



Bronchopulmonary Dysplasia Is Associated with Later Working Memory Subtest Vulnerability and White Matter Microstructural Alterations in Preterm Infants

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Objective: Bronchopulmonary dysplasia (BPD) is a common respiratory complication in preterm infants. Although BPD is a recognized predictor of adverse long-term neurodevelopment, few studies have investigated its association with alterations in white matter (WM) microstructure and neurodevelopmental outcomes. Expanding upon our previous findings of regional WM alterations in infants with BPD, this study aimed to investigate the associations between these microstructural changes and long-term neurodevelopmental outcomes at 18–24 months and 3–5 years.

Methods: A total of 59 preterm infants (gestational age <32 weeks; birth weight <1,500 g) without focal structural brain abnormalities underwent magnetic resonance imaging and diffusion tensor imaging (DTI) at term-equivalent age. Neurodevelopment was assessed using the Korean Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) at 18-24 months of corrected age and the Korean Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition at 3-5 years of age. DTI were analyzed in the corpus callosum (CC), corticospinal tract, and middle cerebellar peduncle (MCP).

Results: There were no significant group differences in BSID-III scores at 18-24 months. However, at 3-5 years, preterm infants with BPD showed lower performance on a visuospatial short-term memory-related subtest. In terms of WM microstructure, working memory performance was significantly associated with alterations in axial diffusivity within the CC and MCP.

Conclusion: These findings suggest that regional WM microstructural alterations at term-equivalent age in infant born preterm with BPD are associated with cognitive vulnerabilities—particularly in verbal comprehension, visual spatial and visuospatial short-term memory-related index—at 3-5 years of age.

Key Words: Bronchopulmonary dysplasia, Preterm infants, Diffusion tensor imaging, White matter, Working memory

Introduction

The survival rate of preterm infants (PT) has improved significantly compared to the past; however, the risk of neurodevelopmental disorders remains even when no clear structural abnormalities are visible on cranial ultrasound or magnetic

resonance imaging (MRI). In particular, the immature brain of a PT born in the third trimester is highly vulnerable to damage caused by infectious and inflammatory factors, which can affect the microstructural integrity of the gray and white matter (WM).¹⁻³ These changes reflect exposure to an adverse extrauterine environment, complications, and perinatal injury, and increase the risk of future neurodevelopmental disorders.⁴⁻⁷

In particular, bronchopulmonary dysplasia (BPD), an inflammatory condition caused by pulmonary hypoplasia, is one of the most serious complications in PT, and its incidence is increasing in tandem with the rising survival rate of extremely PT born at less than 28 weeks' gestational age (GA).^{8,9} BPD has been recognized as an independent risk factor for neurodevelopmental disorders, and it has been reported that the risk of cognitive and motor delays, as well as neurodevelopmental impairment, tends to increase, particularly in cases of moderate or severe BPD.^{10,11} A recent study of 650 children under the age of 3 also reported that the incidence of neurodevelopmental disorders, including autism, attention deficit hyperactivity disorder, cerebral palsy, and/or learning disabilities, increased differentially according to the severity of BPD.¹² While BPD is known to be associated with long-term neurological prognosis,¹³ the specific relationship between WM microstructural alterations and subsequent neurodevelopmental outcomes at 3 to 5 years remains to be fully characterized.

Previous studies examining the interaction between brain development and lung health have suggested that BPD is associated not only with WM damage but also with changes in WM microstructure and delayed brain maturation.¹⁴⁻¹⁶ Furthermore, findings have been reported indicating that hyperoxia in the context of chronic lung disease is associated with WM damage and neurodevelopmental abnormalities.¹⁷ Moreover, a previous study comparing full-term infants without BPD to PT with BPD confirmed that BPD alters WM microstructure and may serve as a potential risk factor for working memory index (WMI) and cerebellar development.¹⁸ Diffusion tensor imaging (DTI) provides voxel-based scalar measures of water diffusion within the brain, reflecting the microstructure of

underlying tissue; low water diffusivity and high fractional anisotropy (FA) are understood to characterize well-aligned, myelinated WM tracts. Altered patterns are also observed in experimental models of demyelination and neonatal WM damage.

A study applying a tract-based spatial statistics protocol optimized for neonatal DTI confirmed that chronic lung disease is associated with reduced FA and increased radial diffusivity (RD) in WM, including the centrum semiovale and corpus callosum (CC), demonstrating that respiratory morbidities such as BPD can affect WM microstructure.¹⁵ Anjari et al.¹ reported that WM abnormalities associated with respiratory disease in a cohort of PT were linked to reduced FA in the left inferior longitudinal fasciculus, suggesting a potential independent association that cannot be explained by general immaturity alone. These results suggest that cerebral WM abnormalities in infants with BPD may occur selectively in certain specific tracts, indicating that BPD is not merely a problem of general immaturity but may also be associated with vulnerabilities in brain connectivity linked to respiratory morbidity. In particular, these oxidative stress and inflammatory responses are known to be associated with WM microstructural alterations in PT, highlighting the importance of evaluations focused on WM indices in the BPD cohort.¹⁹ In our previous study, we investigated the relationship between BPD and brain volume and fiber measured by MRI and DTI.¹⁸ We found that PT with BPD exhibited reduced cerebral WM volume and decreased FA in major WM tracts, including the CC, corticospinal tract (CST), and cerebellar pathways, even in the absence of overt structural brain injury.

This study aimed to elucidate the longitudinal relationship among BPD, WM microstructural changes, and subsequent cognitive decline in PT. We first evaluated the impact of BPD on neurodevelopmental outcomes at 18–24 months using the Korean Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) and at 3–5 years using the Korean Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (K-WPPSI-IV). To investigate the structural basis underlying these outcomes, we then extended our analysis further. Specifically, a

secondary DTI subgroup analysis was conducted to delineate how variations in WM microstructure within the CC, bilateral CST, and middle cerebellar peduncle (MCP) are associated with specific phenotypic cognitive vulnerabilities.

Methods

1. Participants

In this prospective follow-up cohort study, 69 participants were enrolled for neurodevelopmental evaluation at 18–24 months. Of 69 participants, 3 were lost to follow-up, 5 were tested for BSID-III; however, their scores were not calculated because of developmental delays, and 2 were identified as having autism spectrum disorder, consequently, a combined total of 10 participants were excluded.

The following inclusion criteria were used: (1) infants born before 32 weeks of gestation age with a birth weight <1.5 kg; (2) MRI and DTI implemented at term-equivalent age (postmenstrual age [PMA], 36–42 weeks) without focal abnormalities on MRI; (3) a participant who was tested for BSID-III at 18–24 months. We excluded preterm births who exhibited evidence of intraventricular hemorrhage and periventricular leukomalacia in early cranial ultrasound scans at term-equivalent age. Additionally, any PT who diagnosed congenital malformations, congenital infections, neonatal stroke, or chromosomal anomalies were excluded. Finally, a total of 59 infants were enrolled in this study. The participant selection and follow-up process are summarized in Fig. 1.

In this study, BPD was diagnosed using the 2001 National Institute of Child Health and Human Development criteria. Infants who required supplemental oxygen therapy for at least 28 days of life were defined as having BPD. Patients

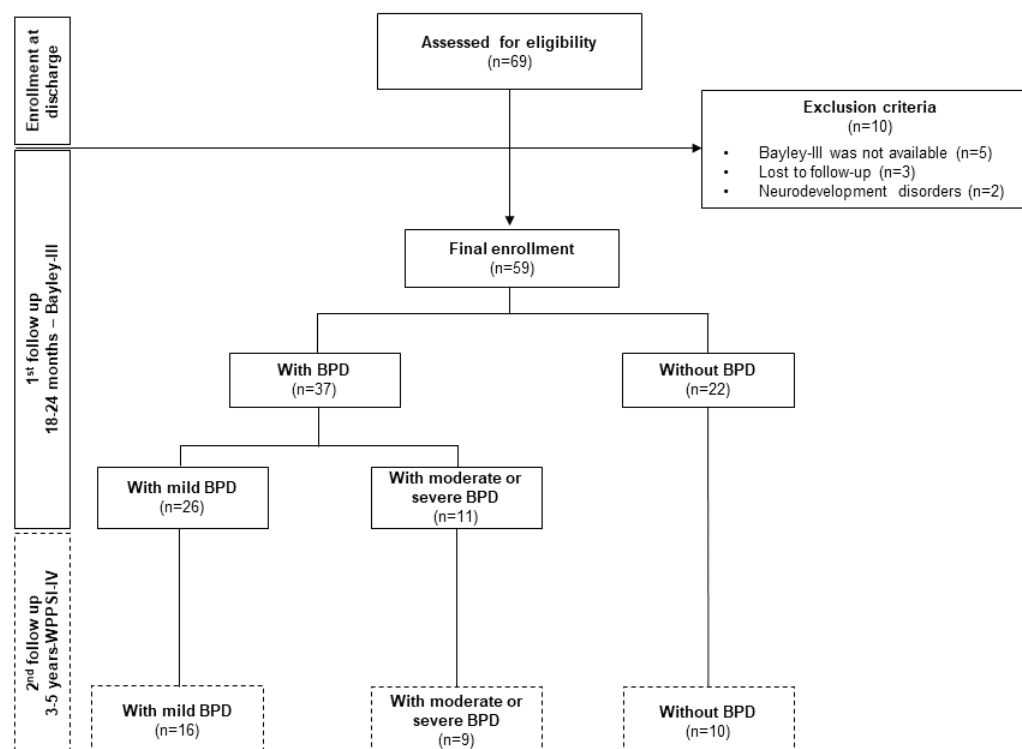


Fig. 1. Flow diagram of participant enrollment, follow-up, and neurodevelopmental assessment. A total of 59 preterm infants were included in the final cohort. BSID-III assessments at 18–24 months were available for all participants, whereas Korean Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (K-WPPSI-IV) assessments at 3–5 years were completed in 35 participants, including 10 infants without bronchopulmonary dysplasia (BPD), 16 with mild BPD, and 9 with moderate-to-severe BPD.

were classified into mild BPD if they did not require supplemental oxygen at 36 weeks of PMA, moderate BPD if they required a fraction of inspired oxygen (FiO_2) between 21% and 30%, and severe BPD if they required 30% or more supplemental oxygen or positive pressure ventilation.

To evaluate the potential risk of selection bias due to follow-up loss, baseline demographic and clinical characteristics between participants included in the K-WPPSI-IV analysis and those lost to follow-up were additionally compared (Supplementary Table 1). No significant differences were observed between the 2 groups in major clinical characteristics, including GA, birth weight, and BPD severity.

2. MRI and DTI acquisition and preprocessing

All participants underwent MRI and DTI at term-equivalent age during natural sleep with a blanket to keep their body temperature. Because preterm births are at risk of respiratory instability, we did not use sedative drug. In addition to monitoring the pulse oximetry, respiration rate and heart rate, the attending physician was accompanied. Preterm newborns were provided earplugs, headphones, or wrap techniques to circumvent acoustic noise ranging from 20 to 30 minutes. The procedure of brain scans was conducted by the institutional neonatal guidelines for scanning methods.^{20,21} DTI were acquired using a single-shot spin-echo-planar sequence with a SENSE factor of 2 and an echo-planar imaging factor of 51 (repeat time, 8,100 ms; echo time, 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 ($b=800$).

The DTI were preprocessed using FMRIB's Software Library (<http://www.fmrib.ox.ac.uk/fsl>). To correct the motion artifacts and eddy-current distortions, FMRIB's Linear Image Registration Tool were used normalizing each diffusion-weighted image to a non-diffusion-weighted image (b_0). The skull in the non-diffusion-weighted volume was removed using the Brain Extraction Tool. After

the diffusion tensor model was remodeled in each voxel using FMRIB's Diffusion Toolbox, FA, axial diffusivity (AD), mean diffusivity (MD), and RD were analyzed. We assessed WM labeled by the Johns Hopkins University neonatal template image. Advanced Normalization Tools were utilized to align and transform individual FA images from native space to the Johns Hopkins University neonate FA template. To ensure and standardize, the Johns Hopkins University neonate templates were assigned to individual FA images in native space. In line with the previous study,¹⁸ we selected regions of interest in the CC, both sides of CST, MCP. The overall DTI preprocessing and structural connectivity analysis pipeline are illustrated in Fig. 2.

3. Neurodevelopmental assessment

We regularly administered development tests by conducting follow-up assessments on PT at 2 specific time points: between 18 to 24 months and between 3 to 5 years of age. Specifically, to evaluate the neurodevelopmental outcomes, we used BSID-III at 18-24 months and the K-WPPSI-IV at 3-5 years. The BSID-III was a useful tool to determine the degree of neurodevelopment of infants aged 1 to 42 months. It was consisted of questionnaires for 5 domains (cognitive, motor, language, socioemotional, and adaptive behavior). The cognitive, motor, and language scores of born in preterm births at corrected age 18 to 24 months were used because of the comparisons of the common domain in all ages. Then, we conducted 2nd follow-up to preterm newborns at 3 to 5 years based on K-WPPSI-IV, comprised of 5 domains (verbal comprehension, visual spatial, WMI, fluid reasoning, process speed index). To compare the common areas of neurodevelopment in preterm births, we specially focused on 3 domains (verbal comprehension, visual spatial, and WMI). The average score of each domain in BSID-III was 100 and the 1 standard deviation was 15 and the average score of subdomains of K-WPPSI-IV was 100 and 1 standard deviation was 10. All the neurodevelopmental assessments were conducted at the Hanyang Inclusive Clinic for Developmental Disorders within the Hanyang University College of Medicine.

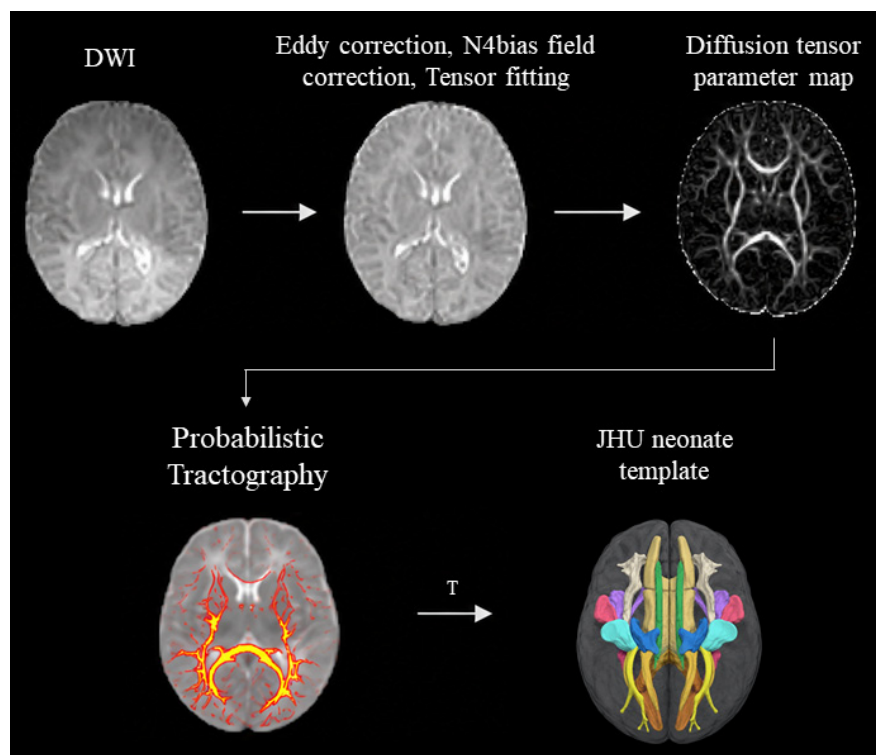


Fig. 2. Schematic overview of diffusion tensor imaging (DTI) preprocessing and structural connectivity analysis pipeline. Raw diffusion-weighted images underwent motion and eddy-current correction and N4 bias field correction, followed by diffusion tensor map generation and probabilistic tractography. White matter integrity matrices were subsequently generated using Johns Hopkins University neonate template-based regions of interest (ROI) labeling. DWI, diffusion-weighted imaging; FA, fractional anisotropy; JHU, Johns Hopkins University; T, transformation.

4. Statistical analysis

The t-test between 2 groups and analysis of variance among 3 groups on continuous variables and X^2 tests on categorical variables were performed to determine the statistical significance of the differences. Differences in DTI measures were analyzed using a 2-way analysis of covariance (ANCOVA) model. To minimize the number of covariates due to the limitation of a small sample size, only PMA at the time of MRI scans, GA, and head circumference were selected and adjusted for. To correct for multiple comparisons, we applied the false discovery rate (FDR) correction. All statistical calculations were performed using SPSS ver. 28.0 (IBM Corp.). $P < 0.05$ was considered statistically significant.

5. Ethics approval

The Hanyang University Hospital Institutional Review Board (IRB No. 2019-01-019-027) approved this study protocol, and informed consent for participation in this study was acquired by the parents. All procedures were performed in compliance with the principles of the Declaration of Helsinki.

Results

1. Demographic and clinical characteristics

We compared the maternal and infants' clinical characteristics between preterm with and without BPD, as well as among the preterm without BPD, with mild BPD, and with moderate or severe BPD (Table 1). There were no sig-

Table 1. Demographic and Clinical Characteristics of the Preterm Infants in This Study

Characteristic	Without BPD (n=22) ^a	With BPD (n=37)	P-value	With mild BPD (n=26) ^b	With moderate or severe BPD (n=11) ^c	P-value	LSD
Maternal characteristics							
Age (yr)	33.77±4.48	34.51±4.42	0.523	33.54±4.47	36.82±2.04	0.081	
Education							
High school	4 (18.2)	7 (18.9)	0.553	4 (15.4)	3 (27.3)	0.523	
College or University	18 (81.8)	28 (75.7)		20 (76.9)	8 (72.7)		
Graduate School	0 (0)	2 (5.4)		2 (7.7)	0 (0)		
GDM	1 (4.5)	2 (5.4)	0.884	1 (3.8)	1 (9.1)	0.794	
Preeclampsia	4 (18.2)	6 (16.7)	0.882	3 (11.5)	3 (30.0)	0.417	
Histologic chorioamnionitis	9 (40.9)	23 (62.2)	0.113	16 (61.5)	7 (63.6)	0.283	
Infant characteristics							
Gestational age (wk)	29.95±2.42	27.16±2.04	<0.001	27.19±1.79	26.91±2.39	<0.001	a>b>c
Birth weight (g)	1,305.45±216.13	1,037.70±238.90	<0.001	1,081.73±224.06	933.64±251.01	<0.001	a>b>c
Head circumference	27.63±2.34	25.76±2.36	0.005	26.07±2.12	25.03±2.81	0.009	a>b, c
Cesarean section	15 (68.2)	30 (81.1)	0.260	22 (84.6)	8 (72.7)	0.392	
Male sex	8 (36.4)	13 (35.1)	0.924	9 (34.6)	4 (36.4)	0.990	
Apgar 1 min (21/26/11)	3.71±1.88	3.11±1.51	0.183	3.35±1.36	2.55±1.75	0.167	
Apgar 5 min (21/26/11)	6.67±1.32	6.05±1.18	0.073	6.27±1.15	5.55±1.13	0.053	
IUGR	7 (31.8)	5 (13.5)	0.091	3 (11.5)	2 (18.2)	0.216	
Antenatal corticosteroid	16 (72.7)	24 (64.9)	0.532	16 (61.5)	8 (67.8)	0.659	
Postnatal corticosteroid	1 (4.5)	7 (18.9)	0.119	3 (11.5)	4 (36.4)	0.039	
Patent ductus arteriosus	12 (54.5)	30 (81.1)	0.030	21 (80.8)	9 (81.8)	0.093	
IVH≥grade III	0 (0)	0 (0)	N/A	0 (0)	0 (0)	N/A	
NEC	0 (0)	9 (24.3)	0.012	8 (30.8)	1 (9.1)	0.010	
ROP≥grade III	1 (4.5)	1 (2.7)	0.196	0 (0)	1 (9.1)	0.351	
PROM	8 (36.4)	17 (45.9)	0.471	11 (42.3)	6 (54.5)	0.609	
Surfactant	14 (73.7)	29 (96.7)	0.017	21 (100.0)	8 (88.9)	0.040	
Days of O ₂ therapy (21/26/10)	14.10±7.97	55.50±29.92	<0.001	47.23±25.80	77.00±30.37	<0.001	a<b<c
TPN days (22/20/9)	25.00±17.65	39.17±24.62	0.026	38.55±26.84	40.56±20.16	0.085	
Infant characteristics at MRI							
Age at MRI scan, weeks	37.73±2.66	37.76±2.20	0.963	37.46±2.08	38.45±2.42	0.512	
Weight at MRI (g) (21/25/7)	2,360.00±293.10	2,381.25±294.69	0.798	2,344.80±281.77	2,511.43±325.29	0.403	
Height at MRI (21/25/7)	33.15±1.63	32.55±1.28	0.141	32.50±1.21	32.71±1.63	0.323	
Head circumference at MRI (cm)	33.23±1.64	32.96±1.65	0.549	32.64±1.39	33.73±2.01	0.153	

Values are presented as mean±standard deviation or number (%). For variables with numbers in parentheses, the numbers indicate the number of participants with available data in the without BPD, mild BPD, and moderate/severe BPD groups, respectively.

BPD, bronchopulmonary dysplasia; LSD, least significant difference; GDM, gestational diabetes mellitus; IUGR, intrauterine growth retardation; IVH, intraventricular hemorrhage; N/A, not applicable; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; PROM, premature rupture of membranes; TPN, total parenteral nutrition; MRI, magnetic resonance imaging.

nificant differences in maternal characteristics and infant characteristics at MRI. However, preterm with BPD was significantly lower in GA ($P<0.001$), birth weight ($P<0.001$), and head circumference ($P=0.005$) than preterm without

BPD even after post-hoc analysis of least significant difference. In contrast, the days of O₂ therapy in preterm with BPD was significantly higher than preterm without BPD ($P<0.001$).

2. The differences of neurodevelopmental outcomes

In the BSID-III score of 18–24 months, there was no significant difference in scores between infants with BPD and without BPD or severe BPD (Table 2). However, preterm with moderate or severe BPD was significantly lower in verbal comprehension ($P=0.017$) and block design assessed in visual spatial ($P=0.016$) than preterm without BPD or with mild BPD. Moreover, Zoo Location reflecting WMI was significantly lower in preterm with BPD than without BPD ($P=0.005$) in K-WPPSI-IV.

3. The differences of DTI measurements according to K-WPPSI-IV and BPD grouping

DTI analyses were performed in the 35 participants who completed K-WPPSI-IV assessment at 3–5 years of age. Participants were further categorized according to neurodevelopmental performance (WMI <90 vs. ≥ 90), regardless of BPD subgroup (Table 3). After adjusting for PMA at MRI, GA, and head circumference at MRI, no significant differences were observed in FA, MD, RD across all brain regions and neurodevelopmental index (all adjusted FDR $P>0.05$). However, the subgroup with lower WMI scores (<90) exhi-

bited subtle differences in AD values compared to the higher score group (>90) in both the CC ($P=0.046$) and MCP ($P=0.046$) after adjustment. Additional analyses adjusting for perinatal and socioeconomic factors, including PDA, NEC, postnatal corticosteroid exposure, maternal age, and maternal education, are presented in Supplementary Table 2.

Discussion

In this study, BPD was associated with poorer preschool-age performance in visuospatial short-term memory, verbal comprehension, and visuospatial function, while AD differences in the CC and MCP emerged when WM microstructure was examined according to WMI status.

Higher rates of patent ductus arteriosus and surfactant use have been repeatedly discussed as indicators of the early disease burden in PT immediately after birth and can be understood as markers reflecting early lung maturation and the burden of respiratory disease.^{22,23} Furthermore, prolonged oxygen therapy suggests that the lungs, in a state

Table 2. Neurodevelopmental Outcomes in Preterm Infants with and without BPD

Variable	Without BPD (n=10) ^a	With BPD (n=25)	P-value	With mild BPD (n=16) ^b	With moderate or severe BPD (n=9) ^c	P-value	LSD
K-WPPSI-IV							
Full Scale IQ	98.20±15.88	91.92±15.08	0.281	96.81±14.36	83.22±12.74	0.053	
VCI	108.40±12.00	97.76±17.46	0.050	103.19±17.68	88.11±12.86	0.017	a, b>c
Receptive vocabulary	12.10±3.18	10.32±3.09 (n=22)	0.144	11.07±3.22 (n=14)	9.00±2.51 (n=8)	0.114	
Information	11.00±1.94	8.91±3.40 (n=23)	0.080	9.60±3.58 (n=15)	7.63±2.77 (n=8)	0.074	
VSI	91.60±16.50	92.16±16.35	0.928	97.00±17.87	83.56±8.58	0.135	
Block design	10.00±2.67	8.87±3.12 (n=23)	0.332	10.07±2.69 (n=15)	6.63±2.88 (n=8)	0.016	a, b>c
Object assembly	7.40±3.47	8.74±3.45 (n=23)	0.315	9.20±3.86 (n=15)	7.88±2.53 (n=8)	0.418	
WMI	102.00±14.70	91.44±18.03	0.110	93.75±17.95	87.33±18.47	0.192	
Picture memory	9.40±4.38	9.00±2.95 (n=23)	0.760	8.93±3.37 (n=15)	9.13±2.17 (n=8)	0.948	
Zoo location	10.90±1.45	8.35±3.41 (n=23)	0.005	8.87±3.07 (n=15)	7.38±4.00 (n=8)	0.052	
BSID-III (22/37), (16/9)							
Cognition	99.55±10.90	96.84±15.65	0.478	98.00±17.22	94.09±11.36	0.581	
Motor	103.55±14.43	97.46±17.25	0.170	98.00±17.65	96.18±17.02	0.941	
Language	97.46±17.25	90.18±12.85	0.749	88.73±16.29	89.45±12.30	0.375	

Values are presented as mean±standard deviation.

BPD, bronchopulmonary dysplasia; LSD, least significant difference; K-WPPSI-IV, Korean Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition; IQ, Intelligence Quotient; VCI, verbal comprehension index; VSI, visual spatial index; WMI, working memory index.

Table 3. White Matter Integrity Measures in Preterm Infants according to Neurodevelopmental Outcome Grouping

Region of interest	FSIQ		<i>P</i> -value ^{a)}	Adjusted FDR <i>P</i> -value ^{b)}	Adjusted FDR <i>P</i> -value ^{c)}	VCI		<i>P</i> -value ^{a)}	Adjusted FDR <i>P</i> -value ^{b)}	Adjusted FDR <i>P</i> -value ^{c)}	VSI		<i>P</i> -value ^{a)}	Adjusted FDR <i>P</i> -value ^{b)}	Adjusted FDR <i>P</i> -value ^{c)}	WMI		<i>P</i> -value ^{a)}	<i>P</i> -value ^{b)}	<i>P</i> -value ^{c)}
	<90 (n=12)	≥90 (n=23)				<90 (n=8)	≥90 (n=27)				<90 (n=14)	≥90 (n=21)				<90 (n=14)	≥90 (n=21)			
FA																				
Corpus callosum	0.18±0.03	0.17±0.12	0.333	0.414	0.430	0.17±0.02	0.17±0.02	0.922	0.924	0.980	0.18±0.03	0.16±0.01	0.304	0.392	0.435	0.17±0.02	0.17±0.03	0.599	0.667	0.698
Corticospinal tract (left)	0.26±0.03	0.24±0.03	0.349	0.414	0.430	0.26±0.02	0.24±0.03	0.159	0.608	0.714	0.26±0.03	0.24±0.02	0.473	0.392	0.435	0.25±0.03	0.25±0.03	0.598	0.667	0.698
Corticospinal tract (right)	0.26±0.03	0.25±0.03	0.954	0.767	0.776	0.26±0.02	0.25±0.03	0.350	0.662	0.714	0.27±0.03	0.24±0.02	0.553	0.392	0.435	0.26±0.03	0.25±0.03	0.622	0.667	0.698
Middle cerebellar peduncles	0.20±0.04	0.19±0.03	0.700	0.975	0.967	0.20±0.02	0.19±0.03	0.634	0.847	0.979	0.21±0.04	0.19±0.23	0.706	0.538	0.484	0.19±0.03	0.19±0.03	0.695	0.667	0.698
AD																				
Corpus callosum	1.74±0.16	1.84±0.07	0.121	0.408	0.332	1.74±0.15	1.82±0.09	0.194	0.202	0.451	1.76±0.14	1.84±0.08	0.387	0.379	0.429	1.81±0.10	1.80±0.12	0.024	0.051	0.046
Corticospinal tract (left)	1.69±0.14	1.76±0.09	0.501	0.680	0.660	1.69±0.14	1.75±0.10	0.647	0.652	0.814	1.69±0.13	1.77±0.08	0.268	0.369	0.415	1.74±0.11	1.73±0.11	0.034	0.051	0.052
Corticospinal tract (right)	1.87±0.12	1.91±0.22	0.996	0.878	0.879	1.83±0.11	1.92±0.10	0.313	0.319	0.451	1.85±0.12	1.93±0.09	0.245	0.369	0.415	1.89±0.11	1.90±0.11	0.085	0.098	0.105
Middle cerebellar peduncles	1.91±0.22	2.03±0.14	0.445	0.680	0.660	1.84±0.10	2.03±0.17	0.064	0.069	0.344	1.91±0.20	2.04±0.14	0.130	0.369	0.415	1.99±0.19	1.99±0.17	0.011	0.051	0.046
MD																				
Corpus callosum	1.48±0.16	1.58±0.07	0.108	0.264	0.232	1.48±0.14	1.56±0.10	0.229	0.313	0.445	1.49±0.14	1.58±0.08	0.289	0.251	0.283	1.55±0.10	1.54±0.13	0.047	0.110	0.216
Corticospinal tract (left)	1.33±0.13	1.41±0.09	0.473	0.713	0.678	1.32±0.12	1.40±0.11	0.349	0.354	0.495	1.33±0.12	1.42±0.09	0.300	0.251	0.283	1.38±0.11	1.39±0.12	0.106	0.161	0.217
Corticospinal tract (right)	1.49±0.12	1.53±0.10	0.841	0.866	0.868	1.45±0.10	1.54±0.10	0.238	0.313	0.445	1.46±0.12	1.55±0.08	0.272	0.251	0.283	1.50±0.10	1.53±0.11	0.292	0.330	0.344
Middle cerebellar peduncles	1.61±0.21	1.71±0.12	0.677	0.713	0.721	1.55±0.10	1.72±0.16	0.089	0.313	0.424	1.61±0.20	1.73±0.11	0.173	0.251	0.283	1.68±0.16	1.68±0.17	0.041	0.110	0.216
RD																				
Corpus callosum	1.35±0.16	1.45±0.07	0.124	0.260	0.244	1.36±0.14	1.43±0.11	0.278	0.282	0.376	1.36±0.14	1.45±0.08	0.266	0.250	0.282	1.42±0.10	1.41±0.13	0.083	0.212	0.228
Corticospinal tract (left)	1.15±0.13	1.24±0.10	0.476	0.608	0.568	1.14±0.12	1.23±0.11	0.252	0.282	0.376	1.15±0.13	1.25±0.09	0.335	0.250	0.282	1.20±0.11	1.21±0.12	0.199	0.300	0.307
Corticospinal tract (right)	1.30±0.12	1.35±0.11	0.767	0.865	0.868	1.26±0.09	1.35±0.11	0.225	0.282	0.376	1.27±0.12	1.37±0.08	0.309	0.250	0.282	1.31±0.10	1.34±0.12	0.495	0.558	0.572
Middle cerebellar peduncles	1.46±0.21	1.56±0.11	0.842	0.852	0.861	1.40±0.10	1.56±0.15	0.120	0.282	0.376	1.45±0.20	1.57±0.10	0.223	0.250	0.282	1.52±0.15	1.53±0.04	0.092	0.212	0.228

Values are presented as mean±standard deviation.

FSIQ, Full Scale Intelligence Quotient; FDR, false discovery rate; VCI, verbal comprehension index; VSI, visual spatial index; WMI, working memory index; FA, fractional anisotropy; AD, axial diffusivity; MD, mean diffusivity; RD, radial diffusivity; PMA, postmenstrual age; MRI, magnetic resonance imaging; GA, gestational age.

^{a)}Adjusted PMA at MRI. ^{b)}Adjusted FDR *P*-value= Adjusted for PMA at MRI and GA. ^{c)}Adjusted FDR *P*-value=Adjusted for PMA at MRI, GA, and head circumference. AD, MD, RD=10⁻³ mm²/s.

of disrupted alveolar and microvascular development, may have been exposed to oxidative stress and inflammatory stimuli for a longer period after birth.^{22,24} Inflammation and oxidative stress associated with BPD may induce microstructural WM alterations during the developmental window of PT, when the differentiation of oligodendrocyte precursor cells and axon-oligodendrocyte interactions are active.^{25,26} AD, an indicator reflecting the directional organization and maturity of axons in WM, may be useful for assessing the characteristics of BPD-related WM alterations.^{27,28}

Neurodevelopmental differences associated with BPD were observed in the BPD group, with impaired performance on the working memory task, while deficits in verbal comprehension and visual spatial ability were identified in the moderate or severe BPD group. These results suggest that cognitive vulnerabilities associated with BPD are concentrated in specific functional domains such as visuospatial short-term memory, verbal comprehension, and spatial-temporal organization. Cognitive vulnerabilities in PT may be more pronounced in functions that are highly network-dependent, such as WMI and spatio-temporal processing.²⁹ These findings suggest that lower working memory performance in the BPD group is associated with reduced AD within the CC and MCP. This link indicates that functional deficits observed in early childhood may reflect underlying structural neurodevelopmental changes in infants born preterm with BPD.^{30,31} The observation that developmental indicators are particularly reduced in the moderate-to-severe BPD group is consistent with previous reports suggesting that the long-term neurodevelopmental risks of mild BPD may be relatively limited.³²⁻³⁴ This reflects a state in which factors such as early respiratory instability, exposure to infectious and inflammatory agents, and the overall burden of neonatal illness have accumulated to a greater extent, jointly exacerbating WM damage and subsequent cognitive decline.^{13,17} Lower performance on the Zoo Location subtest may reflect subtle vulnerabilities in visuospatial short-term memory-related processing in PT with BPD.

Based on the identified WMI deficits, significant reductions in AD within the CC and MCP suggest that lower AD

in these regions is associated with the decreased working memory performance observed in PT with BPD. In the cerebral WM, water diffuses preferentially along the axis of the axons and is restricted in directions perpendicular to the axons; this directional dependence is already observed during the pre-myelination period.^{35,36} In normal development, FA increases and AD decreases as WM matures.^{37,38} Because AD changes during normal WM maturation, the biological interpretation of subtle AD differences in PT remains complex and should not be directly interpreted as evidence of axonal injury. The developmental window in PT is characterized by a predominance of pre-oligodendrocytes and an immature antioxidant defense system, making them vulnerable to inflammation and oxidative stress; thus, diffuse WM injury and dysmaturation are likely to occur even in the absence of distinct cystic lesions.^{19,39} In animal models and pathological-imaging correlation studies, stress associated with prematurity has been linked to axonal microstructural stress states, such as cytoskeletal disruption, axonal beading, axonal swelling, and morphological changes.²⁸ Previous studies have also repeatedly reported WM microstructural abnormalities in PT in commissural and projective pathways, including the CC.^{1,18} Taking these trends into account, subtle AD variations within the CC and MCP may reflect microstructural differences associated with neurodevelopmental performance in PT. The persistent association between AD variations in the MCP and visuospatial short-term memory-related performance after additional adjustment for perinatal and socioeconomic factors may support the relevance of cerebellar-cerebral connectivity in neurodevelopmental outcomes among PT.

Due to the observational study design, this study cannot completely rule out residual confounding variables. Furthermore, because of the small sample size, we were unable to perform subgroup analyses based on clinical characteristics such as small for GA or postnatal steroid exposure; consequently, the study may not have adequately reflected the heterogeneity within the BPD group. Although AD is a useful indicator reflecting axonal diffusion, caution is required when using a single indicator to directly infer specific pathophysiological mechanisms.

Therefore, the changes in AD observed in this study should be interpreted as limited WM microstructural signals; rather than concluding that they represent axonal damage or developmental abnormalities, they should be carefully interpreted in conjunction with other diffusion markers and the clinical context. Because the DTI analyses were conducted in participants regardless of BPD subgroup, the observed associations should be interpreted as exploratory relationships within the overall preterm cohort rather than BPD-specific effects.

The present study suggests that subtle variations in AD within the CC and MCP at term-equivalent age may be associated with specific neurodevelopmental vulnerabilities, particularly visuospatial short-term memory-related performance, in PT.

However, long-term neurodevelopmental follow-up studies using comprehensive developmental assessments in moderate-to-severe BPD cohorts remain scarce. Therefore, despite its small sample size, this exploratory study warrants future large-scale, multi-center investigations to validate these findings.

Supplementary Materials

Supplementary materials related to this article can be found online at <https://doi.org/10.14734/PN.2026.37.2.66>.

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Conflict of Interest

No potential conflict of interest relevant to this article

was reported.

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Authors' Contributions

Conceptualization: IWL, HJL, WH; Data curation: HK, GYL; Formal analysis: IWL, HK, YHJ; Investigation: IWL, WH; Project administration: HJL; Resource: HJL, WH; Writing-original draft: IWL; Writing-review & editing: all authors.

References

- 1) Anjari M, Srinivasan L, Allsop JM, Hajnal JV, Rutherford MA, Edwards AD, et al. Diffusion tensor imaging with tract-based spatial statistics reveals local white matter abnormalities in preterm infants. *Neuroimage* 2007; 35:1021-7.
- 2) Li K, Sun Z, Han Y, Gao L, Yuan L, Zeng D. Fractional anisotropy alterations in individuals born preterm: a diffusion tensor imaging meta-analysis. *Dev Med Child Neurol* 2015;57:328-38.
- 3) Wood NS, Costeloe K, Gibson AT, Hennessy EM, Marlow N, Wilkinson AR, et al. The EPICure study: associations and antecedents of neurological and developmental disability at 30 months of age following extremely preterm birth. *Arch Dis Child Fetal Neonatal Ed* 2005;90:F134-40.
- 4) Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. *JAMA* 2002;288:728-37.
- 5) Davis NM, Ford GW, Anderson PJ, Doyle LW, Victorian Infant Collaborative Study Group. Developmental coordination disorder at 8 years of age in a regional cohort of extremely-low-birthweight or very preterm infants. *Dev Med Child Neurol* 2007;49:325-30.
- 6) Foulder-Hughes LA, Cooke RW. Motor, cognitive, and behavioural disorders in children born very preterm. *Dev Med Child Neurol* 2003;45:97-103.
- 7) Marlow N, Wolke D, Bracewell MA, Samara M, EPICure Study Group. Neurologic and developmental disability at six years of age after extremely preterm birth. *N Engl J Med* 2005;352:9-19.
- 8) Lui K, Lee SK, Kusuda S, Adams M, Vento M, Reichman B, et al. Trends in outcomes for neonates born very preterm and very low birth weight in

- 11 high-income countries. *J Pediatr* 2019;215:32-40.
- 9) Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. *JAMA* 2015;314:1039-51.
- 10) Jensen EA, Dysart K, Gantz MG, McDonald S, Bamat NA, Keszler M, et al. The diagnosis of bronchopulmonary dysplasia in very preterm infants: an evidence-based approach. *Am J Respir Crit Care Med* 2019;200:751-9.
- 11) Malavolti AM, Bassler D, Arlettaz-Mieth R, Faldella G, Latal B, Natalucci G. Bronchopulmonary dysplasia-impact of severity and timing of diagnosis on neurodevelopment of preterm infants: a retrospective cohort study. *BMJ Paediatr Open* 2018;2:e000165.
- 12) Rueff DA, Gee J, Ruddy-Humphries A, West M, Rubin E, Chetta K, et al. The association between bronchopulmonary dysplasia severity and neurodevelopmental disorders. *J Perinatol* 2026 Feb 10 [Epub]. <https://doi.org/10.1038/s41372-025-02372-4>.
- 13) Katz TA, de Ridder R, Bancalari E, Higgins RD, Isayama T, Jensen EA, et al. Prognostic accuracy of BPD definitions for long-term outcomes in preterm infants: a systematic review. *Pediatrics* 2025;156:e2025070741.
- 14) Albertine KH. Brain injury in chronically ventilated preterm neonates: collateral damage related to ventilation strategy. *Clin Perinatol* 2012;39:727-40.
- 15) Ball G, Counsell SJ, Anjari M, Merchant N, Arichi T, Doria V, et al. An optimised tract-based spatial statistics protocol for neonates: applications to prematurity and chronic lung disease. *Neuroimage* 2010;53:94-102.
- 16) Boardman JP, Counsell SJ, Rueckert D, Hajnal JV, Bhatia KK, Srinivasan L, et al. Early growth in brain volume is preserved in the majority of preterm infants. *Ann Neurol* 2007;62:185-92.
- 17) Grelli KN, Keller RL, Rogers EE, Partridge JC, Xu D, Barkovich AJ, et al. Bronchopulmonary dysplasia precursors influence risk of white matter injury and adverse neurodevelopmental outcome in preterm infants. *Pediatr Res* 2021;90:359-65.
- 18) Lee JM, Choi YH, Hong J, Kim NY, Kim EB, Lim JS, et al. Bronchopulmonary dysplasia is associated with altered brain volumes and white matter microstructure in preterm infants. *Neonatology* 2019;116:163-70.
- 19) Back SA, Miller SP. Brain injury in premature neonates: a primary cerebral dysmaturation disorder? *Ann Neurol* 2014;75:469-86.
- 20) Copeland A, Silver E, Korja R, Lehtola SJ, Merisaari H, Saukko E, et al. Infant and child MRI: a review of scanning procedures. *Front Neurosci* 2021;15:666020.
- 21) Dubois J, Alison M, Counsell SJ, Hertz-Pannier L, Hüppi PS, Benders MJNL. MRI of the neonatal brain: a review of methodological challenges and neuroscientific advances. *J Magn Reson Imaging* 2021;53:1318-43.
- 22) Thébaud B, Goss KN, Laughon M, Whitsett JA, Abman SH, Steinhorn RH, et al. Bronchopulmonary dysplasia. *Nat Rev Dis Primers* 2019;5:78.
- 23) Villamor E, van Westering-Kroon E, Gonzalez-Luis GE, Bartoš F, Abman SH, Huizing MJ. Patent ductus arteriosus and bronchopulmonary dysplasia-associated pulmonary hypertension: a Bayesian meta-analysis. *JAMA Netw Open* 2023;6:e2345299.
- 24) Kalikkot Thekkeveedu R, Guaman MC, Shivanna B. Bronchopulmonary dysplasia: a review of pathogenesis and pathophysiology. *Respir Med* 2017;132:170-7.
- 25) Back SA. White matter injury in the preterm infant: pathology and mechanisms. *Acta Neuropathol* 2017;134:331-49.
- 26) Ritter J, Schmitz T, Chew LJ, Bühner C, Möbius W, Zonouzi M, et al. Neonatal hyperoxia exposure disrupts axon-oligodendrocyte integrity in the subcortical white matter. *J Neurosci* 2013;33:8990-9002.
- 27) Cheong JL, Thompson DK, Wang HX, Hunt RW, Anderson PJ, Inder TE, et al. Abnormal white matter signal on MR imaging is related to abnormal tissue microstructure. *AJNR Am J Neuroradiol* 2009;30:623-8.
- 28) Counsell SJ, Shen Y, Boardman JP, Larkman DJ, Kapellou O, Ward P, et al. Axial and radial diffusivity in preterm infants who have diffuse white matter changes on magnetic resonance imaging at term-equivalent age. *Pediatrics* 2006;117:376-86.
- 29) Mürner-Lavanchy I, Ritter BC, Spencer-Smith MM, Perrig WJ, Schroth G, Steinlin M, et al. Visuospatial working memory in very preterm and term born children—impact of age and performance. *Dev Cogn Neurosci* 2014;9:106-16.
- 30) Cowan N. Differentiation of two working memory tasks normed on a large U.S. sample of children 2-7 years old. *Child Dev* 2021;92:2268-83.
- 31) Short SJ, Elison JT, Goldman BD, Styner M, Gu H, Connelly M, et al. Associations between white matter microstructure and infants' working memory. *Neuroimage* 2013;64:156-66.
- 32) Brumbaugh JE, Colaizy TT, Patel NM, Klein JM. The changing relationship between bronchopulmonary dysplasia and cognition in very preterm infants. *Acta Paediatr* 2018;107:1339-44.
- 33) Gou X, Yang L, Pan L, Xiao D. Association between bronchopulmonary dysplasia and cerebral palsy in children: a meta-analysis. *BMJ Open* 2018;8:e020735.
- 34) Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001;163:1723-9.
- 35) Moseley ME, Cohen Y, Kucharczyk J, Mintorovitch J, Asgari HS, Wendland MF, et al. Diffusion-weighted MR imaging of anisotropic water diffusion in cat central nervous system. *Radiology* 1990;176:439-45.
- 36) Wimberger DM, Roberts TP, Barkovich AJ, Prayer LM, Moseley ME, Kucharczyk J. Identification of "premyelination" by diffusion-weighted MRI. *J Comput Assist Tomogr* 1995;19:28-33.
- 37) Rasmussen JM, Kruggel F, Gilmore JH, Styner M, Entringer S, Consing KN, et al. A novel maturation index based on neonatal diffusion tensor imaging reflects typical perinatal white matter development in humans. *Int J Dev Neurosci* 2017;56:42-51.
- 38) Yoshida S, Oishi K, Faria AV, Mori S. Diffusion tensor imaging of normal brain development. *Pediatr Radiol* 2013;43:15-27.
- 39) Buser JR, Maire J, Riddle A, Gong X, Nguyen T, Nelson K, et al. Arrested preoligodendrocyte maturation contributes to myelination failure in premature infants. *Ann Neurol* 2012;71:93-109.