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Volumetric Analysis of Regional Cerebral Development in Preterm Children

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Abstract

Preterm birth is frequently associated with both neuropathologic and cognitive sequelae. This study examined cortical lobe, subcortical, and lateral ventricle development in association with perinatal variables and cognitive outcome. High-resolution volumetric magnetic resonance imaging scans were acquired and quantified using advanced image processing techniques. Seventy-three preterm and 33 term control children ages 7.3–11.4 years were included in the study. Results indicated disproportionately enlarged parietal and frontal gray matter, occipital horn, and ventricular body, as well as reduced temporal and subcortical gray volumes in preterm children compared with control subjects. Birth weight was negatively correlated with parietal and frontal gray, as well as occipital horn volumes. Intraventricular hemorrhage was associated with reduced subcortical gray matter. Ventricular cerebrospinal fluid was negatively correlated with subcortical gray matter volumes but not with white matter volumes. Maternal education was the strongest predictor of cognitive function in the preterm group. Preterm birth appears to be associated with disorganized cortical development, possibly involving disrupted synaptic pruning and neural migration. Lower birth weight and the presence of intraventricular hemorrhage may increase the risk for neuroanatomic abnormality.

Introduction

Very low birth weight preterm children are at increased risk for neuroanatomic abnormalities that may underlie the cognitive-behavioral deficits frequently observed among this population [1,2]. Medical complications of preterm birth, such as hypoxia, often result in various forms of neuropathology that may disrupt development in the preterm brain. Hypoxic-ischemic sequelae include periventricular leukomalacia which tends to produce both focal and diffuse white matter injury [3]. Intraventricular hemorrhage is another common outcome of hypoxic injury. Neurologic consequences of intraventricular

hemorrhage include hemorrhagic cerebral infarction, hydrocephalus, and germinal matrix destruction [4]. However, the presence of such obvious neuropathology is not requisite for the development of cognitive impairments in preterm children [5].

Investigations of subtle deficits in the brain morphology of preterm children have been limited, but existing studies report decreased total cerebral tissue volume, as well as regional abnormalities including reduced tissue volume in the corpus callosum, hippocampus, amygdala, sensory-motor cortex, cerebellum, and basal ganglia [6-8]. Additionally, preterm children tend to manifest decreased cortical surface area and complexity [9], as well as decreased gray/white matter differentiation [10]. Voxel-based morphometric studies of very low birth weight children demonstrate that abnormalities in the right ventral extrastriate cortex [11] and left parietal lobe [12] are associated with visuospatial and calculation deficits, respectively. Additionally, a functional magnetic resonance imaging study of language ability in preterm children revealed aberrant activation patterns in neural pathways associated with semantic processing [13].

The present study utilized volumetric magnetic resonance imaging analysis of 73 preterm children at age 8 years, and 33 age- and sex-matched term control subjects to further delineate the effects of preterm birth on brain morphology, in particular, as related to cerebral lobe, lateral ventricle, and subcortical gray matter development. Because very low birth weight preterm children frequently demonstrate significant learning impairments [5], we expected decreased temporal lobe volumes. We also predicted sex differences in cerebral lobe volumes given the increased morbidity in male preterm children [14].

Methods

Patients

All patients were recruited and evaluated at the Yale University School of Medicine, New Haven, Connecticut and at Brown University School of Medicine, Providence, Rhode Island. The institutional review boards of both universities approved the procedures. All children and their parents provided informed written consent for the study. The magnetic resonance imaging scans were performed at Yale University School of Medicine and analyzed at the Stanford Psychiatry Neuroimaging Laboratory.

The preterm patients consisted of children enrolled in the follow-up portion of the Randomized Indomethacin Intraventricular Hemorrhage Prevention Trial [15] at Yale University School of Medicine and Brown University School of Medicine based on geographic proximity to New Haven, Connecticut. Overall, 287 of the surviving 340 children (84%) were evaluated at age 8 years corrected age (i.e., age from the obstetric due date). Two hundred of these 284 study children (70%) resided within geographic proximity to New Haven, Connecticut and did not have contraindications for magnetic resonance imaging (usually orthodontia); all were invited to participate in the imaging study. From this pool of 200 eligible preterm patients, 134 scans were obtained (67%).

Term control children, aged 7 to 11 years, were recruited from randomly selected names on a telemarketing list of 5000 families in the same geographic region and from local advertisements. The families were identified as having children of the appropriate age and living in the same ZIP code areas as the preterm children, as previously described [8]. Control subjects were frequency matched with preterm patients to provide similar distributions of age, sex, and minority status (i.e., caregiver report of white or nonwhite) in the two groups.

Neonatal Assessment

As previously described [15], neonates of 600-1250 gm birth weight were recruited to participate in a multicenter, randomized, intraventricular hemorrhage prevention trial. All infants were examined with serial cranial ultrasonography beginning at the sixth postnatal hour and continuing through the expected obstetric due date; the grading systems for intraventricular hemorrhage, periventricular leukomalacia, and ventriculomegaly are described elsewhere [16]. Prenatal, perinatal, and postnatal data were obtained prospectively by maternal interviews and from chart review, and all infants underwent gestation age assessment on the first postnatal day [17].

Cognitive assessments were performed by research staff blinded to the child's study group and medical status. Intellectual functioning or intelligence quotient was measured using the Wechsler Intelligence Scale for Children–Third Edition [18]. Reading and math skills were assessed using the Peabody Individual Achievement Test Revised [19].

Magnetic Resonance Imaging Acquisition

Magnetic resonance images of each subject's brain were acquired with a single GE-Signa 1.5 Telsa scanner (General Electric, Milwaukee, Wisconsin). Sagittal brain images were acquired with a three-dimensional volumetric radiofrequency spoiled gradient echo pulse sequence using the following scan parameters: TR = 24 ms, TE = 5 ms, flip angle = 45°, NEX = 1, matrix size = 256 × 192, field of view = 30 cm, slice thickness = 1.2 mm, 124 contiguous slices.

Magnetic Resonance Imaging Analysis

All image processing was completed at Stanford University. Scans from other sites were transferred digitally. Raters blinded to diagnosis and medical status visually inspected the images to exclude those that could not be processed owing to excessive motion artifact. This process resulted in 61 of the 134 preterm scans being excluded because of observable motion or vascular flow artifact. One additional preterm subject's scan was excluded because of the presence of a brain tumor detected on qualitative examination, leaving a total of 73 usable scans. Of 70 control scans, 37 were excluded. There were no significant statistical differences between patients with “usable” or “unusable” scans in terms of sex, age, or cognitive functioning. Magnetic resonance imaging scans were imported into BrainImage (Stanford University, Stanford, CA) for semiautomated whole brain segmentation and quantification in the sagittal plane using previously described and validated methods [20,21]. Interrater reliability obtained by interclass correlation exceeded 0.95.

In addition, to yielding results for whole brain, cerebral lobe tissue (gray, white, and cerebrospinal fluid), and subcortical or deep gray matter (basal ganglia and thalamus), measurements for lateral ventricular cerebrospinal fluid also were generated from the semiautomated process. The lateral ventricles were then further parcellated into right and left frontal, temporal, and occipital horns, as well as ventricular body using an automated procedure.

Statistical Analysis

Data were first examined for normality to conform to the assumptions of the parametric statistics employed. Analysis of variance was used to determine group differences in total cerebral tissue, cerebral gray and white matter volumes. Multiple analysis of covariance was used to examine group differences in cerebral lobe tissue with frontal, parietal, temporal, and occipital lobe tissue volumes as dependent variables, postnatal age at scan and cerebral tissue as covariates, and group and sex as independent variables. Two multiple analyses of

covariance, one for gray and one for white matter, were used to investigate the possibility of group-specific variations in tissue-specific (gray/white) lobe volume that were disproportionate to variations in total cerebral volumes. These two analyses utilized group and sex as independent variables, and postnatal age at scan, total cerebral gray (or white) volume as covariates, and the four gray or white lobe volumes (i.e., frontal, temporal, parietal, and occipital) as dependent variables.

Analysis of between-group effects for lateral ventricular cerebrospinal fluid was performed using analysis of covariance, with group and sex as independent variables and postnatal age and total cerebral cerebrospinal fluid volume as covariates. A multiple analysis of covariance was used to determine if a specific profile of ventricular subregion enlargement characterized the preterm group. Four ventricular subregions (body, frontal horn, temporal horn, occipital horn) comprised the dependent variables, group and sex were used as independent variables, and postnatal age and total cerebral cerebrospinal fluid volume as covariates. Analysis of covariance with subcortical gray matter volume as the dependent variable, postnatal age and total cerebral gray matter volume as covariates, and group and sex as independent variables also was calculated.

To explore the relationships between neuroanatomic variation and cognitive outcome in the preterm group, partial, two-sided correlations were calculated between regional volumes and (1) cognitive testing scores and (2) specific a priori perinatal variables controlling for total brain volume. Two-sided bivariate correlations were calculated between perinatal variables and cognitive testing scores for the preterm group. Neuroanatomic variables included those that differentiated the preterm group from the control group. Perinatal variables included birth weight, gestation age, maternal education, presence of bronchopulmonary dysplasia, intervention with indomethacin, and presence of intraventricular hemorrhage at 6 hours.

Partial correlations also were used to investigate statistical associations between specific neuroanatomic variables. For example, given the findings of ventricular enlargement and reduced subcortical volumes in preterm children [8], partial correlations between lateral ventricular cerebrospinal fluid, subcortical gray, cerebral gray, and cerebral white matter volumes were calculated after controlling for total brain volume.

Similarly, because enlargement of the occipital horn has been observed to be a particularly prominent component of ventriculomegaly in children with very low birth weight [8], partial correlations were generated between occipital horn cerebrospinal fluid, occipital lobe gray, occipital lobe white, and subcortical gray volumes while controlling for total brain volume. As a “control” analysis to investigate whether local tissue reduction would affect other components of the lateral ventricle, a comparison partial correlation was run for frontal horn cerebrospinal fluid, frontal gray, frontal white, and subcortical gray volumes while controlling for total brain volume.

Results

Sample Characteristics

The mean birth weight for the 73 preterm patients was 966 ± 168 gm, and the mean gestation age was 28.3 ± 1.9 weeks. Forty-one of the preterm patients were male. Male and female preterm patients were matched on perinatal variables and risk factors (Table 1). Maternal education for the preterm group was, on average, at a post-high school level (mean = 13.4 ± 2.1). Demographic and cognitive data are listed in Table 2. On average, children in the preterm group were slightly (7 months), although significantly older than those in the control group ($P = < 0.0001$). The two groups were group matched for all other variables. As expected, the preterm group also had lower mean intelligence quotient scores than

control children ($F = 7.5$; degrees of freedom [df] = 1,103; $P = 0.007$). Intelligence quotient data were not available for two of the control subjects. Preterm patients' performance on the reading recognition and reading comprehension achievement tests was comparable to that of control subjects. However, their math scores were, on average, significantly below the control subjects ($F = 7.4$, df = 1, 83, $P = 0.01$). Achievement scores were collected later in the study and therefore not available for all patients.

Cerebral Lobes

Total cerebral volume was significantly reduced in the preterm group compared with control subjects ($F = 10.0$, df = 1,106, $P = 0.002$). This finding involved cerebral gray ($F = 9.1$, df = 1,106, $P = 0.003$) and cerebral white matter ($F = 6.7$, df = 1,106, $P = 0.01$). There was a significant sex by diagnosis interaction for cerebral white matter ($P = 0.01$) indicating that preterm males had significantly less white matter than term males, whereas preterm females were comparable to term females.

Multiple analysis of covariance indicated a significantly altered profile of cerebral lobe gray volumes in the preterm group compared with the control group (Wilk's Lambda $F = 14.2$, df = 4,97, $P < 0.0001$). Examination of the estimated marginal means after adjusting for the effects of the covariates revealed that, in relation to overall cerebral gray matter volume, temporal lobe gray matter volume was disproportionately reduced ($F = 15.2$, $P < 0.0001$), whereas parietal lobe ($F = 20.5$, $P < 0.0001$) and frontal lobe ($F = 4.9$, $P = 0.03$) gray matter volumes were disproportionately increased in the preterm group (Table 3, Fig 1). Total cerebral gray volume ($P < 0.0001$) and sex ($P = 0.01$) were significant covariates but age was not ($P = 0.09$). There was no significant diagnosis by sex effect ($P = 0.15$).

In terms of cerebral lobe white matter, there were no significant effects for white matter volumes in the individual lobes. However, there was a trend for lower temporal lobe white matter in the preterm group ($P = 0.09$).

Lateral Ventricular Volumes

Results indicated disproportionately enlarged lateral ventricular cerebrospinal fluid volumes in the preterm group ($F = 14.1$, df = 1,100, $P < 0.0001$). Analysis of the ventricular subregions revealed a significant main effect of group (Wilk's Lambda $F = 6.2$, df = 4,97, $P = 0.0001$). Examination of the estimated marginal means revealed disproportionately enlarged ventricular body ($F = 10.5$, $P = 0.002$) and occipital horns ($F = 20.8$, $P < 0.0001$) in the preterm group. No group difference was observed for the temporal and frontal horns. Age ($P = 0.25$), sex ($P = 0.82$), and cerebral cerebrospinal fluid ($P = 0.65$) were not significant covariates. There was no significant sex by diagnosis effect ($P = 0.85$; see Table 3).

Because the total ventricular and occipital horn cerebrospinal fluid volumes displayed mild to moderate positive skewing for the preterm group, between-group analyses were repeated with a nonparametric (Mann-Whitney) test. Identical results were observed for all ventricular comparisons (P values for total, body, and occipital horn cerebrospinal fluid all < 0.0001 , preterm > control).

Subcortical Tissue Volumes

Table 3 also indicates that subcortical gray matter volume was disproportionately reduced ($F = 32.2$, df = 1,100, $P < 0.0001$). Sex ($P = 0.98$) and age ($P = 0.18$) were not significant covariates, but cerebral gray matter volume was significant ($P < 0.0001$). There was no sex by diagnosis effect ($P = 0.66$).

Correlation of Neuroanatomic, Cognitive, and Perinatal Variables (Preterm Group)

Exploratory correlational analyses indicated that increased birth weight was associated with decreased parietal gray ($r = -0.32$, $P = 0.01$), frontal gray ($r = -0.23$, $P = 0.05$) and occipital horn volumes ($r = -0.23$, $P = 0.05$). There was a trend for a negative correlation between temporal gray and gestation age ($r = -0.22$, $P = 0.07$). Decreased subcortical gray matter was related to the presence of intraventricular hemorrhage at 6-11 hours after birth ($r = -0.27$, $P = 0.02$). No other relationships between neuroanatomic and perinatal variables were significant. Additionally, no significant relationships between cognitive and neuroanatomic variables were observed, although the correlation between subcortical gray matter and performance intelligence quotient approached significance ($r = 0.22$, $P = 0.06$). Maternal education accounted for up to 22% of the variance in cognitive functioning; however, no other perinatal variable (e.g., birth weight, intraventricular hemorrhage) was significantly related to cognitive outcome (see Table 4).

Relationship Among Neuroanatomic Variables

As shown in Table 5, correlational analyses disclosed that, for the preterm group, lateral ventricular cerebrospinal fluid volume was significantly negatively correlated with subcortical gray volume ($r = -0.54$, $P < 0.0001$). For control subjects, lateral ventricular volume was significantly negatively correlated with cerebral white matter ($r = -0.36$, $P = 0.04$). Subcortical gray matter volume was significantly correlated with cerebral gray matter volume ($r = 0.40$, $P < 0.0001$) in the preterm group but not the control group. In the preterm group, occipital horn volume was significantly, negatively correlated with occipital white matter volume ($r = -0.26$, $P = 0.03$) and subcortical gray matter volume ($r = -0.53$, $P < 0.0001$). These correlations were not observed in the control group. Frontal horn volume was significantly negatively correlated with subcortical gray matter volume ($r = -0.47$, $P < 0.0001$) in the preterm group only.

Discussion

Neuroanatomic Outcome

The current investigation characterized cerebral lobe and lateral ventricular development in preterm children. We demonstrated disproportionately increased frontal and parietal lobe gray matter, increased volume of the occipital horn and body of the lateral ventricle, and reduced temporal lobe gray matter in the preterm children compared with term control subjects. These findings are consistent with previous studies of preterm brain morphology [22].

Additionally, the current study introduces novel findings regarding the relationship among neuroanatomic regions that may partly explain aberrant neurodevelopment in preterm children. It is unclear why frontal and parietal volumes of the preterm group were enlarged relative to overall cerebral size, whereas the temporal lobe tended to be diminished. However, disrupted pruning mechanisms are possible explanations. The undeveloped brain is characterized by synaptic overproduction. Synapses and dendrites are then systematically eliminated as the brain begins to mature [23,24]. Pruning tends to vary by brain region, occurring more slowly in frontal areas compared with temporal. Thus increased anterior tissue may reflect delayed or disrupted synaptic pruning in the preterm brain. Because synapse elimination tends to vary by brain region and is highly influenced by environmental factors [25], some areas could potentially be more or less delayed in this developmental process as a result of preterm birth and the timing of the injury to the developing brain.

Relatively decreased temporal lobe volume in the preterm group additionally or alternatively may represent increased tissue atrophy in this region. Preterm birth is frequently associated

with hypoxic-ischemic events [26]. Apoptosis can be activated by hypoxia [27], and the temporal lobe tends to be more vulnerable to ischemic infarct because of its relative position in the cerebral blood supply and low cerebral perfusion [28]. Given the increased vulnerability of white matter to ischemic injury [3], white matter loss in the temporal lobe would be expected. There was a trend, albeit nonsignificant, for a group difference in temporal lobe white matter. Additionally, temporal lobe tissue atrophy or aberrant neurodevelopment resulting from ischemic damage would likely involve a reciprocal increase in temporal lobe cerebrospinal fluid. A post hoc evaluation of the relationship between temporal lobe white matter and temporal lobe cerebrospinal fluid indicated a significant negative correlation in the preterm group ($r=-0.24$, $P=0.04$) but not in the term group. However, associations between temporal lobe tissue reduction and incidence of bronchopulmonary dysplasia or intraventricular hemorrhage were not observed. The frequency of these known complications of preterm birth was not of high enough incidence in the present preterm sample to fully explore this issue. Therefore it is likely a combination of pathologic processes, including ischemia and disrupted pruning mechanisms, among others, that contribute to the morphologic abnormalities associated with preterm birth.

An alternative explanation for the disproportionate cerebral lobe development in the preterm brain involves the stereotaxic atlas template used to normalize the brains into a standard three-dimensional space and calculate regional tissue volumes. A poor fit of this template to the preterm brains may account for the anterior shift of cortical tissue. However, qualitative analysis of the template on the preterm brains indicated an appropriate fit. A discrepancy in the atlas correspondence that we could not detect qualitatively would imply that a shape difference might exist in the preterm brain. We plan to investigate this possibility in future studies using three-dimensional shape analysis methods.

In this investigation, as in previous reports, ventriculomegaly and diminished subcortical gray matter volume were observed in children with very low birth weight [8,29]. In the present study, reduction in subcortical gray matter volume was strongly correlated with enlarged ventricular cerebrospinal fluid volume in the preterm group. This correlation suggests that ventriculomegaly in the preterm group may in part be due to an *ex vacuo* expansion of this cerebrospinal fluid space secondary to subcortical tissue loss. When analyses were focused on the correlates of increased volume of occipital horn cerebrospinal fluid in the preterm group, it appeared that, in addition to decreases in subcortical gray matter volume, local reductions in occipital lobe tissue further contributed to enlargement of this region. There was no evidence of a similar local tissue reduction effect contributing to enlargement of the frontal horn of the lateral ventricle in the preterm group. These findings suggest that developmental and pathologic processes leading to increased lateral ventricular volumes in children with very low birth weight are significantly altered compared with typically developing control subjects. In particular, whereas reduction of subcortical gray matter may be an important contributor to overall ventriculomegaly, regionally specific diminution of local tissue in the occipital lobe may further contribute to enlargement of the occipital horn commonly observed in children with very low birth weight.

Perinatal Variables and Neuroanatomic Outcome

Birth weight was the most significant perinatal variable associated with cortical morphology in the preterm group. Others studies of preterm children have demonstrated a relationship between lower birth weight and increased cognitive deficits [30]. However, many studies have not found a correlation between birth weight and cognitive outcome [31,32] or brain morphology [8,22] in preterm children. The present study demonstrated significant negative correlations between birth weight and parietal and frontal gray, as well as occipital horn volumes. Given that these volumes were disproportionately enlarged in the preterm group, it seems that increased (i.e., healthier) birth weight may reduce the magnitude of these

neuroanatomic abnormalities. However, the inconsistency regarding birth weight and neurodevelopment across studies may suggest that a complex combination of factors contributes to neurodevelopment in preterm children.

We also found that the presence of intraventricular hemorrhage was associated with reduced subcortical gray matter volumes. Although our sample did not include any severe cases of intraventricular hemorrhage, previous studies suggest that even mild intraventricular hemorrhage may cause damage to subcortical regions [33]. Intraventricular hemorrhage often results in ventricular expansion [4,34]. Based on our findings, there is a strong relationship between ventriculomegaly and decreased subcortical gray matter volume as described above. Thus the relationship observed here between intraventricular hemorrhage and reduced subcortical gray matter volume appears to operate via enlarged ventricular space.

Cognitive Outcome

Although, on average, intelligence quotient and achievement scores among the preterm patients in the present study were within normal limits, intelligence quotient and math scores were significantly lower than those of term control subjects. Some investigations of cognitive outcome in preterm children suggest that certain abilities improve over time, possibly by adolescence [35]. Therefore the preterm brain may eventually compensate for early neuropathology.

Neural plasticity mechanisms may differ between preterm children as a result of genetic factors. In the present study, maternal education was significantly related to intellectual functioning, reading, and math achievement in the preterm group whereas neuroanatomic and perinatal factors, such as birth weight and intraventricular hemorrhage, were not. Other studies of preterm children also have found an association between cognitive outcome and maternal or paternal education [36]. The putative notion of cognitive reserve may partly explain some of the variation among functional outcome in preterm children related to an inherited potential. Cognitive reserve theories suggest that higher intellectual ability or educational level may be protective factors, increasing the ability to recover from or compensate for neurologic disease or injury [37]. Although no studies to date have examined cognitive reserve in preterm children, studies of adolescents born preterm [38,39] demonstrated relatively normal neuropsychological functioning despite persistent brain abnormalities. This finding may suggest that preterm children with greater cognitive reserve compensate for early brain damage. However, the authors of these studies did not evaluate the relationship between parental intelligence quotient/education on the cognitive outcome of the preterm patients. Exploration of these relationships utilizing longitudinal designs will be necessary to determine if cognitive reserve and plasticity issues influence outcome in preterm children.

Consistent with our previous study of this same preterm cohort [40], we demonstrated a significant sex by diagnosis effect for cerebral white matter affecting preterm males. However, we did not demonstrate any sex effects for cerebral lobe volumes in the present study. Although a sex effect was present in terms of males having larger volumes than females, as expected, there were no significant sex by diagnosis interactions associated with the individual cerebral lobes. Studies have reported that male preterm children are at increased risk for negative outcome [14,36]. Continued investigation of sex differences in neurodevelopment is required to determine if there are neural markers of the increased morbidity in preterm males.

In summary, although preterm, very low birth weight children may tend to have decreased overall cerebral volumes, an examination of specific lobe development demonstrates

disproportionately reduced temporal lobe and subcortical gray matter volumes and enlarged frontal and parietal gray volumes. Additionally, the occipital horn and body of the lateral ventricle were increased in the preterm group compared with the term control subjects. Disrupted or delayed synaptic pruning or other mechanisms responsible for plasticity are possible factors involved in the disorganized neural development of the preterm brain. Lower birth weight and maternal education, as well as reduced subcortical gray matter volume may be risk factors for increased neuroanatomic and cognitive deficits. Continued investigations, especially those involving longitudinal designs, are necessary to further delineate the factors involved in the neuroanatomic and functional outcomes of preterm birth.

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Figure 1.

Children born preterm demonstrated disproportionately enlarged frontal and parietal lobe volumes and reduced temporal lobe volumes compared with term control subjects.

Table 1

Perinatal variables for preterm subjects

	Male	Female	P Value
Number	41	32	
Gestation age (wk)	28.1 (2.0)	28.5 (1.8)	0.40
Birth weight (gm)	973 (169)	957 (169)	0.69
Maternal education	13.4 (2.2)	13.4 (2.0)	0.90
Intraventricular hemorrhage, any grade, 6-11 hr after birth	4 (10%)	5 (17%)	0.49
Bronchopulmonary dysplasia*	22 (54%)	12 (40%)	0.24
Indomethacin	24 (59%)	14 (44%)	0.24
Amnionitis	7 (17%)	3 (10%)	0.29
Intraventricular hemorrhage, grade 3-4, at 5 postnatal days	0	0	na
Periventricular leukomalacia	0	0	na
Ventriculomegaly	0	1 (3%)	0.44

Data are expressed as mean (S.D.).

Abbreviation: na = Not applicable

* Need for supplemental oxygen and abnormal chest x-ray at 28 days of age.

Table 2

Group demographic and cognitive variables

	Preterm	n	Control	n	P Value
Age	9.2 (0.70)	73	8.5 (0.71)	33	<0.0001
Age range	8.4–11.4	73	7.3–10	33	
Males	41		15		0.40
Full scale IQ	95 (17)	73	104 (15)	31	0.01
Verbal IQ	98 (19)	73	106 (15)	31	0.02
Performance IQ	93 (16)	73	102 (17)	31	0.01
Reading comprehension	99 (19)	73	100 (13)	20	0.77
Reading recognition	97 (19)	73	101 (15)	20	0.39
Math	90 (20)	73	104 (17)	20	0.01

Data are expressed as mean (S.D.).

Table 3

Neuroanatomic volumes for preterm and control groups

	Preterm	Control	F	df	P Value
Cerebral tissue	1033 (79)	1074 (106)	10	1,106	0.002
Cerebral gray	642 (47)	667 (63)	9.1	1,106	0.003
Cerebral white	392 (39)	407 (55)	6.7	1,106	0.01
Subcortical gray	41 (2.6)	44 (2.8)	32.2	1,106	<0.0001
Ventricular CSF	15 (8.9)	7.5 (6.7)	14.1	1,106	<0.0001
Frontal horn	2.9 (1.8)	2.2 (1.9)	2.9	1,106	0.09
Body	5.3 (3.4)	2.8 (3.6)	10.5	1,106	0.002
Temporal horn	0.18 (0.19)	0.15 (0.20)	0.37	1,106	0.54
Occipital horn	6.6 (4.2)	2.3 (4.4)	20.8	1,106	<0.0001
Frontal lobe					
Frontal lobe gray	236 (8.6)	231 (9.0)	4.9	1,106	0.03
Frontal lobe white	142 (7.8)	140 (8.1)	2.1	1,106	0.16
Parietal lobe					
Parietal lobe gray	164 (6.7)	157 (6.9)	20.5	1,106	<0.0001
Parietal lobe white	108 (5.8)	107 (6.0)	0.40	1,106	0.53
Temporal lobe					
Temporal lobe gray	132 (6.0)	138 (6.3)	15.2	1,106	<0.0001
Temporal lobe white	62 (5.1)	64 (5.3)	2.9	1,106	0.09
Occipital lobe					
Occipital lobe gray	76 (8.0)	79 (8.3)	1.9	1,106	0.17
Occipital lobe white	47 (6.2)	47 (6.4)	0.05	1,106	0.83

Data are shown as mean (S.D.); values are in cm³. All values represent volumes after statistically adjusting for brain volume and age, with the exception of cerebral volumes. Abbreviations CSF = Cerebrospinal fluid df = Degrees of freedom

Table 4

Significant neuroanatomic, cognitive, and perinatal partial correlations in the preterm group

	<i>r</i>	<i>P</i>
Full scale IQ–maternal education	0.47	<0.0001
Verbal IQ–maternal education	0.47	<0.0001
Performance IQ–maternal education	0.37	0.001
Reading comprehension–maternal education	0.27	0.03
Reading recognition–maternal education	0.23	0.05
Math–maternal education	0.35	0.01
Parietal gray–birth weight	−0.32	0.01
Frontal gray–birth weight	−0.23	0.05
Occipital horn–birth weight	−0.23	0.05
Subcortical gray–IVH6HR	−0.27	0.02

Abbreviations IQ = Intelligence quotient IVH6HR = intraventricular hemorrhage, any grade, 6–11 hours after birth

Table 5

Partial correlations among neuroanatomic variables

Variables	Preterm		Term	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Lateral ventricle–subcortical gray	−0.54	<0.0001	−0.36	0.04
Subcortical gray–cerebral gray	0.40	<0.0001	0.30	0.10
Occipital horn–occipital white	−0.26	0.03	−0.03	0.90
Occipital horn–subcortical gray	−0.53	<0.0001	−0.08	0.65
Frontal horn–subcortical gray	−0.47	<0.0001	−0.11	0.53