than their VIQ. In contrast, the four patients with VIQ values in this range had MQ scores that were on average 4 points lower than their VIQ. This leads us to conclude that, like adult amnesics and also like case 4, these four patients do indeed have MQ scores that are substantially lower than those predicted on the basis of their VIQs.

for Children/Institute of Child Health Research Ethics Committee.
Tests of delayed recall provided a striking demonstration of the severity of the memory impairment in the five children (Table 2); all of the children performed close to the lowest possible level on delayed recall of the Wechsler Memory Scale stories and designs, on delayed recall of the word list contained in the Children’s Auditory Verbal Learning Test, and on delayed reproduction of the Rey–Osterrieth figure.

Although all five children attended mainstream school, they were all struggling with memory and learning problems when they were referred to us for neuropsychological investigations. These problems had become apparent only following their entry to school, and were not well understood by parents or teachers. The following report by a parent of one of the patients (case 5), written when the child was aged 10 years, typifies the difficulties that the children encounter and provides some clues as to why the nature and extent of these problems may go unrecognized.

‘It seems that his particular problem is his very poor memory, which may or may not be connected with his epilepsy. This is reflected, for example, in his inability to follow a series of instructions. He often cannot report back something immediately after he has heard it and may continually forget something that he has been told repeatedly. He has problems with orientation at home and at school and often gets lost in unfamiliar settings. Although his understanding of language is good, his use of language is often simplistic and he ‘grapes’ for words. He has no problems relating to others and is reasonably confident. In fact, he has learnt to cover up for his memory problem and is often misjudged by adults as being more capable than he really is due to his convincing talk. However, his talk is usually very inaccurate, especially when recalling events—he often merges several memories into one event, and also remembers things that never happened!'

These problems with everyday memory were identified in parental questionnaires (Sunderland et al., 1983), and were confirmed by results obtained from the Rivermead Behavioural Memory Test (Wilson et al., 1985), which includes test items such as remembering a route, where a belonging was placed, the date, a message to be delivered, a name for a pictured individual, a story, and pictures. Out of a possible screening score of 12 and with a cutoff for impairment of nine or fewer correct items, the five patients all showed severe impairments, with a mean score 3.2 ± 1.3.

The neuropathology underlying these memory impairments was investigated with magnetic resonance. Neuroradiological assessment, based on visual examination of T1- and T2-weighted MRI scans, showed bilateral hippocampal atrophy in all five cases, but no other consistent abnormalities. Case 1 showed an increase in T2-weighted signal intensity in the periventricular and particularly the peritrigonal white matter, accompanied by a loss of white matter bulk and thinning of the corpus callosum; the only other abnormalities that were identified were cerebellar atrophy in case 2 and incidental mastoid disease in case 3.

A number of quantitative magnetic resonance techniques were also used in an attempt to identify relatively subtle pathology that might not be obvious on visual inspection of the scans (Figs 1 and 2). Hippocampal volume measurements confirmed bilateral hippocampal atrophy in all cases, and there were elevated hippocampal T2 values (indicating abnormalities of the remaining hippocampal tissue) in three of the five cases.1HMRS abnormalities, reflecting more diffuse temporal lobe pathology, were relatively modest in the four cases examined; one of the children had NAA/(Cho + Cr) ratios in the normal range bilaterally, while the other three showed abnormalities that were unilateral and, in two of the cases, only mild.

While these three quantitative magnetic resonance methods provide important information about hippocampal and more widespread temporal lobe pathology, they do have the limitation that they are necessarily selective with respect to the brain regions examined. A major advantage of voxel-based morphometry is that it covers the whole brain. Using

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<tr>
<th>Table 2 Results of tests of memory function</th>
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<tr>
<td><strong>Story recall</strong> (%)</td>
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<td>Delayed</td>
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<td><strong>Geometric design</strong> (%)</td>
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<td>Immediate</td>
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<td>Delayed</td>
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<tr>
<td><strong>Children’s Auditory Verbal Learning Test</strong> (%)</td>
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<tr>
<td>Immediate memory span</td>
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<td>Delayed</td>
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* Immediate and 90-min delayed recall of stories from the Wechsler Memory Scale. † Immediate and 40-min delayed reproduction of geometric designs from the visual memory subtest of the Wechsler Memory Scale. § Standard scores for immediate memory span (the sum of the recall for two 16-word lists immediately after their first presentation) and delayed recall (20 min after completion). Floor level on this test is 60.  Normative data.
this technique, we were able to confirm the presence of hippocampal abnormalities, which showed bilaterally as regions of reduced grey matter density (Fig. 2C). Moreover, voxel-based morphometry also revealed reductions in grey matter bilaterally in the regions of the putamen (Fig. 2B), which were significant at a corrected level of $P < 0.05$. No other brain regions showed significant differences when the data were corrected for multiple comparisons. However, consistent with the known effects of hypoxic–ischaemic injury (see Discussion), additional abnormalities could also be seen, at uncorrected $P$ values $< 0.001$, in the ventral part of the thalamus (Fig. 2A) and in the brainstem (Fig. 2C).

**Discussion**

The five cases described here all show a pattern of severe impairment of episodic memory with relative preservation of semantic memory following episodes of perinatal or postnatal hypoxia. However, none of the children showed hard neurological signs, all of them having passed motor milestones at normal ages.

In evaluating the relationship of the memory impairments to the early hypoxic–ischaemic episodes, a key issue is the severity of these episodes. The accepted criteria for a diagnosis of neonatal hypoxic–ischaemic encephalopathy include: (i) evidence of foetal distress; (ii) depression at birth (i.e. depression of the level of reactivity, spontaneous activity and motility); and (iii) overt neonatal neurological symptoms within hours or a few days after birth, in the form of hypotonia and seizures (Volpe, 1995). Cases 1 and 2 fully met these criteria, and the occurrence of repeated seizures places them in the severe part of the spectrum of neonatal hypoxic–ischaemic encephalopathy. In case 3, there was circumstantial evidence of foetal distress and an abnormal neonatal period with seizures, making the diagnosis of hypoxic–ischaemic encephalopathy likely. In the remaining two cases (cases 4 and 5), postnatal hypoxic events rather than perinatal difficulties were probably the major problem, but prenatal factors may also have played a role, inasmuch as one was extremely premature and a twin, while the other had a cardiac malformation, as a result of which they both may have been more susceptible to hypoxia induced by apnoeas. Prenatal factors may have played a role in the first two cases also, as suggested by the presence of maternal diabetes and polyhydramnios in case 1 and macrosomy in cases 1 and 2. Indeed, it is likely that, in many cases of hypoxic–ischaemic encephalopathy, prenatal insult may have occurred, as shown by the presence of lesions of clear prenatal origin on neuropathological examination of infants dying with a diagnosis of hypoxic–ischaemic encephalopathy (Barabas et al., 1993; Gaffney et al., 1994). Some investigators have even questioned both the perinatal and hypoxic–ischaemic origin of hypoxic–ischaemic encephalopathy and have proposed the use of the non-committal term ‘neonatal encephalopathy’ (Nelson and Leviton, 1991; Leviton and Nelson, 1992). Whatever the term used, our observations demonstrate that the neonatal syndrome termed ‘hypoxic–ischaemic encephalopathy’ can be followed by isolated cognitive sequelae.

Our magnetic resonance findings, in particular those based on the technique of voxel-based morphometry, have proved invaluable in identifying a causal relationship between the hypoxic–ischaemic episodes and the cognitive impairments.
shown by these children. Voxel-based morphometry is a relatively new technique with a number of advantages, including its ability to cover the whole brain. Validation of results obtained with the technique has been provided by an earlier study of a family with an inherited speech and language disorder, in which voxel-based morphometry and independent volumetric measurements both identified bilateral abnormalities of the caudate nucleus (Vargha-Khadem et al., 1998).

Further validation is provided in the present study by the concordance of the voxel-based morphometric findings with the direct measurements of hippocampal volume. Thus there can be little doubt about the bilateral abnormalities that we have now revealed, not only in the hippocampus but also in the putamen, particularly as the abnormalities of both the right and the left putamen each reach significance when corrected for multiple comparisons. The abnormalities in the thalamus and brainstem should be regarded at this stage rather more cautiously, partly because they do not reach significance when corrected, but also because segmentation of grey matter within these regions is more difficult because the signal intensities lie between those of grey and white matter. Nevertheless, the overall pattern of MRI findings that we have observed is highly consistent with some of the known effects of acute hypoxic–ischaemic injury: the special sensitivity of the hippocampus to hypoxia is well established; neonatal MRI investigations have emphasized the involvement of the basal ganglia and thalamus (Rutherford et al., 1994, 1995; Barkovich and Hallam, 1997; Mercuri et al., 1999); and the brainstem is also often affected (Volpe, 1995; Kinney and Armstrong, 1997), with diffuse cortical involvement only in severe cases (Volpe, 1995).

Thus it appears that, in all five children, their pathology and associated memory impairments can be attributed primarily to hypoxic–ischaemic episodes sustained very early in life. We suggest that the degree of hypoxia–ischaemia was sufficient to produce selective damage to particularly vulnerable regions of the brain, but not sufficient to result in more severe or more global brain damage, and hence more severe neurological and cognitive deficits. Consistent with this suggestion, the abnormalities in the basal ganglia and ventral part of the thalamus (both of which could relate to the signs of clumsiness and mild inco-ordination shown by almost all of the children) were not sufficiently obvious to show up on conventional neuroradiological examination of the MRI scans.

Given the known role of the hippocampus in memory function, we conclude that it is the severe bilateral hippocampal pathology that is responsible for the pronounced memory impairments shown by these five cases. Indeed, the pattern of memory deficit, namely a profound impairment of episodic memory with relative preservation of semantic memory, adds weight to the argument that the hippocampus plays a critical role in supporting the formation of context-rich episodic memories and that, in the face of hippocampal pathology, semantic memory can be supported by other cortical structures, possibly the cortex subjacent to the hippocampus (Vargha-Khadem et al., 1997). It also helps to explain why a precise diagnosis was not straightforward. First, their semantic memory was sufficiently well preserved to enable the children to attend mainstream schools (albeit with considerable difficulties in some cases) and to mask the nature and extent of their episodic memory deficit. Secondly, their symptoms might naively be attributed to a benign form of forgetfulness or lapses of attention. Thirdly, even in normal children the formation and retrieval of episodic memories does not become evident until around the age of 5 or 6 years, as children become more reliable reporters of events, and so any impairments in the system subserving episodic memory are unlikely to become apparent up to this age. Fourthly, as indicated in the above-mentioned parental report, the children may spontaneously adopt strategies for covering up their deficiencies.

Our findings thus suggest that there may be a population of children who have impairments of episodic memory resulting from bilateral hippocampal pathology induced by
hypoxic–ischaemic episodes, and that these impairments may well be unrecognized, or at least underestimated, for the reasons discussed above. Despite the relative preservation of semantic memory in these children, their profound loss of episodic memory may nevertheless cause severe difficulties at home and at school, and in young adulthood this developmental amnesia may be sufficiently debilitating to preclude an independent life and employment.

We believe that hippocampal volume measurements performed early in life may be predictive of such problems, and that there is a case for carrying out quantitative MRI analyses of at-risk children in the first few years of life. Early identification of bilateral hippocampal atrophy would alert parents and teachers to potential memory problems and encourage the evaluation of appropriate remediation or rehabilitation programmes. For example, it might be possible to adopt alternative learning strategies, in order to take advantage of those aspects of the memory system, including semantic memory, that are relatively well preserved. In the meantime, it should be possible to establish the prevalence of this condition by further investigations of groups of children who had suffered well-characterized perinatal hypoxic–ischaemic episodes but who escaped with no hard neurological signs.

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