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Brain Volume Reductions within Multiple Cognitive Systems in Male Preterm Children at Age Twelve

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Abstract

Objectives—To more precisely examine regional and subregional microstructural brain changes associated with preterm birth.

Study design—We obtained brain volumes from 29 preterm children, age 12 years, with no ultrasound scanning evidence of intraventricular hemorrhage or cystic periventricular leukomalacia in the newborn period, and 22 age- and sex-matched term control subjects.

Results—Preterm male subjects demonstrated significantly lower white matter volumes in bilateral cingulum, corpus callosum, corticospinal tract, prefrontal cortex, superior and inferior longitudinal fasciculi compared with term male subjects. Gray matter volumes in prefrontal cortex, basal ganglia, and temporal lobe also were significantly reduced in preterm male subjects. Brain volumes of preterm female subjects were not significantly different from those of term female control subjects. Voxel-based morphometry results were not correlated with perinatal variables or cognitive outcome. Higher maternal education was associated with higher cognitive performance in preterm male subjects.

Conclusions—Preterm male children continue to demonstrate abnormal neurodevelopment at 12 years of age. However, brain morphology in preterm female children may no longer differ from that of term female children. The neurodevelopmental abnormalities we detected in preterm male subjects appear to be relatively diffuse, involving multiple neural systems. The relationship between aberrant neurodevelopment and perinatal variables may be mediated by genetic factors, environmental factors, or both reflected in maternal education level.

Children born prematurely are at risk for cognitive impairments with deficits in executive functioning, language, visual-motor integration, attention, and scholastic performance.¹ Although neuroimaging studies have begun to provide an initial picture of the neural correlates of preterm birth,^{2–7} additional studies are needed to more precisely elucidate the functional neuroanatomy underlying cognitive dysfunction in affected children. In this study, we aimed to more precisely examine regional and subregional microstructural changes associated with this injury to the developing brain by using our 12-year-old prematurely born cohort. We hypothesized that preterm birth would result in long-lasting changes in brain development. Extending our earlier studies, this analysis used voxel-based

morphometry (VBM) to measure volumetric data. VBM is an automated structural analysis used to detect regional microstructural morphologic differences in brain magnetic resonance imaging (MRI).⁸ Unlike volumetric tracing methods, VBM does not depend on user-defined brain regions, but rather presents a comprehensive localization of tissue volume or density differences between groups.⁸

Several VBM studies of preterm birth have been conducted.^{9–12} However, we used VBM analyses as part of a unique, multimodal study of neurodevelopment in preterm children that included semi-automated volumetric and manual region of interest measurements on the basis of specific gyral boundaries to confirm our VBM findings.

METHODS

Subjects

All subjects were enrolled in the follow-up component of the Multicenter Randomized Indomethacin IVH Prevention Trial.¹³ The preterm subjects were sequentially recruited for the MRI study when they reached 12 years of age. The preterm cohort consisted of children with no ultrasound scanning evidence of intraventricular hemorrhage (IVH), periventricular leukomalacia, and/or low-pressure ventriculomegaly in the newborn period. These participants had normal neurologic findings at age 12 years and no contraindications to MRI (ie, orthodontia or ventriculoperitoneal shunts). To minimize the possible effects of ventriculomegaly on white matter tracks, we required total ventricular cerebrospinal fluid volume to be within 2 SDs of the mean ventricular volume of the term control group. Of 71 preterm subjects, 29 (12/28 females, 17/43 males, $\chi^2 = .08$, $P = .81$) met these criteria. These children were representative of the total cohort of preterm subjects with no evidence of IVH, periventricular leukomalacia, or low-pressure ventriculomegaly from which they were selected with respect to sex, handedness, IQ scores, minority status, and maternal education. There were no significant differences in handedness, minority status, or maternal education between male subjects and female subjects.

Twenty-three healthy term children, aged 12 years, were recruited from randomly selected names on a telemarketing list of families in the same geographic region and from local advertisements.¹⁴ One female subject (of 13 total) was excluded for having ventricular cerebrospinal fluid volume >2 SDs from the mean. There were no between-group differences in demographic variables including handedness, sex, and age. However, minority status differed between preterm and term male subjects ($P = .04$; Table I).

MRI Acquisition

MRIs of each subject's brain were acquired with a single GE-Signa 1.5 T scanner (General Electric, Milwaukee, WI). Sagittal brain images were acquired with a 3-dimensional volumetric radio frequency spoiled gradient echo pulse sequence with these scan variables: TR = 24 msec, TE = 5 msec, flip angle = 45°, NEX = 1, matrix size = 256 × 192, field of view = 30 cm, slice thickness = 1.2 mm, 124 contiguous slices.

VBM Analysis

The optimized VBM process¹⁵ included: 1) segmentation and extraction of the brain in native space, 2) normalization of the images to a standard space with a customized pediatric matter template (created with images from all 51 subjects), 3) segmentation and extraction of the normalized brain (extraction is repeated to ensure that no non-brain tissues remain), 4) modulation of the normalized images to correct for tissue volume differences caused by the normalization procedure, and 5) smoothing of the normalized, segmented, modulated images with a 12-mm FWHM kernel to reduce the effects of noise. Statistical analysis of VBM data

used the general linear model framework of Statistical Parametric Mapping (SPM2) software (Wellcome, UK) to obtain probability maps indicating voxels characterized as gray or white matter. An analysis of variance model was used to test between group and group by sex differences in whole brain gray or white matter volumes. Absolute threshold masking (threshold = .15) was used to minimize gray-white boundary effects, and implicit masking was used to disregard voxels with zero values. The statistics for VBM analyses were normalized to Z scores, and significant clusters of activation were determined with a height threshold of $P < .001$, with family-wise error correction for multiple comparisons.

Semi-automated Volumetric Measurements

On the basis of results from the whole brain VBM analyses aforementioned, regional measurements were obtained with our semi-automated whole brain segmentation and quantification method, as previously described and validated.^{16,17} In brief, this technique involves non-uniformity correction, semi-automated removal of non-brain tissue, automated tissue segmentation, and semi-automated division of cerebrum into lobes with a stereotactic-based parcellation method. Statistical analyses of semi-automated volumes were accomplished by using analysis of variance with SPSS software version 15 for Windows.

Region of Interest Analysis

On the basis of VBM results, ROIs were manually delineated on a mean image created from all subjects' normalized whole brain images. ROIs were then used as explicit masks in the SPM2 general linear model as aforementioned. This constrained the between-group analyses to the boundaries of the ROIs. We manually delineated left and right superior temporal gyri (STG) on the mean image of all male subjects and on the mean image of all female subjects. The STG was chosen because this region represented the peak location of VBM gray matter volume difference. Our white matter findings are supported by convergent diffusion tensor imaging analyses that demonstrated reduced white matter integrity in the inferior fronto-occipital fasciculus, anterior portions of the uncinate fasciculi bilaterally (ie, inferior frontal gyrus), and the splenium of the corpus callosum.¹⁸ Therefore, we focus here on the gray matter findings. The specific boundaries and methods for measuring the STG are described elsewhere.¹⁹ All statistical thresholds for ROI analyses were identical to those used for the whole brain analyses.

Correlations

We explored relationships among birth weight, gestational age, and cognitive outcome and brain development in preterm birth by using multiple regression analysis in SPM2 with VBM whole brain within-group results for male and female subjects ($P < .01$, family-wise error). Maternal education was correlated with cognitive variables in SPSS. For cognitive outcome, all subjects enrolled in the IVH trial were administered a battery of neuropsychological testing that included measures of language, visuomotor integration, intellectual ability, reading proficiency, and phonological processing. On the basis of our findings as detailed in the Results section, we used selected measures from this battery as detailed in Table II. These measures were chosen on the basis of their correspondence with expected function of underlying neuroanatomic alterations in the preterm group compared with control subjects and their being significantly lower in preterm births compared with control subjects.

RESULTS

Voxel-based Morphometry

Preterm male subjects demonstrated significantly reduced gray and white matter volumes in multiple brain regions compared with term male subjects, and brain morphology of preterm female subjects was not significantly different from that of term female subjects (Figures 1 and 2).

Equal Groups Analyses

Because preterm male subjects outnumbered term male subjects in our sample nearly 2-to-1 (preterm female subjects were equally matched to term female subjects at $N = 12$), we repeated our VBM analyses with the same variables and thresholds for gray and white matter whole brain volumes by using a random sample of 10 (of 17) preterm male subjects such that both groups of male subjects were equivalent (at $N = 10$). This subgroup of preterm male subjects did not differ significantly from the main group of preterm male subjects in age, cognitive function, minority status, or handedness. The term and preterm male subjects in this equal-groups comparison continued to differ in cognitive function, but were matched for demographic variables, including minority status (Appendix 1; available online at www.jpeds.com). These analyses yielded nearly identical results to our initial findings (Appendix 2; available at www.jpeds.com).

Semi-automated Volumetric Measurements

Consistent with VBM measurements, results of semiautomated analyses indicated that cerebral gray, cerebral white, frontal, and temporal total tissue volumes were significantly lower in preterm male subjects compared with term male subjects, but did not differ significantly between the female subject groups (Table III). Further analysis indicated that only temporal lobe tissue volume was disproportionately reduced after controlling for total brain volume ($F = 6.1$, $P = .02$).

Regions of Interest

Consistent with the whole brain analysis, when between-group statistics were restrained to the specific STG gyral boundaries, preterm male subjects demonstrated significantly lower bilateral STG volumes than term male subjects, and preterm female subjects were not significantly different from term female subjects. Lower STG volumes in preterm male subjects primarily involved posterior STG and were more pronounced on the left (Figure 2).

Correlations

Results indicated no significant relationships between birth weight, gestational age, cognitive performance, and brain morphology in male or female preterm subjects. Maternal education was significantly correlated with intellectual functioning and language ability in preterm male subjects only (Table II).

DISCUSSION

With optimized VBM, we demonstrated extensive regions of decreased gray and white matter volumes in preterm male subjects compared with term control male subjects. Although VBM methods alone may have certain limitations, including confounded between-group differences caused by registration errors,²⁰ we confirmed our VBM findings by using complementary, semi-automated whole brain and manual ROI measurements. We also used custom templates and priors on the basis of both preterm and term data, so that registration

errors would be distributed similarly across the groups. Additionally, we used modulated data that further reduces volumetric errors caused by registration.¹⁵

Although the main sample of preterm male subjects had significantly more subjects of minority status than the term male group, the subjects in our equivalent male groups analyses were matched for minority status and all other demographic variables, and these analyses confirmed our primary results. Our findings are consistent with several other reports that indicate an increased brain vulnerability to the effects of preterm birth in male subjects. This study significantly expands on the scope and specificity of these sex differences and the neurodevelopmental consequences of early brain injury in preterm birth.

Earlier we showed that both male and female preterm children at 8 years of age demonstrated significant neuroanatomic abnormalities and lower cognitive function compared with control subjects.^{3,21,22} This report offers the first evidence that neurodevelopment in preterm female subjects may begin to converge on that of term control subjects between ages 8 and 12 years. Our results suggest that, at 12 years of age, brain morphology and all cognitive abilities tested in preterm female subjects may be more similar to that of term female subjects. However, male subjects continue to show aberrant neurodevelopment and deficits in cognitive function related to preterm birth at 12 years of age.

Male-female differences associated with preterm birth may be caused by increased genetic endowment related to redundancy in certain X-chromosome genes, other genetic and environmental factors, or both. Suspected X-chromosome involvement in increased male vulnerability stems from the excess of male subjects in whom developmental disabilities affecting cognitive function are diagnosed, including mental retardation,²³ autism,²⁴ specific language impairment,²⁵ and attention deficits.²⁶ Environmental influences on brain structure and function via experience-dependent neuroplasticity also involve the X-chromosome. Many of the molecular mechanisms involved in the neurobiologic changes underlying neuroplasticity are regulated by X-chromosome gene function.^{19,27–29} However, this sample size is relatively small, particularly in comparison to our sample of 8-year-old children, and thus the lack of significance in the female between-group analyses should be interpreted with caution. Replication of these findings in a larger sample is required.

We found gray and white matter reductions in several regions in preterm male subjects that may subserve several cognitive functions. Superior temporal gyrus, middle temporal gyrus, fusiform gyrus, inferior frontal gyrus, and the corpus callosum have been shown to be involved in language and reading development in typically developing children.^{30–33} Language and reading skills are lower in preterm children, particularly in boys.^{6,34–36} Other studies also have reported decreased volume in the corpus callosum associated with preterm birth.^{37–39} The cingulum, which was reduced in preterm male subjects compared with control subjects, is involved in visual-spatial attention, sensorimotor function, and executive control according to both human and animal models.^{40–42} Well-established primary motor and sensorimotor pathways including precentral gyrus, corticospinal and corticopontine tracts, superior thalamic radiation, middle cerebellar peduncle, basal ganglia, internal capsule, and corona radiata^{43–45} also were significantly reduced in our sample of preterm male subjects. Boys born prematurely are known to be more likely to have moderate to severe cerebral palsy compared with girls,⁴⁶ and male sex has been related to poor general neuromotor behavior outcome at age 7 years.⁴⁷ We demonstrated significantly reduced volumes in inferior, middle, superior frontal gyri, cingulate gyrus, and frontal-striatal and frontal-parietal white matter pathways believed to be important for executive functions in typically developing children.^{48–50} There is some evidence that preterm boys perform more poorly than girls in general on tests of executive function.⁵¹ However, it is not known

whether this represents a group by sex interaction effect or merely a sex effect. Hippocampus, amygdala, and cingulate volumes were reduced in male preterm subjects compared with control subjects. These structures are important for memory, learning, and emotion processing across the lifespan.^{52–56} Earlier studies also have demonstrated hippocampal abnormalities and impairments in memory function in preterm children.^{14,57–59} Hippocampal damage has been linked to hypoxic injury after preterm birth, resulting in reduced hippocampal neurons and impaired learning.⁵⁹

Cognitive deficits in preterm male subjects may stem from disorganized neurodevelopment resulting in inefficient recruitment of neural resources. This inefficiency may arise from disrupted functional connectivity between various cognitive systems. This possibility is supported by these results that demonstrate significant volume reductions in association pathways, including superior and inferior longitudinal, fronto-occipital, and anterior uncinate fasciculi. These pathways connect multiple, often distant brain regions involved in a number of critical cognitive functions. Disrupted connectivity in preterm male subjects requires further study using complementary neuroimaging techniques such as DTI tractography and functional MRI. However, on the basis of the results presented here, it is predicted that preterm male subjects will show decreased white matter connectivity and lower peak and more diffuse brain activation patterns.

However, we did not find any relationships between brain morphology and cognitive outcome or variables associated with preterm birth (ie, birth weight, gestational age). Correlations between these variables and neurodevelopmental outcome are likely confounded by other factors, including cognitive reserve. Cognitive reserve refers to increased efficiency of cognitive networks or greater neural capacity stemming from genetic endowment, environmental enrichment, or both.⁶⁰ Cognitive reserve is believed to slow or lessen the manifestations of brain insults and therefore tends to mediate the relationship between neurobiologic states and cognitive outcome. Maternal education is a proxy for cognitive reserve because of the relatively high heritability of IQ.^{61,62} Accordingly, we found that increased maternal education was significantly correlated with increased intellectual and language functioning in preterm children. Higher maternal education likely suggests increased genetic endowment and greater environmental enrichment.⁶³ Early interventions should include environmental enrichment through stimulating physical and mental activities to increase cognitive reserve.⁶⁴

Continued longitudinal studies of prematurely born children with an emphasis on sex-related cognitive and neurodevelopmental changes and the inclusion of genetic techniques are necessary to explore the long-term impact of preterm birth on the developing brain. The increased vulnerability of prematurely born boys to neurodevelopmental and cognitive deficits should inform early intervention approaches, but should also be carefully considered during later school years because we have shown continued morphometric abnormalities and corresponding functional deficits at age 12 years. Future studies also should include analyses of genetic factors that may contribute to variation in cognitive outcome,⁶⁵ particularly those involving the X-chromosome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Glossary

IVH Intraventricular hemorrhage

MRI	Magnetic resonance imaging
ROI	Region of interest
SPM2	Statistical Parametric Mapping
STG	Superior temporal gyri
VBM	Voxel-based morphometry

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Figure 1.

Optimized VBM group by sex (ie, term male subjects minus preterm male subjects) whole brain results showing regions of reduced gray (**A**) and white (**B**) matter volumes in preterm male subjects compared with term male subjects (clusters = height threshold of $P < .001$ corrected). Regional volumes were not significantly different between preterm and term female subjects.

Figure 2.

STG ROI analyses of gray matter volumes indicate significantly lower volumes in bilateral posterior STG of preterm male subjects compared with term male subjects, with greater volume reduction in the left hemisphere consistent with earlier reported language deficits. STG volumes in preterm female subjects did not differ from those of term female subjects.

Table 1

Demographic data for the preterm and term control groups shown as mean (SD)

	Male		Female		Preterm vs Term		Male		Female	
	Preterm	Term	Preterm	Term	F	P value	F	P value	F	P value
N	17	10	12	12						
Age	12.2 (.19)	12.4 (1)	12.3 (.29)	12.5 (.98)	1.02	.32	.52	.48	.5	.49
Maternal education (years)	13.2 (2.7)	13.4 (3.)	14 (1.9)	13.4 (3.7)	.03	.86	.02	.88	.24	.63
Right handed	14 (83%)	9 (90%)	10 (83%)	12 (100%)	Chi = 1.9	.22	Chi = .29	.59	Chi = 2.2	.14
Minority status	8 (47%)	1 (10%)	6 (50%)	6 (50%)	Chi = 1.7	.2	Chi = 4.4	.04	Chi = 0	1
Gestational age (months)	28.3 (1.6)		28.7 (2.7)							
Birth weight (g)	945 (142)		1000 (156)							

Table II

Cognitive data for preterm children and term control subjects shown as mean (SD)

	Males		Males		Females		Preterm vs Term		Males		Females	
	Correlation with maternal education		Preterm	Term	Preterm	Term	F	P value	F	P value	F	P value
WISC FSIQ *	$r = .59, P = .007$		86 (13)	107 (12)	93 (17)	101 (19)	11.4	.001	16.2	<.0001	1.2	.28
CELF total *	$r = .51, P = .02$		83 (16)	97 (12)	94 (18)	106 (19)	9.3	.004	6	.02	2.7	.12
TOWRE total			91 (16)	98 (17)	104 (15)	99 (17)	.33	.57	1.2	.28	.43	.52
VMI total *	$r = .08, P = .38$		81 (14)	98 (15)	90 (14)	89 (11)	4.1	.05	8.9	.006	.07	.8
PPVT total			91 (26)	105 (11)	96 (21)	102 (25)	1.8	.2	2.4	.13	.42	.52
CTOPP NWR *	$r = -.03, P = .46$		11 (1.8)	8.4 (1.6)	10 (1.8)	10 (2.2)	4.6	.04	9	.007	.16	.69
CTOPP RN			17 (5.5)	19 (7)	21 (5.7)	21 (4.3)	.44	.51	.5	.48	.06	.81
Gray SRQ			86 (20)	96 (22)	100 (20)	104 (23)	2	.16	1.6	.22	.2	.66

WISC, Wechsler Intelligence Scale for Children⁶⁶; FSIQ, Full Scale Intelligence Quotient; CELF, Clinical Evaluation of Language Fundamentals⁶⁷; TOWRE, Test of Word Reading Efficiency⁶⁸; VMI, Test of Visual-Motor Integration⁶⁹; PPVT, Peabody Picture Vocabulary Test⁷⁰; CTOPP, Comprehensive Test of Phonological Processing⁷¹; NWR, non-word repetition; RN, rapid naming; SRQ, Silent Reading Quotient.⁷²

* Tests included in structure-function correlations with VBM data.

Table III

Results of semi-automated volumetric analyses (expressed as cubic centimeters) for male and female subjects

Region	Mean (SD)			F	P value	Mean (SD)			F	P value
	Preterm male	Term male				Preterm female	Term female			
Frontal gray	232.6 (20.1)	251.9 (28.1)		4.32	.05	229.7 (27.6)	229.6 (24.8)		.001	.98
Frontal white	149.8 (17.4)	171.1 (26.2)		6.46	.02	147.8 (19.7)	159.2 (18)		.413	.53
Temporal gray	131.5 (13.9)	146.3 (12.9)		7.51	.01	125.3 (13.2)	128.8 (13.4)		2.22	.15
Temporal white	63.8 (12.1)	77.2 (8.1)		9.74	.005	65 (8.3)	67.5 (10.6)		.427	.52
Cerebral gray	641 (58)	695 (64)		4.94	.04	616 (60)	626 (68)		.156	.7
Cerebral white	412 (52)	470 (66)		6.41	.02	413 (47)	436 (48)		1.4	.25