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Bronchopulmonary Dysplasia Is Associated with Altered Brain Volumes and White Matter Microstructure in Preterm Infants

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Keywords

Diffusion tensor imaging · Brain volumes · Very-low-birth-weight infant · Bronchopulmonary dysplasia · Brain microstructure

Abstract

Background: Bronchopulmonary dysplasia (BPD), an inflammatory disease involving disrupted lung development, is associated with neurodevelopmental outcome in preterm infants. ***Objective:*** This study examined the brain volume and white matter (WM) microstructure in preterm infants at term-equivalent age and explored the effects of BPD on brain development. ***Method:*** We studied 56 preterm infants (33 with BPD and 23 without BPD) with no evidence of focal abnormalities on conventional magnetic resonance imaging (MRI) at term-equivalent age. Regional brain volumes and diffusion tensor images were examined using advanced segmentation techniques to acquire quantitative volume measurements, and the JHU neonatal template was used for the atlas-based analysis. We compared these infants with 22 healthy term infants of a similar postmenstrual age. ***Results:*** The preterm infants with BPD had smaller cerebral WM (p = 0.005) volumes than the preterm infants without BPD, independent of sex, gestational age, age at MRI scan, and total intracranial volume. Independent of sex, gestational age, and age at MRI scan, the preterm infants with BPD exhibited marked reductions in fractional anisotropy in the corpus callosum (p = 0.006), corticospinal tract (p = 0.003), and superior cerebellar peduncle (p = 0.002) compared with the infants with no BPD, with a significance level of $p \leq 0.008$ as a Bonferroni correction for multiple comparisons. ***Conclusion:*** Our study highlights the potential impairing influence of BPD on WM and cerebellar development in preterm infants compared with those without BPD at term-equivalent age, suggesting its clinical significance for neurodevelopment in BPD infants.

Introduction

Although overall survival rates have improved for preterm infants, these infants remain at risk of neurodevelopmental impairment that cannot be explained by apparent brain lesions visible on ultrasound or magnetic resonance imaging (MRI). Preterm birth in the third trimester of pregnancy affects the microstructural integrity of gray

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matter and white matter (WM), which can reflect harmful environments and perinatal insults according to the degree of prematurity at birth [1, 2]. Bronchopulmonary dysplasia (BPD), an inflammatory disease that arises from arrested lung development, is an independent risk factor for neurodevelopmental impairments that result from early preterm birth [2–4]. Although recent studies have emphasized preventing BPD via restricted treatment with steroidal therapy, long-term follow-up studies have documented the widespread delay of neurodevelopment in up to half of preterm infants with BPD [5, 6].

Diffusion tensor imaging (DTI) parameters of fractional anisotropy (FA) have provided significant insight into the relationships between brain structure and neurodevelopmental outcomes in preterm infants, enabling quantitative measurements of microstructural abnormalities during the neonatal period [7]. Few studies of neonatal DTI in preterm infants have elucidated whether BPD itself contributes to early decreases in brain volume or WM abnormalities [3, 8]. Anjari et al. [3] reported that BPD in preterm infants was independently associated with WM disruption in the inferior longitudinal fasciculus. Ball et al. [8] identified an additional association of BPD with changes in WM microstructures, such as the corpus callosum (CC) and centrum semiovale, with an optimized tract-based spatial statistics protocol for neonates at near-term ages [9, 10]. It is suggested that cerebral WM abnormalities in infants with BPD seem to predominate in specific brain regions, reflecting a complex relationship between BPD and reductions in the volume and FA of neonatal DTI. We hypothesized that there would be differences in structural alterations between infants with and those without BPD regarding local brain volumes and brain microstructures.

The aim of the present study was to characterize the association between BPD and brain volume/microstructure in preterm infants at term-equivalent age who had no evidence of focal abnormalities on conventional MRI after controlling for confounding factors.

Subjects and Methods

Participants

This study is part of a prospective research program involving short- and long-term postnatal follow-ups of preterm infants at the Hanyang Inclusive Clinic for Developmental Disorders within the Hanyang University College of Medicine. Between December 2015 and May 2017, 69 preterm infants were referred to the level 3 Neonatal Intensive Care Unit of Hanyang University Hospital and were eligible for participation in this study. The following inclusion criteria were used: (1) infants born before 32 weeks of gestation with a birth weight <1.5 kg and (2) MRI-DTI performed at term-equivalent age (postmenstrual age [PMA], 37–41 weeks) without focal abnormalities on MRI. Early cranial ultrasound scans obtained within 7 days of birth, 2 weeks later, and 4 weeks later, as well as subsequent MRI scans obtained at term-equivalent age, were assessed for brain injury, including intraventricular hemorrhage (IVH) and periventricular leukomalacia for preterm infants. We excluded infants who exhibited evidence of IVH more severe than grade I, as diagnosed by cranial ultrasonography or MRI. Any infants with congenital malformations, congenital infections, neonatal stroke, or chromosomal anomalies were excluded.

Three infants were excluded because of brain abnormalities with IVH more severe than grade I. Five infants were excluded because of artifactual motion during MRI or scanning at a PMA >42 weeks. Three infants had died or been transferred to another hospital before reaching term-equivalent age, and no parental informed consent could be obtained for 2 infants. Finally, 56 of the 69 preterm infants were included. Concurrently, we prospectively studied 22 healthy, term-born control infants who had normal findings on MRI, normal neonatal courses, and normal neurological examination results.

Clinical Characteristics of the Study Infants

Prenatal and neonatal data were prospectively recorded for each infant, including maternal age, maternal education, gestational diabetes, preeclampsia, placenta previa, histological chorioamnionitis, gestational age (GA), birth weight, sex, Apgar scores, intrauterine growth restriction, and antenatal/postnatal steroid use. Neonatal outcomes included patent ductus arteriosus, germinal matrix hemorrhage, culture-proven sepsis, necrotizing enterocolitis, retinopathy of prematurity, the duration of total parenteral nutrition (TPN), the presence of BPD, and the infant's PMA at the time of MRI. The diagnosis and severity of BPD were based on the need for supplementary oxygen at 28 days of age and at 36 weeks of GA, as follows: mild BPD (breathing air); moderate BPD (<30%); and severe BPD (≥30% supplementary oxygen and/or continuous positive airway pressure or ventilator) [4].

Magnetic Resonance Imaging

MRI brain scans were obtained during natural sleep at term-equivalent age between 35 and 42 weeks PMA in preterm infants and within 1 month after birth (PMA 37–41 weeks) in term-born control infants using a 3.0-T MRI scanner (Philips real-time compact magnet 3.0-T MRI system; Achieva 3.0T X-Series) with a 16-channel SENSE head coil. The T1-weighted images included sagittal and axial T1 spin-echo sequences (400/25/2, TR [repetition time, ms]/TE [echo time, ms]/signal intensity average) and axial T2 turbo spin-echo sequences (3,000/100/1). To ensure that neonates were sleeping during the scan, they were well fed before the scan and well wrapped in a blanket. The subjects were placed on cushions that occupied the space between the subject and the radiofrequency coil. DTI was performed using a single-shot spin-echo-planar sequence with a SENSE factor of 2 and an echo-planar imaging factor of 51 (TR/TE, 8,100/75 ms; matrix size, 112 × 112; field of view, 224 mm; 74 axial sections). The slice orientation was axial with a 2.0-mm thickness and parallel to the anterior-posterior commissure line. Forty to 50 slices covered the entire hemisphere and the brainstem. Diffusivities were measured along 15 directions using an electrostatic gradient model (b = 800).

Table 1. Baseline demographic and clinical characteristics of the preterm and term infants included in this study

Characteristics	Preterm with BPD (n = 33)	Preterm with no BPD (n = 23)	Term (n = 22)	p value
Maternal characteristics				
Age, years	34.4±4.2	32.7±4.9	32.8±3.3	0.31
GDM	1/33 (3.0)	1/23 (4.3)	0	0.87
Preeclampsia	3/23 (15.2)	4/23 (17.4)	0	0.22
Histologic chorioamnionitis	15/33 (45.5)	10/23 (43.5)		1.00
Infant characteristics				
Gestational age, weeks	27.3±2.0[a]	28.2±1.8	39.0±1.0	<0.001
Birth weight, g	1,005.6±244.2[a]	1,284.8±145.4	2,915.0±593.0	<0.001
Cesarean section	25/33 (75.8)	16/23 (69.6)	6 (35.3)	0.06
Male sex	13/33 (39.4)	8/23 (34.8)	11 (64.7)	0.11
Apgar 1 min	3.6±1.5	3.7±1.7	6.4±2.5	<0.001
Apgar 5 min	6.3±1.2	6.6±1.1	8.1±1.8	<0.001
IUGR	7/33 (21.2)	5/23 (21.7)		1.00
Antenatal corticosteroid	25/33 (75.8)	17/23 (73.9)		1.00
Postnatal corticosteroid	8/33 (24.2)	1/23 (4.3)		0.06
PDA	26/33 (78.8)	13/23 (56.5)		0.08
PDA ligation	10/33 (30.3)	2/23 (8.6)		0.07
IVH grade I	12/33 (36.4)	5/23 (21.7)		0.37
Culture-proven sepsis	9/33 (27.2)	5/23 (21.7)		0.07
NEC (requiring surgery)	1/33 (3.0)	1/23 (4.3)		1.00
ROP	10/33 (30.3)	3/23 (13.0)		0.08
Days on mechanical ventilator	22.4±18.4	9.2±6.3		0.002
Days of O_2 therapy	56.5±26.7	14.5±8.2		<0.001
TPN days	34.8±13.0	27.6±20.3		0.06
Infant characteristics at MRI				
Age, weeks	36.9±2.1	36.9±1.769	38.451±1.101	0.003
Weight, g	2,553.9±567.8	2,451.3±337.9	3,067.1±512.1	<0.001
Height, cm	47.0±3.6	47.0±3.0	51.6±2.8	<0.001
Head circumference, cm	33.1±1.7	33.4±1.7	34.8±1.2	0.002

Data are the mean ± SD or n (%). MRI, magnetic resonance imaging; BPD, bronchopulmonary dysplasia; GDM, gestational diabetes mellitus; IUGR, intrauterine growth retardation; PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; TPN, total parenteral nutrition. [a] $p < 0.001$ compared with preterm with no BPD.

Brain Volumes

Brain volumes were measured using an advanced segmentation technique: Morphologically Adaptive Neonatal Tissue Segmentation (MANTiS; http://developmentalimagingmcri.github.io/mantis), which extends the unified segmentation approach to tissue classification using neonate tissue probability maps and then implements it within neonatal brains [11, 12]. This pipeline classifies a T2-weighted MR image of the brain into the following six regions: cortical gray matter, cerebral WM, cerebellum, subcortical gray matter (including deep nuclear gray matter, the hippocampus, and the amygdala), brainstem, and cerebrospinal fluid. First, brain extraction was performed using the Brain Extraction Tool (BET) in FMRIB's Software Library (http://www.fmrib.ox.ac.uk/fsl). Then, the initial tissue was classified using the "new segment" tool in SPM12 with a neonate probability map included in MANTiS. Morphological watershed segmentation and filtering were processed for reliable segmentation, despite large ventricles or high-intensity WM. Except the BET, the above processes were performed automatically using the MANTiS pipeline.

DT Image Processing

The diffusion-weighted images were processed using FMRIB's Software Library (http://www.fmrib.ox.ac.uk/fsl). Motion artifacts and eddy-current distortions were corrected by normalizing each diffusion-weighted image to a non-diffusion-weighted image (b0) using FMRIB's Linear Image Registration Tool. To extract brain tissues, the skull in the non-diffusion-weighted volume was removed using the BET. Subsequently, the DT model was reconstructed in each voxel using FMRIB's Diffusion Toolbox, and FA was calculated.

We examined subcortical WM defined by the JHU neonatal template image [13]. Individual FA images in native space were aligned and warped to the JHU neonate FA template using advanced normalization tools [14, 15]. The JHU neonate templates

were placed on individual FA images in native space. To evaluate the relationship between BPD and commissural fibers, projection fibers, and the cerebellum, we selected regions of interest (ROIs) in the CC, posterior limb of the internal capsule, corticospinal tract (CST), cerebral peduncle, superior cerebellar peduncle (SCP), and middle cerebellar peduncles.

Statistical Analyses

Statistical calculations were performed using SPSS 21.0 (SPSS, Chicago, IL, USA). A p value of <0.05 was considered statistically significant. We used Student's t test or χ^2 analysis to compare clinical variables between groups. The left and right values for each region were averaged when no significant differences were found between left and right for each region after conducting paired t tests.

We used a general linear model to compare group differences in brain volumes, controlling for sex, GA (for analysis of preterm infants), PMA at MRI, and intracranial volume after correction for multiple comparisons. Differences in DTI measures between groups were analyzed in a general linear model after adjusting for sex, GA (for analysis of preterm infants), and PMA at MRI. We used a Bonferroni correction of 0.05/6 = 0.008 for a two-sided alpha threshold for the six parts of brain tissue or six fibers. In addition, generalized estimating equations with robust SEs were used to analyze risk factors affecting brain volumes and FA values between infants with BPD and infants with no BPD. The association between brain volume and clinical factor was analyzed with brain volume (repeated measures) in the same model: the predictor variable was BPD, and known confounders included sex, GA, PMA at MRI, sepsis, TPN days, and postnatal dexamethasone. The association of FA in the DTI measures with clinical factors was analyzed with six ROIs (repeated measures) in the same model: the predictor variable was BPD, and known confounders included sex, GA, PMA at MRI, sepsis, TPN days, and postnatal dexamethasone.

Results

Infant Characteristics

Fifty-six preterm infants and 22 healthy full-term infants were included. The mean GA of the preterm infants with and those without BPD and of the full-term infants was 27.2, 28.2, and 38.9 weeks, respectively. Compared with full-term infants, preterm infants underwent MRI at an earlier GA (p = 0.003) and were smaller in weight, length, and head circumference (Table 1). Table 1 shows the clinical features of the preterm infants; 33 exhibited BPD ("BPD group"), whereas 23 did not exhibit BPD ("no-BPD group"). Compared with the no-BPD group, the BPD group exhibited a lower GA and birth weight (both $p < 0.001$). During the neonatal period, preterm infants with BPD differed slightly in that they exhibited a high rate of postnatal corticosteroid use (24.2%) and a high incidence of culture-proven sepsis (27.2%). As expected, preterm infants with BPD exhibited significantly different durations of mechanical ventilator use, O_2 therapy, and TPN days.

Brain Volumes

The cerebral WM (p = 0.02), cerebellum (p = 0.01), and brainstem (p = 0.04) were smaller in volume in preterm infants without BPD than in full-term infants, but the differences were not significant after Bonferroni correction for multiple comparisons within regions. When we compared specific volumes between the BPD and the no-BPD group among preterm infants in a general linear model, we found reductions in cerebral WM volume (101.8 ± 12.3 vs. 120.0 ± 14.1 cm^3) and cerebellar volume (20.2 ± 7.0 vs. 21.5 ± 12.1 cm^3) in the BPD group. The difference in cerebral WM volume (p = 0.005) remained significant after controlling for sex, GA, PMA at MRI, and total intracranial volume, with a significance level of $p \leq 0.008$ after correction for multiple comparisons (Table 2).

DTI Parameters

The preterm infants exhibited a lower WM FA than the full-term infants, reflecting delayed development and maturation in the preterm infants. As there was no significant difference between the right and the left hemisphere, these values were averaged. FA in the SCP (p = 0.03) was decreased in the preterm infants without BPD compared to the full-term infants, although the difference did not remain significant for the SCP after correcting for multiple comparisons with a significance level of $p \leq 0.008$. We compared the FA results of the preterm infants with BPD with those of the preterm infants without BPD. There were microstructural abnormalities with significantly decreased FA in the infants with BPD compared with the infants without BPD. The difference in FA in the CC (p = 0.006), CST (p = 0.003), and SCP (p = 0.002) remained significant after controlling for sex, GA, and PMA at MRI, with a significance level of $p \leq 0.008$ after correction for multiple comparisons (Table 2).

Association between Regional Brain Volumes or FA and Clinical Variables

Using the generalized estimating equation method, clinical factors affecting brain volumes and FA in the six ROIs were identified, and they are shown in Table 3. We found that moderate/severe BPD (p = 0.015) was independently associated with brain volume, and that both mild (p = 0.013) and moderate/severe (p = 0.021) BPD were independently associated with FA of the DTI parameter (Table 3).

Table 2. Brain volumes and FA of the preterm and term infants included in this study

	Preterm with BPD (n = 33)	Preterm with no BPD (n = 23)	Term (n = 22)	Adj. p value[a] (preterm without BPD vs. term)	Adj. p value[b] (with vs. without BPD)
Brain volumes, cm^3					
Total brain volume	376.1±74.1	412.1±111.2	556.1±335.2	0.06[c]	0.15[d]
Cortical gray matter	150.5±47.0	157.3±50.9	244.1±172.1	0.41	0.12
Cerebral white matter	101.8±12.3	120.0±14.1	150.1±86.4	0.02	**0.005**
Cerebellum	20.2±7.0	21.5±12.1	36.8±26.5	0.01	0.04
Subcortical gray matter	24.0±1.3	26.5±0.8	42.1±22.2	0.49	0.11
Brainstem	5.5±1.1	6.1±1.3	9.2±5.8	0.04	0.09
Cerebrospinal fluid	72.2±25.9	78.5±32.9	73.7±73.2	0.21	0.06
FA					
Corpus callosum	0.21±0.03	0.23±0.05	0.25±0.08	0.10	**0.006**
Posterior limb of internal capsule	0.33±0.03	0.34±0.03	0.35±0.06	0.15	0.04
Corticospinal tract	0.19±0.02	0.22±0.04	0.23±0.17	0.89	**0.003**
Cerebral peduncle	0.23±0.04	0.25±0.03	0.27±0.09	0.68	0.30
Superior cerebellar peduncle	0.19±0.02	0.22±0.07	0.25±0.11	0.03	**0.002**
Middle cerebellar peduncles	0.22+0.05	0.22+0.05	0.27±0.09	0.07	0.17

Data are the mean ± SD. BPD, bronchopulmonary dysplasia; FA, fractional anisotropy; GA, gestational age; PMA, postmenstrual age; MRI, magnetic resonance imaging. [a] Controlling for sex, PMA at MRI, and total intracranial volume. In bold, values are marked that achieve statistical significance of $p \leq 0.008$ as a Bonferroni correction for multiple comparisons of the six parts of brain tissue or six fibers. [b] Controlling for sex, GA, PMA at MRI, and total intracranial volume. In bold, values are marked that achieve statistical significance of $p \leq 0.008$ as a Bonferroni correction for multiple comparisons of the six parts of brain tissue or six fibers. [c] Adjusted for sex and PMA at MRI scan. [d] Adjusted for sex, GA, and PMA at MRI.

Table 3. Generalized estimating equation analysis results of the factors affecting brain volume and FA in preterm infants

Variables	Brain volume (cm^3)		FA	
	95% CI of estimated exp. (β) (estimated exp. [β])	p value	95% CI of estimated exp. (β) (estimated exp. [β])	p value
Male sex	–14.419 to 19.374 (2.477)	0.779	–0.030 to 0.020 (–0.005)	0.688
Gestational age (weeks)	–0.413 to 6.835 (3.211)	0.084	–0.005 to 0.009 (0.002)	0.597
PMA at MRI scan (weeks)	–1.728 to 13.831 (6.051)	0.123	–0.010 to 0.011 (0.001)	0.977
Culture-proven sepsis	–20.895 to 13.057 (–3.919)	0.656	–0.014 to 0.023 (0.005)	0.610
TPN days	–0.049 to 1.117 (0.534)	0.074	–0.001 to 0.001 (0.001)	0.743
Postnatal corticosteroid	–19.719 to 14.648 (–2,536)	0.775	–0.048 to 0.020 (–0.014)	0.424
BPD – mild	–32.774 to 4.307 (–14.233)	0.133	–0.061 to –0.007 (–0.034)	0.013
BPD – moderate/severe	–29.348 to –2.484 (–16.916)	0.015	–0.060 to –0.003 (–0.032)	0.021

FA, fractional anisotropy; PMA, postmenstrual age; MRI, magnetic resonance imaging; BPD, bronchopulmonary dysplasia; TPN, total parenteral nutrition.

Discussion

Preterm infants exhibited brain abnormalities in regional brain volumes and microstructures at term-equivalent age compared with full-term infants, independent of PMA at the time of MRI. Notably, we found that these impairments in preterm infants with BPD were associated with smaller WM volume and reduced WM FA on DTI analysis in the CC, CST, and SCP, even in the absence of apparent brain injury on MRI.

BPD is a major risk factor for adverse neurological development in neonates [5, 16]. Long-term follow-up studies of infants with BPD have shown that the increased survival of preterm infants is correlated with higher rates of neurodevelopmental deficits in early childhood, even in the absence of substantial brain lesions [17, 18]. Although prematurity itself is a determinant of neurodevelopmental impairment over the long term, it remains unclear whether brain development is independently affected by prematurity levels or related risk factors. In our study, reductions in cerebral WM volume were more prominent in preterm infants with BPD after correcting for several variables reflecting neonatal morbidity. This finding suggests that smaller brain tissue volumes are not merely due to prematurity but due to a combination of perinatal risk factors present in BPD [19]. Using quantitative MRI measurements of both brain volume and WM development, the current study more thoroughly describes the WM microstructures of preterm infants without WM injury or IVH more severe than grade I. DTI using advanced MRI can reveal changes in WM connections and myelination by detecting water anisotropy, which is influenced by the degree and direction of water molecule permeability within tissues [20]. While FA increases with brain maturation, mean diffusivity decreases with maturation [7]. Functional impairments with respect to cognition, attention, and language skills in preterm-born children have been explained by altered gray matter and WM microstructures as early as at term-equivalent age [21, 22]. Consistent with the current study, many studies have revealed that the WM microstructure in preterm infants at term-equivalent age shows a significant reduction in FA in the commissural fibers and projection tracts compared with that observed in full-term infants [1, 23]. DTI can highlight microstructural abnormalities in the neonatal period that are not evident on conventional MRI.

However, independent of the confounding effects of sex, GA, PMA at imaging, and multiple clinical risk factors, it is difficult to determine a specific association between BPD and differences in WM microstructure at near-term ages. Few previous studies have directly measured early microstructural WM alterations in the CC that are specifically related to the effects of BPD on preterm infants who exhibit no apparent brain injuries at term-equivalent age [3, 24]. Our current study reveals a regional microstructural vulnerability in the commissural tracts of CC. This vulnerability is reflected in maturational differences and rates, which contribute to increased vulnerability to WM injury during the perinatal period [8, 25]. The CC is a collection of rapidly developing WM tracts that carry the association fibers connecting the two hemicerebrums during the late third trimester [26]. Moreover, the splenium contains vision-related WM tracts, including the ventral visual stream correlates of the inferior longitudinal fasciculus and the inferior frontooccipital fasciculus [27]. These findings support the concept that selective WM microstructural alterations in preterm children likely contribute to the pathogenesis of neurosensory and cognitive impairments in infants with BPD.

Consistent with prior studies of BPD, a higher incidence of WM microstructural abnormalities was found in the projection fibers, including the CST; these fibers play an important role in the degree of motor impairment [24]. Commissural and deep projection pathways have been suggested to mature and become myelinated early and more quickly than subcortical projection and association tracts with respect to the rate of microstructural maturation. These changes may lead to increased susceptibility to direct WM damage that is involved in hypoxic-ischemic injuries, barotrauma associated with mechanical ventilation, and pulmonary inflammation during the course of the disease [7, 28].

The only two previous studies of cerebellar volume that have been reporting on preterm infants with BPD considered infants after postnatal exposure to dexamethasone [9, 10]. These previous studies suggested that the reductions in cerebellar volume were not specifically associated with BPD; rather, they were associated with dexamethasone administration among BPD infants after adjustment for associated clinical factors. Considerable differences could be attributed to the lack of correction (in the prior studies) for total intracranial volume and heterogeneity of subject characteristics, including severe IVH. In the current study, we corrected for these factors. Our study thus extends upon this limited literature, providing evidence for the effects of BPD on FA of the cerebellum in preterm infants with BPD, independent of dexamethasone administration and clinical risk factors.

We acknowledge the lack of early MRI data as an inevitable limitation in excluding the presence of early brain injury adequately, since the lack of thermoregulation in preterm infants precluded us from conducting an early MRI scan. However, regular cranial ultrasound scans from 3 days of the birth of preterm infants performed at the bedside were evaluated for brain injuries, including IVH and periventricular leukomalacia.

This study indicates that BPD in preterm infants is an independent risk factor associated with reductions in re-

gional brain volumes and an abnormal WM microstructure at term-equivalent age. Further follow-up studies of the study infants should examine whether neurodevelopment in preterm infants with BPD is mitigated by this smaller brain volume and delays microstructural brain maturation. Large cohort studies are needed to determine whether these early differences in vulnerability of preterm infants with BPD are sustained and are of prognostic value for children who may need early developmental intervention.

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Statement of Ethics

An institutional review board approved the study protocol and scanning procedures, and informed consent was obtained from the parents of all enrolled children to participate in the research study.

Disclosure Statement

The authors have no conflicts of interest to declare.

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