

Caudate and Hippocampal Volumes, Intelligence, and Motor Impairment in 7-Year-Old Children Who Were Born Preterm

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ABSTRACT

Children who survive very preterm birth without major disability have a high prevalence of learning difficulty, attention deficit, and minor motor impairment (MMI). To determine whether these difficulties are associated with structural brain abnormalities, we studied 105 preterm children (<32 wk) at 7 y with tests of IQ and MMI (Movement ABC) and detailed magnetic resonance brain scans. Scans were assessed qualitatively for visible cerebral lesions. Volume measurements of the caudate nuclei and hippocampal formations were made. Total brain volume (TBV) was estimated from the head circumference. Qualitative assessment of the scans showed evidence of cerebral lesions in 20 (19%), which were associated with lower IQ and more frequent MMI. IQ correlated with right and left caudate volume (Spearman's ρ 0.304 and 0.349; $p < 0.01$). This association persisted (except for verbal IQ) when caudate volume was expressed as a percentage of estimated TBV to allow for overall brain size. No significant correlations with hippocampal volumes were observed. These differences persisted when only scans from children without

visible lesions on scan were considered. MMI was significantly associated only with TBV and was more common in children with evidence of thinning of the posterior corpus callosum, although most children with MMI have a normal corpus callosum. Lower IQs in children who were born preterm are related to poorer development of the caudate relative to the rest of the brain, independent of other lesions. These findings suggest abnormal brain development after perinatal injury or postnatal nutritional deficits is responsible for cognitive deficits in preterm children. (*Pediatr Res* 55: 884–893, 2004)

Abbreviations

CSF, cerebrospinal fluid
MMI, minor motor impairment
MRI, magnetic resonance imaging
PIQ, performance IQ
TBV, total brain volume
VLBW, very low birth weight

Ten to 15% of children who were born in the United Kingdom at very low birth weight (<1500 g) will have major physical impairments that usually require special educational provision, but the majority will enter mainstream school (1). Studies of these children have shown that as many as 40% may show learning difficulties, often associated with problems of visuospatial perception, minor motor impairments (MMIs), and behavioral difficulties (2, 3). The origin of these difficulties has been attributed to a delay in neurologic maturation, early cerebral injury, social factors, or poor early growth (4).

Magnetic resonance imaging (MRI) has proved to be a useful tool for the investigation of anomalies of cerebral

maturation in a minimally invasive way. Very low birth weight (VLBW) infants show a relatively high prevalence of MRI-defined cerebral lesions later in childhood (5). Most of these represent degrees of periventricular leukomalacia or more diffuse white matter atrophy. Although evidence of extensive white matter damage correlates well with major neurologic impairment, there seems to be little if any correlation between signs of lesser damage and intellectual, motor, and behavioral problems at school age (5).

With the introduction of volumetric methods to MRI during the past decade, correlations have been noted between the volumes of parts of the brain and school performance in children. Associations between the volumes of the caudate nuclei and the hippocampus and learning difficulties and attention deficit have been demonstrated in school-age children who were born at term (6, 7). Results in children who were born very preterm have been conflicting and have described differences in cerebellar, basal ganglia, total

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brain, and gray matter volumes (8–12). This study was designed to test the hypothesis that children who were born very preterm and have cognitive deficits and associated MMIs at school age would show different caudate and hippocampal volumes from those who were doing well.

METHODS

As part of a study of school performance of all very preterm children who were born to mothers who resided in a geographically defined area of Merseyside, UK, during a 2-y period, parents were asked whether they would allow their child to have a cerebral MRI scan (13). The study was approved by the Local Children's Research Ethics Committee, and written informed parental consent was obtained.

All children who were born in 1991 and 1992, whose mothers resided in Liverpool postal districts, and who were born at <32 completed weeks of gestation were included in the study. Those who were known to be alive at discharge from any of the eight hospitals that serve the area were traced through their general practitioner to confirm their current health status before their parents were approached. Children who were attending mainstream schools, with or without special provision, and whose parents agreed to their being studied were matched by sex, age, and first language to a full-term classmate control. Depending on parental and school wishes, the children were tested at 7–8 y of age, at school or at the Institute of Child Health, Royal Liverpool Children's Hospital.

Intelligence was tested using the short form of the Wechsler Intelligence Scales for Children Version III (14). Motor impairments were tested for using the Movement ABC (15). Measurements of height, weight, and head circumference and a standardized neurologic examination were done. These tests were performed by an occupational therapist and a graduate psychologist who were used as research assistants for the project. A parental questionnaire collected demographic data, and a perinatal data sheet was completed from the clinical case notes by a clerical assistant. Cranial ultrasound results were as reported by the local consultant radiologists. A score below the fifth percentile on the Movement ABC was considered indicative of MMI. MRI scans were performed on a subset of the subjects in the main study whose parents consented to scanning in addition to the other studies. Payment of travel expenses only was made. Magnetic resonance brain scans were performed on a Philips Gyroscan NT5 scanner with a field strength of 0.5 Tesla (Philips Medical Systems, Best, Netherlands). The scans consisted of five sequences: sagittal T1 weighted spin-echo, axial T1-weighted spin-echo, axial T2-weighted turbo spin-echo, coronal fluid-attenuated inversion recovery, and a T1-weighted fast field echo volume acquisition.

The fast-field echo sequence (TR = 200 ms, TE = 30 ms, TI = 13 ms, flip angle = 30 degrees) was used to produce a coronal volume acquisition with a slice thickness of 2 mm and a 1-mm overlap. From this sequence, caudate and hippocampal volumes were measured on a Easivision workstation (Philips Medical Systems).

For reducing scan times during volume acquisition only, the scans did not always include the entire brain, so total brain volume (TBV) could not be measured from MRI. Instead, an estimate of TBV was calculated using the head circumference measured at the time of testing. We used a published formula that relates brain size at postmortem examination to occipitofrontal head circumference (OFC) (16). This cannot allow for differences in extracerebral space or ventricular volume but is an approximation. Caudate and hippocampal volumes could then be expressed as a percentage of estimated TBV to allow for differences in brain size.

Qualitative assessment of magnetic resonance brain scans. Scans were systematically assessed for visible lesions consistent with thinning of the corpus callosum (Fig. 1), ventricular enlargement (Fig. 2), periventricular leukomalacia (Fig. 3), and porencephaly (Fig. 4) by an experienced pediatric radiologist (L.A.).

Periventricular leukomalacia was recognized by a characteristic triad of abnormalities: abnormally high signal within the periventricular white matter on T2-weighted turbo spin-echo and fluid-attenuated inversion recovery images; loss of periventricular white matter, particularly in the periatlial regions; and compensatory focal ventricular enlargement adjacent to regions of abnormal signal intensity (17). Porencephaly was recognized as a well-defined cavity within the brain substance, communicating with the lateral ventricle and containing fluid with identical signal characteristics to cerebrospinal fluid (CSF).

Quantitative analysis of magnetic resonance brain scans. Hippocampal volumes were measured using the technique previously described by Jack *et al.* (18, 19). The anterior and posterior boundaries were defined, including the whole of the head of the hippocampus anteriorly and using the crus of the fornix as the posterior anatomic landmark. The in-plane boundaries were then traced sequentially on each slice. The head of the hippocampus was separated from the amygdala by the uncus recess of the temporal horn of the lateral ventricle; in cases in which the uncus recess was not patent, an arbitrary horizontal line was drawn through the most superomedial portion of the temporal horn. The boundaries of the hippocampal body and tail were defined laterally by CSF in the temporal horn of the lateral ventricle, superiorly by CSF in the choroid fissure, medially by CSF in the uncus and ambient cistern, and inferiorly by the interface between the gray matter of the subiculum and the white matter of the parahippocampal gyrus (Fig. 5). These anatomic landmarks have been shown to define reliably 90–95% of the total hippocampal volume (20).

Volumes of the caudate nuclei were measured using a similar technique. The boundaries of the caudate nucleus were defined anteriorly and laterally by the interface with the white matter of the frontal lobe and the anterior limb of the internal capsule, and medially by CSF in the lateral ventricle (Fig. 6). The posterior boundary was arbitrarily defined by the most anterior coronal section to show the crus of the fornix, as used to define the posterior boundary of the hippocampus. The slender tail of the caudate nucleus, which

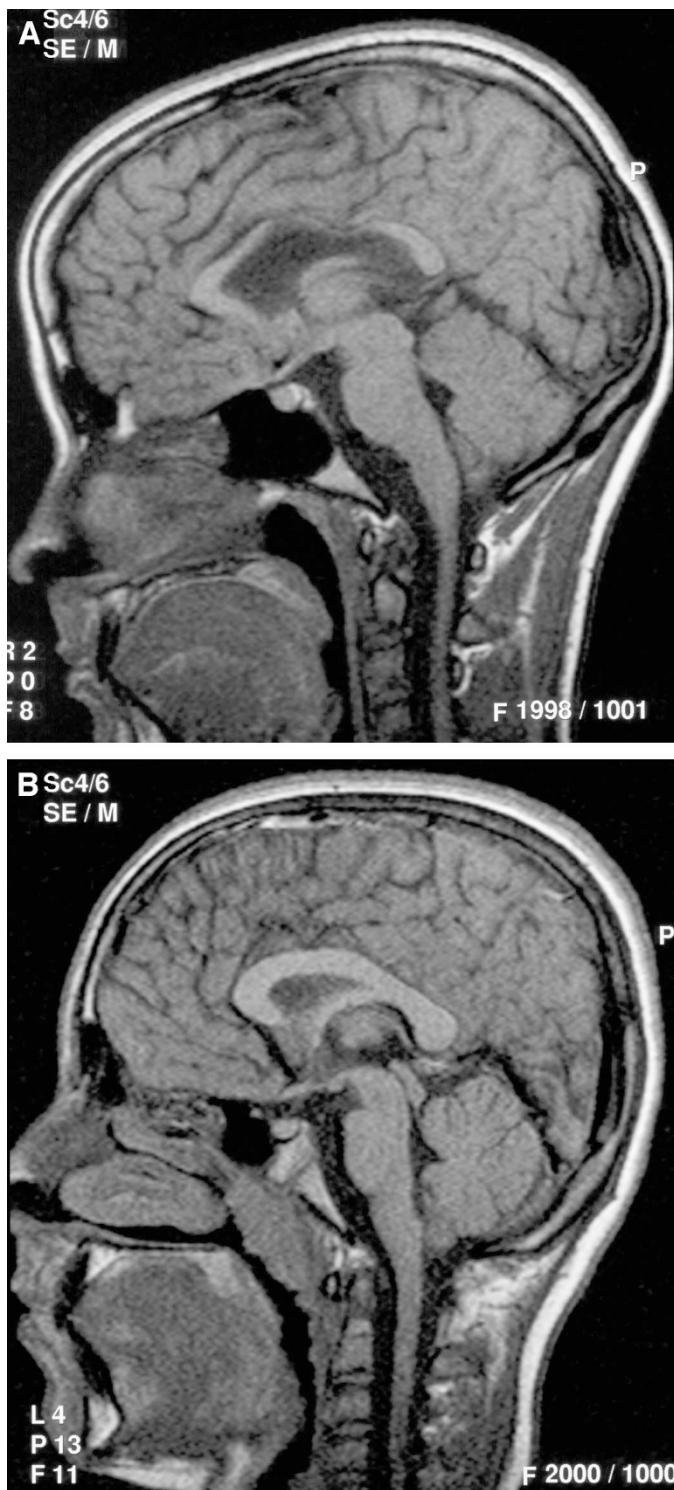


Figure 1. (A) Thinning of the corpus callosum. (B) Normal scan for comparison (midline sagittal T1-weighted MRI scans).

extends around the posterior part of the lateral ventricle, was not measured.

Once boundaries had been drawn on each coronal image, volumes were calculated automatically by the workstation using a volume of interest function. The ratio of the volumes of the structures (left:right) was calculated as a percentage.



Figure 2. Ventricular dilation (axial T2-weighted MRI scan).

The reliability of this technique was assessed as follows. Volume measurements on a convenience sample of 25 scans were made independently by two observers. Intraobserver and interobserver variation was calculated by the Bland-Altman method (21). For volume measurements of the hippocampal formations, 95% confidence intervals of agreement (intraobserver) were between -161 and 165 mm³. For interobserver variation, 95% confidence intervals of agreement were between -145 and 163 mm³. These results ($<\pm 7\%$) are comparable with those in previous studies (18, 20) that have indicated that MRI-based measurements of these brain structures can be made with a high degree of reproducibility. All volume measurements were made by one of the authors (L.A.), who was blind to the clinical assessments. Statistical analysis of the data were performed using SPSS version 10.

RESULTS

A total of 382 children had been discharged from the eight hospitals that serve the area during the period covered by the study, and 335 were alive and attending mainstream school at 7 y. A total of 286 parents permitted their children to be tested at school, and 126 parents initially consented to their children's undergoing MRI scans; 15 later changed their minds or failed to attend, three were unable to cooperate and satisfactory scans were not obtained, scan data were lost for

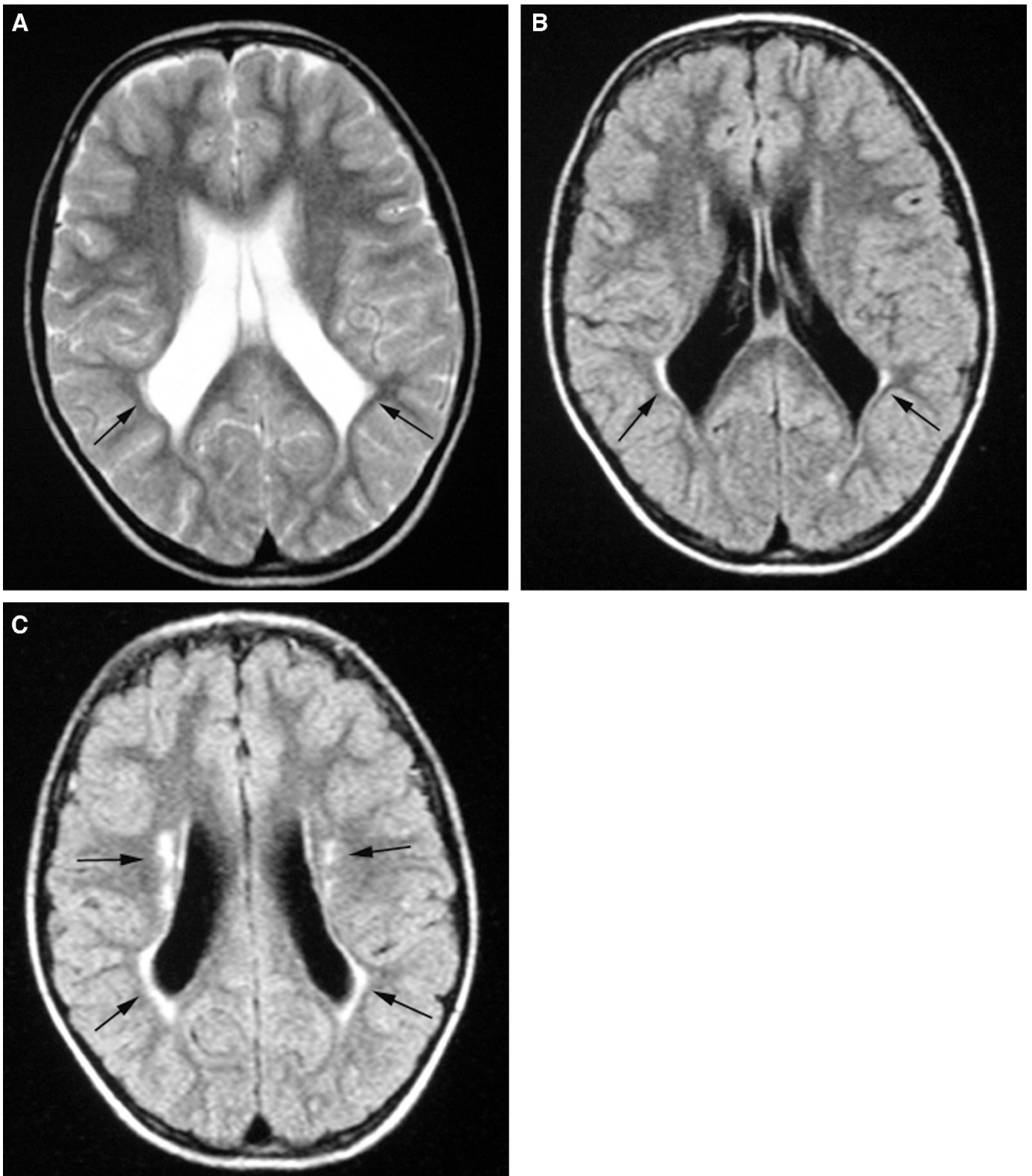


Figure 3. Periventricular leukomalacia. Axial T2-weighted (*A*) and fluid-attenuated inversion recovery images (*B* and *C*) show high signal intensity in the periventricular white matter (arrows).

two children because of a technical failure, and in one child artifact from fixed dental braces prevented accurate volume measurement. A total of 105 children had satisfactory scans. No sedation was used. Scans were completed within 6 mo of

testing at school. Mean age at testing was 7 y 4 mo. The perinatal characteristics of children who were scanned are shown in Table 1. The characteristics of the children who were scanned and not scanned at age 7 y are similar,



Figure 4. Porencephaly in the left cerebral hemisphere (coronal T1-weighted MRI scan).

although children who were scanned had a significantly smaller head circumference and higher performance IQ (PIQ; Table 2). Of the 105 preterm children scanned, 20 (19%) showed a cerebral lesion on MRI. Lesions consistent with periventricular leukomalacia were present in 14 (12%), any ventricular dilation in 14 (11%), thinning of the posterior part of the corpus callosum in eight (9%), and with porencephaly in two (2%) (Table 3). Several children had more than one lesion type.

Mean and median values for IQ and ABC scores are given in Table 2. Mean estimated TBV was 1,225,000 (138,000) mm³. TBV was correlated with ABC ($r = -0.233$, $p = 0.02$) but not when children with visible MRI abnormalities were excluded. When only children with “normal” scans were considered, TBV was correlated with PIQ ($r = 0.252$, $p = 0.029$).

Mean (SD) right and left caudate volumes were 4633 (807) and 5425 (789) mm³, and right and left hippocampal volumes were 2906 (490) and 2813 (429) mm³, respectively. Median (interquartile range) right and left caudate volumes as a percentage of TBV were 3.8 (3.4–4.1) and 3.7 (3.2–4.1) and for the right and left hippocampus were 2.4 (2.1–2.6) and 2.3 (2.0–2.6).

Table 4 shows the mean values for volumes in children with IQs above and below 80, and Table 5 shows the mean values in children with ABC scores above and below the fifth percentile. Table 6 shows the correlations between the volume data and ABC and IQ scores for all children, and Table 7 shows the correlations for only children who did not have a visible lesion on MRI scan. Significant correlations between IQ scores and caudate volumes are seen, which largely persist when children without visible lesions alone are considered. Significant corre-

lations for caudate volumes as a percentage of TBV persist only for PIQ. No significant correlations between hippocampal volumes and ABC or IQ scores were observed. This was also true when hippocampal volumes were correlated with subsets of the IQ test used.

DISCUSSION

In our previous work (5), we described the results of MRI brain scans in a cohort of adolescents (age 15–17 y) who had a history of VLBW (<1500 g) but no major disability and were born between 1980 and 1983. There was a high prevalence (42.5%) of structural brain abnormalities, although these abnormalities showed poor correlation with IQ and attention-deficit/hyperactivity disorder (12). Similar results have been found in other studies. Skranes *et al.* (8) found no correlation between MRI abnormality and IQ in VLBW children without disability at 6 y of age, and Kragehlo-Mann *et al.* (9) found no difference in performance in intelligence tests in very preterm children, with and without MRI abnormalities. Stewart *et al.* (10) and Rushe *et al.* (11) reported the results of MRI brain scans and neuropsychological outcome at age 14–15 y of a cohort of 75 participants who were born at <33 wk gestation; 55% of this group had structural brain abnormalities demonstrated on MRI brain scans, but those with abnormal MRI brain scans did not perform less well on any measure of cognitive function. There was also a lack of correlation of gestational age and birth weight with neuropsychological outcome but a significant correlation between abnormal MRI scans and behavioral problems. In the group of VLBW children that we studied at age 15–17 y, we found positive associations between full-scale IQ and caudate volumes, and attention-deficit/hyperactivity disorder and hippocampal volumes (12).

The subjects of our present study were born in 1991 and 1992. The selection of subjects was geography and gestation based rather than hospital and birth weight based. The prevalence of structural brain abnormalities was 18.5%, much lower than in our previous study. The reason for this difference is uncertain. Recruitment criteria for the two groups were different, and improvements in neonatal care may have had an effect on the prevalence of perinatal brain injury. Table 1 shows the perinatal characteristics of the present cohort, which shows that most were not particularly ill in the neonatal period, but they are more likely to represent the population as a whole than a hospital-based cohort from a referral center. In both studies, there was self-selection, in that the children and their parents had to consent to be scanned. Table 2 suggests that those who were scanned were broadly similar at age 7 y to the rest, although those who were scanned had significantly smaller OFC and higher PIQ.

In this cohort, volumes of the right and left caudate nuclei were significantly correlated with IQ but not with ABC scores (Tables 4–6). There was no significant correlation between IQ and ABC scores and hippocampal volume measurements. The relationship between IQ and caudate volume could simply represent the well-known correlation between brain size and IQ. When caudate volumes were expressed as a percentage of

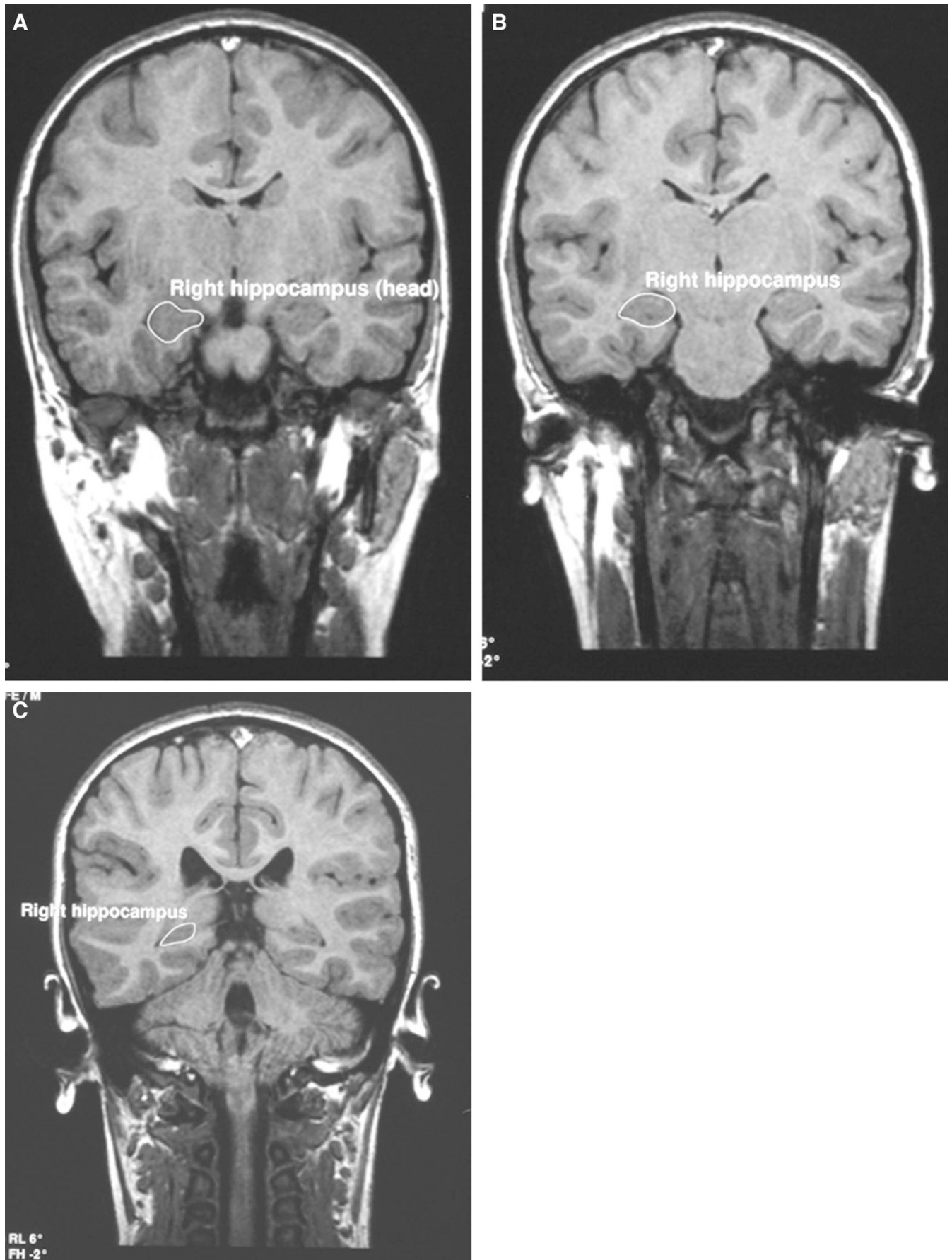


Figure 5. Measurement of hippocampal volume. Regions of interest drawn on coronal T1-weighted fast-field echo images. (A) Head of hippocampus. (B) Body of hippocampus. (C) Posterior limit of measurement of the tail of the hippocampus at the level of the crus of the fornices.

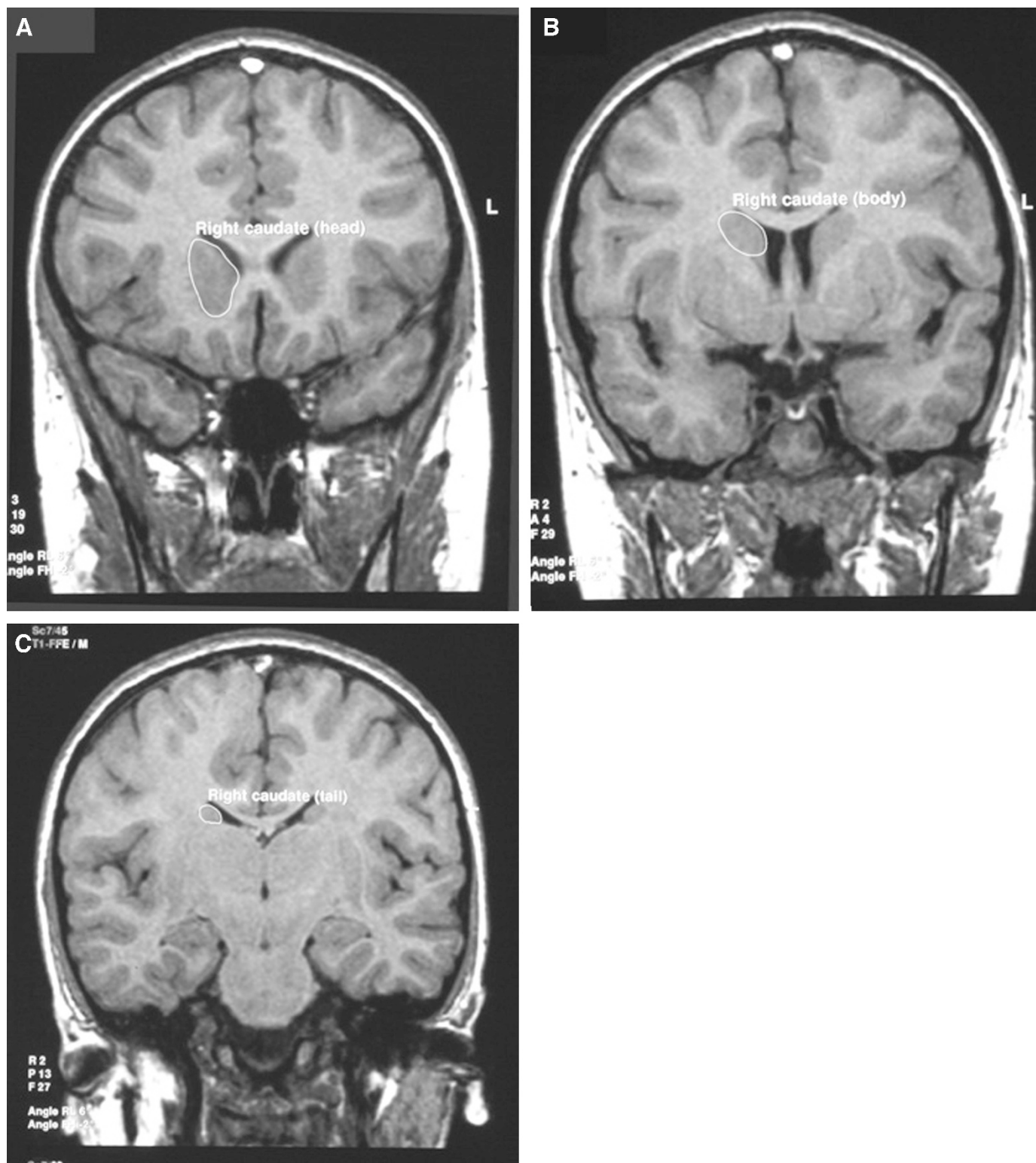


Figure 6. Measurement of caudate volume. Regions of interest drawn on coronal T1-weighted fast-field echo images. (A) Head of caudate nucleus. (B) Body of caudate nucleus. (C) Tail of caudate nucleus (posterior limit of measurement).

estimated TBV, the correlations remained significant except for that between verbal IQ and right caudate volume percentage, suggesting that this was not the case (Table 6). When only the 85 children with apparently normal MRI scans were examined, the correlations were weaker yet remained significant

for most comparisons (Table 7). Volumes as a percentage of TBV remained significantly correlated only with PIQ (Table 7). Isaacs *et al.* (22) reported the results of a study of 11 adolescents with a history of prematurity (<30 wk gestation). They had significantly smaller hippocampal volumes bilaterally

Table 1. Characteristics of infants in perinatal period who had an MRI scan

Gestation (wk)	29.7 (2.2)
Birth weight (g)	1386 (370)
Head circumference (cm)	28.4 (2.2)
Male sex	54/105
Maternal hypertension	18/97
Preterm rupture of membranes	27/97
Antepartum hemorrhage	17/97
Antenatal steroids	26/97
Fetal distress	28/97
Cesarean section	54/97
Days ventilated	1 (0–5)
Days added oxygen	2 (0–6)
Confirmed sepsis	39/95
Seizures	3/95
Periventricular hemorrhage left side (ultrasound)	10/95
Periventricular hemorrhage right side (ultrasound)	8/95

Mean (SD) or median interquartile range [IQR] or proportions.

Table 2. Characteristics of infants with and without MRI scan at 7 y

	No MRI scan	MRI scan	<i>p</i>
Height (cm)	122 (5.7)	121 (5.9)	0.25
Weight (kg)	24.5 (4.9)	23.5 (4.2)	0.10
OFC (cm)	51.7 (1.9)	51.1 (1.8)	0.02
ABC score (IQR)	8.5 (3.5–16.5)	8.25 (3.125–15)	0.89
Verbal IQ (SD)	93 (14.7)	93 (12.9)	0.75
Performance IQ (SD)	86 (15.2)	91 (15.6)	0.01
Total IQ (SD)	89 (14.5)	90 (14.1)	0.28

ally and showed specific defects in certain aspects of everyday memory. Regression analyses indicated that hippocampal volume was the best predictor of performance in tests of everyday memory. Some of the subscales of the IQ test that we used involve aspects of short-term memory, but we were unable to show a correlation between them and hippocampal size. The hippocampal volumes measured in our present cohort were not smaller than would be expected for an age of 7 y. Peterson *et al.* (23) studied a group of 25 preterm children at 8 y of age with quantitative MRI scans and found that regional cortical

volumes and basal ganglia and hippocampal volumes were smaller in preterm children than in control subjects. When corrected for TBV, basal ganglia and hippocampal volumes seemed to be disproportionately reduced. In this group, full-scale IQ seemed to correlate most strongly with regional cortical volume, although some association with basal ganglia volumes was demonstrated. This is in keeping with our findings in this cohort. The selection criteria for this group differed from our present study in that children were selected on the basis of birth weight (<1250 g), and children with MMI were not excluded.

Our results suggest that the final volume attained by key cerebral structures such as the caudate nuclei are important determinants of cognitive function in preterm children. We were not able to study many other regions of the brain volumetrically, although recent studies in children who were born preterm have highlighted volume differences in the cerebellum (24) and in total and gray matter volumes that have correlated with later cognitive function. Any of these differences may represent evidence for disordered development of the preterm brain after perinatal injury, rather than a focal lesion affecting cognitive function.

The hippocampus and basal ganglia are particularly susceptible to injury in preterm infants; hippocampal abnormalities were found in 67% of autopsies of preterm infants (25). Hypoxia, metabolic disorders, nutritional impairment, and infections all may affect the developing brain. The hippocampus is known to be selectively vulnerable to hypoxic-ischemic injury (26), hypoglycemia (27), and hypothyroidism (28). Lucas *et al.* (29) showed that IQ in preterm children at age 7–8 y showed significant differences depending on nutritional intervention shortly after birth. Brain growth is most rapid around the time of term in human infants, and the period between birth and term is one of relative malnutrition for many preterm infants. Nutritional impairment of these vulnerable infants at this time may be of particular importance in limiting the development of key cerebral structures. Neonatal interventions to counteract this might lead to improved function later in this group of infants.

Table 3. Test scores in presence or absence of cerebral lesions on MRI scans

	ABC	FIQ	PIQ	VIQ
Any lesion (20)	10 (6.125–25)	83 (11.3)	84 (13.4)	86 (12.7)
No lesion	7 (3–13)	93 (13.7)	93 (15.5)	94 (12.6)
	<i>p</i> = 0.124	<i>p</i> = 0.004	<i>p</i> = 0.018	<i>p</i> = 0.012
PVL (14)	10 (7.5–22)	86 (5.3)	87 (6.4)	89 (11.8)
No PVL	7 (3–13.5)	92 (14.5)	92 (16.3)	93 (13.1)
	<i>p</i> = 0.147	<i>p</i> = 0.017	<i>p</i> = 0.063	<i>p</i> = 0.215
Ventriculomegaly (14)	10 (6.3–21.6)	85 (8.2)	86 (8.0)	88 (13.3)
No ventriculomegaly	7.75 (3–15)	92 (14.3)	92 (16.2)	94 (12.8)
	<i>p</i> = 0.178	<i>p</i> = 0.020	<i>p</i> = 0.026	<i>p</i> = 0.152
Thinning CC (8)	20 (9.25–32)	81 (14.3)	77 (12.9)	88 (14.5)
No thinning CC	7.75 (3–13)	92 (13.4)	93 (15.0)	93 (12.8)
	<i>p</i> = 0.010	<i>p</i> = 0.028	<i>p</i> = 0.004	<i>p</i> = 0.314
Porencephaly (2)	20.75 (8.5–33)	77 (12.7)	77 (18.3)	83 (5.7)
No porencephaly	8 (3–15)	92 (13.6)	92 (15.3)	93 (13.0)
	<i>p</i> = 0.284	<i>p</i> = 0.140	<i>p</i> = 0.174	<i>p</i> = 0.213

FIQ, full-scale IQ; VIQ, verbal IQ; PVL, periventricular leukomalacia; CC, corpus callosum.

Table 4. Comparison of caudate and hippocampal volume measurements in preterm children with IQ ≥ 80 and IQ < 80

	IQ ≥ 80 (n = 81)	IQ < 80 (n = 19)	p	95% CI of the difference between means
Right hippocampus	2875 \pm 474	2901 \pm 554	0.83	-279 to 227
Left hippocampus	2808 \pm 432	2738 \pm 430	0.534	-153 to 293
Right caudate	4763 \pm 733	4193 \pm 1003	0.006	169 to 970
Left caudate	4673 \pm 692	3991 \pm 1003	0.001	296 to 1066

Mean \pm SD, mm³.

CI, confidence interval.

Table 5. Comparison of caudate and hippocampal volume measurements in preterm children with movement ABC more than the fifth percentile and movement ABC less than the fifth percentile

	ABC ≥ 5 th (n = 80)	ABC < 5 th (n = 25)	p	95% CI of the difference between means
Right hippocampus	2950 \pm 476	2822 \pm 507	0.259	-96 to 353
Left hippocampus	2847 \pm 414	2735 \pm 471	0.267	-87 to 310
Right caudate	4672 \pm 732	4502 \pm 1036	0.367	-202 to 625
Left caudate	4608 \pm 729	4256 \pm 928	0.052	-4 to 710

Mean \pm SD, mm³.**Table 6.** Correlations (Spearman's rho) between caudate and hippocampal volumes and scores on Movement ABC and IQ tests, all subjects

	RCV	RCV%	LCV	LCV%	RHV	RHV%	LHV	LHV%
ABC	-0.111	0.003	-0.187	-0.067	-0.076	-0.028	-0.140	-0.003
FIQ	0.304**	0.223*	0.349**	0.235*	0.045	0.018	0.068	-0.014
PIQ	0.354**	0.353**	0.366**	0.332**	-0.066	-0.054	0.020	0.020
VIQ	0.276**	0.176	0.343**	0.223*	0.175	0.144	0.139	0.046

RCV, right caudate volume;

LCV, left caudate volume;

RHV, right hippocampal volume;

LCV, left hippocampal volume.

Percentages are volumes as percentage of estimated TBV.

* $p < 0.05$.** $p < 0.01$.**Table 7.** Correlations (Spearman's rho) between caudate and hippocampal volumes and scores on Movement ABC and IQ tests, normal MRI scans only

	RCV	RCV%	LCV	LCV%	RHV	RHV%	LHV	LHV%
ABC	-0.023	0.044	-0.118	-0.041	-0.066	-0.008	-0.080	-0.002
FIQ	0.208	0.159	0.239*	0.156	0.014	0.011	0.013	-0.029
PIQ	0.252*	0.276*	0.240*	0.228*	0.126	-0.070	-0.065	-0.013
VIQ	0.261*	0.181	0.315**	0.211	0.208	0.189	0.143	0.072

Percentages are volumes as percent of estimated TBV.

* $p < 0.05$.** $p < 0.01$.

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