

Diffusion Tensor Imaging Analysis of White Matter Microstructural Integrity in Infants With Retinopathy of Prematurity

Seong Joon Ahn,¹ Hyun-Kyung Park,^{2,3} Byung Ro Lee,¹ and Hyun Ju Lee^{2,3}

¹Department of Ophthalmology, Hanyang University Hospital, Hanyang University College of Medicine, Seoul, Republic of Korea

²Department of Pediatrics, Hanyang University Hospital, Hanyang University College of Medicine, Seoul, Republic of Korea

³Division of Neonatology and Developmental Medicine, Hanyang University Hospital, Seoul, Korea

Correspondence: Hyun Ju Lee, Department of Pediatrics, Hanyang University Seoul Hospital, 17 Haengdang-dong, Seongdong-gu, Seoul 133-792, Korea; blesslee77@hanmail.net.

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PURPOSE. To investigate white matter maturation in preterm infants with and without retinopathy of prematurity (ROP) and to determine whether ROP is associated with white matter microstructural integrity at term-equivalent ages.

METHODS. In 82 preterm and 34 full-term infants who had undergone brain magnetic resonance imaging diffusion tensor imaging at term-equivalent ages, white matter microstructural integrity was assessed based on mean fractional anisotropy (FA) and mean diffusivity (MD) values in 23 predefined regions of interest by using atlas-based analyses. The values were compared among preterm and full-term infants, and a general linear model was used to evaluate the association of the values with ROP or severe (i.e., stage ≥ 3) ROP.

RESULTS. Significant differences in FA and MD values were observed among preterm and full-term infants in 17 (73.9%) and 15 (65.2%) of the 23 white matter areas evaluated, respectively. However, ROP was significantly associated with MD values in only two areas (superior longitudinal fasciculus [$P = 0.030$] and cerebral peduncle [$P = 0.005$]). Severe ROP was significantly associated with FA values within the anterior limb of the internal capsule ($P = 0.049$) and MD values within the stria terminalis ($P = 0.035$). A network analysis showed that preterm infants with severe ROP had lower small-world index values than those without.

CONCLUSIONS. Preterm birth may be more strongly associated with white matter maturation at term-equivalent ages than ROP, but severe ROP may be associated with decreased structural connectivity.

Keywords: diffusion tensor imaging, magnetic resonance imaging, retinopathy of prematurity, white matter

Retinopathy of prematurity (ROP) is a vision-threatening disorder associated with an arrest of normal retinal vascular development in preterm neonates.^{1,2} The incidence of ROP varies according to study and the gestational ages (GAs) of the included preterm infants, ranging from 10% to 35% for severe ROP.^{2–4} ROP is an important cause of childhood blindness worldwide, necessitating careful screening and appropriate management to prevent blindness.

Current screening guidelines recommend retinal examinations for at-risk preterm infants.⁵ However, these patients may have comorbidities such as intraventricular hemorrhage (IVH), poor brain growth, and related neurologic dysfunction. As visual impairment in children born very preterm can also be caused by cerebral white matter abnormalities affecting the visual pathways, in addition to ROP,^{6,7} such comorbidities may lead to an underdeveloped visual system, poor neurologic development, and more severe visual impairment. Because the retina is a part of the central nervous system (CNS), ROP may represent the state of neurologic development in preterm infants. Several recent papers have shown that ROP, of which the pathogenic hallmark is abnormal retinal vessels, is also a

disease of the neural retina, based on evidence obtained by electroretinography.^{8–10} Allred et al.¹¹ reported that infants with ROP exhibited more frequent brain lesions on ultrasound images and higher rates of cerebral palsy than their healthy counterparts. However, detailed assessments of brain abnormalities in such patients have yet to be conducted using magnetic resonance imaging (MRI). One previous MRI study involving preterm infants reported that white matter abnormalities may predict neurodevelopmental outcomes, including visual impairment,¹² which has not been extensively studied in infants with ROP.

Diffusion tensor imaging (DTI) can be used to investigate white matter abnormalities, as this method reflects changes in white matter connectivity and myelination by detecting the direction of water molecule diffusion in the tissues.^{13–15} In the present study, we used DTI to investigate the association between white matter development and ROP in preterm and full-term infants with and without ROP. We further investigated whether ROP severity in preterm infants was associated with abnormalities in white matter maturation and structural brain networks.



METHODS

Participants

A prospective observational cohort of 85 infants born prior to the GA of 37 weeks was recruited from the neonatal intensive care unit of Hanyang University Seoul Hospital between December 2015 and April 2018. Inclusion criteria were as follows: no congenital malformations, congenital infection, neonatal stroke, or chromosomal anomalies; and availability of MRI at near-term age (GA, 35–41 weeks). We excluded three infants with evidence of (1) intraventricular or intracranial hemorrhage greater than grade I, (2) overt white matter injury on conventional MRI, or (3) poor image quality due to motion artifacts. Full-term infants, in whom GA ranged from 37.0 to 41.4 weeks, admitted to the same neonatal intensive care unit for respiratory distress or jaundice, and who had normal MRI findings and normal neurologic function, were also recruited for the full-term control group.

Prenatal and neonatal data were prospectively recorded, including maternal details, sociodemographic factors, GA, birth weight, sex, Apgar scores, intrauterine growth restriction, and antenatal/postnatal steroid use for each infant. Neonatal outcomes included patent ductus arteriosus, germinal matrix hemorrhage, culture-proven sepsis, necrotizing enterocolitis, ROP, bronchopulmonary dysplasia, and GA at the time of MRI. The institutional review board of Hanyang University Hospital approved our study protocol and scanning procedures, and informed consent for participation was obtained from the children's parents prior to the study. This study was conducted in accordance with the principles of the Declaration of Helsinki.

ROP Screening and Treatment

Preterm infants born prior to the GA of 31 weeks or with a birth weight ≤ 1500 g were screened for the presence of ROP.^{5,16,17} ROP was classified in accordance with the International Classification of Retinopathy of Prematurity criteria.^{18–21} Severe ROP was defined as stage 3 ROP or worse.⁷ Patients exhibiting zone I ROP with plus disease or stage 3 and those exhibiting zone II ROP (stage 2 or 3) with plus disease received treatment, either antivascular endothelial growth factor or laser photocoagulation.⁵ There were no cases of retinal detachment, requiring retinal detachment surgery, among the screened infants.

Magnetic Resonance Imaging

MRI scans were obtained during natural sleep at a GA of 35 to 41 weeks in preterm and full-term infants. All scans were obtained using a 3.0 T MRI scanner (Philips Real Time Compact Magnet 3.0-Tesla MRI system, Achieva 3.0-Tesla X-series; Philips Healthcare, Best, The Netherlands) equipped with a 16-channel SENSE head coil. The T1-weighted images included sagittal and axial T1 spin-echo sequences (400/25/2, repetition time [TR]/echo time [TE]/signal intensity averages) and axial T2 Turbo spin-echo sequences (3000/100/1). DTIs were obtained using a single-shot spin-echo planar sequence with a SENSE factor of two and an echo-planar imaging factor of 51 (TR/TE, 5243/76; voxel size, $1.97 \times 1.97 \times 2$ mm; field-of-view, 150×150 , 45 axial sections). The slice orientation was axial, with a 2.0 mm thickness parallel to the anterior-posterior commissure (AC-PC) line. Forty to 50 slices covered the entire hemisphere and brainstem. We ensured that neonates remained still while sleeping during the scan by feeding them well before the scan, positioning them appropriately within a blanket, and monitoring their position during the scan.

Cushions were also placed within the space between the participant and the RF coil.

Image Processing

The diffusion-weighted images were processed using the FMRIB Software Library (<http://www.fmrrib.ox.ac.uk/fsl> in the public domain). Motion artifacts and eddy current distortions were corrected by normalizing each diffusion-weighted volume to the nondiffusion-weighted volume (b0), using the FMRIB Linear Image Registration Tool. Each brain mask was created using Brain Extraction Tool. Subsequently, DTIs were reconstructed for each voxel using FMRIB's Diffusion Toolbox, following which fractional anisotropy (FA) and mean diffusivity (MD) values were calculated.

For region-of-interest (ROI) analysis, we used the JHU neonatal template, which was parcellated into 23 regions per hemisphere, including white matter and subcortical regions.^{22–24} All FA images were aligned and warped to the JHU neonate FA image with advanced normalization tools.²⁵ The images were then segmented into 23 regions overlaid onto individual native FA images covering the commissural fibers (i.e., the anterior and posterior corpus callosum), association fibers (i.e., the superior longitudinal fasciculus, superior and inferior frontooccipital fasciculi, and external capsule), limbic fibers (i.e., the fornix, cingular and hippocampal parts of the cingulum, and stria terminalis), projection fibers (i.e., the anterior, superior, and posterior corona radiata; anterior and posterior internal capsule; cerebral peduncle; posterior thalamic radiation; and sagittal stratum), and deep cortex (i.e., the thalamus, caudate nucleus, putamen, and globus pallidus) (Fig. 1). DTI parameters obtained in same brain segment from both hemispheres were averaged to produce those for each brain structure.

Connectivity Measures

The processes used for generating the connectivity matrix are presented in Figure 2. Structural T1-weighted and diffusion images were coregistered using FMRIB's Software Library (<http://www.fmrrib.ox.ac.uk/fsl> in the public domain). The nodes of each participant in diffusion space were extracted by transferring the 122 parcellated cortical regions in the JHU neonatal brain atlas for connectivity analysis. The number of edges between nodes was defined based on reconstructed white matter fibers by using diffusion MRI tractography. Whole-brain deterministic tractography was performed using DSI Studio²⁶ (<http://dsi-studio.labsolver.org> in the public domain). The density of connectivity between two cortical ROIs was estimated as the sum of all streamlines connecting two ROIs divided by the length of the streamlines and normalized by the average volume of each pair of ROIs.

Network analyses were performed in 88 preterm and full-term infants. In these patients, overall network connectivity at the global level was examined by measuring nodal strength, path length, modularity, and the small-world index using the Brain Connectivity Toolbox in MATLAB (MathWorks, Inc., Natick, MA, USA). Nodal strength was calculated by summing all neighboring edge weights of a node as a measure of the local quantity of a network. The mean nodal strength was assessed by calculating the average of the local strength of each node within the network. The characteristic path length, which represents network integration, was calculated by measuring the average shortest path length between all pairs of nodes in the network. The network integration represents the ability to rapidly combine specialized information from distributed nodes, whereas the network segregation represents high connectivity within interconnected groups of nodes and low

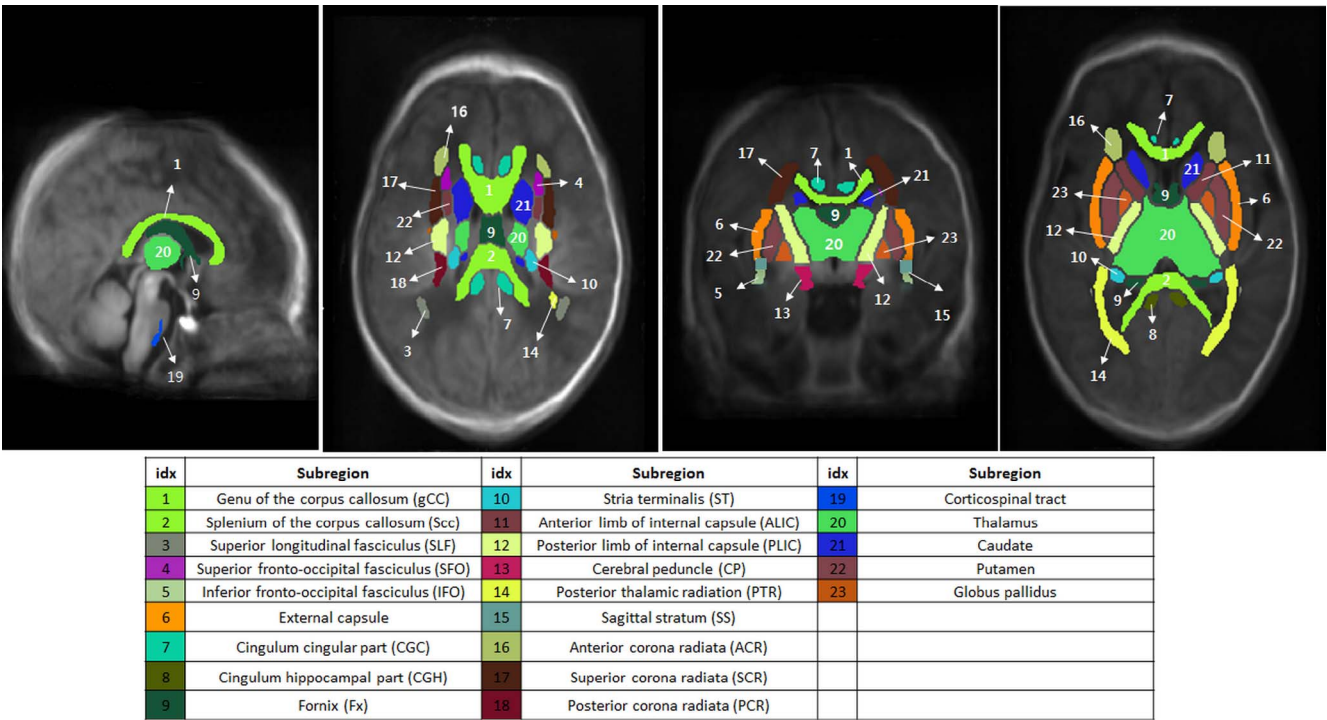


FIGURE 1. Photographic examples of MRI images obtained at the time of 37 weeks GA from a preterm infant born at 28 weeks GA. These images show atlas-based analyses used for obtaining mean FA and MD values. A total of 23 ROIs were used in this study.

connectivity to other groups of nodes, which can be quantified into measures of modularity. Modularity was defined as the fraction of the edges connecting nodes within the groups minus the expected fraction if edges were distributed in the absence of any group in an equivalent random graph.²⁷ The small-world index was used to define networks that were more clustered than random networks and computed as the ratio between the normalized clustering coefficient and the normalized path length, reflecting both integration and segregation.²⁸

Statistical Analyses

Statistical analyses were performed using SPSS 19.0 (IBM Corp., Armonk, NY, USA). Clinical characteristics and DTI parameters

were compared among the groups by using the analysis of variance (ANOVA). Student's *t*-tests, Mann-Whitney *U* tests, Fisher's exact tests, or χ^2 tests were used to compare clinical variables between preterm infants with and without ROP. Among preterm infants, a general linear model was used to confirm the association of each of ROI with ROP by using clinical variables such as GA, age at MRI scan, and IVH as covariates, as these exhibited significant association in the univariate analyses. Subgroup analyses were performed to evaluate the association between each of ROI and severe ROP. We also used the same model to examine group differences in structural brain networks, controlling for GA at birth, GA at the time of MRI, and IVH. Continuous variables are represented as the mean $\pm$ standard deviation. The level of statistical significance was set at $P < 0.05$.

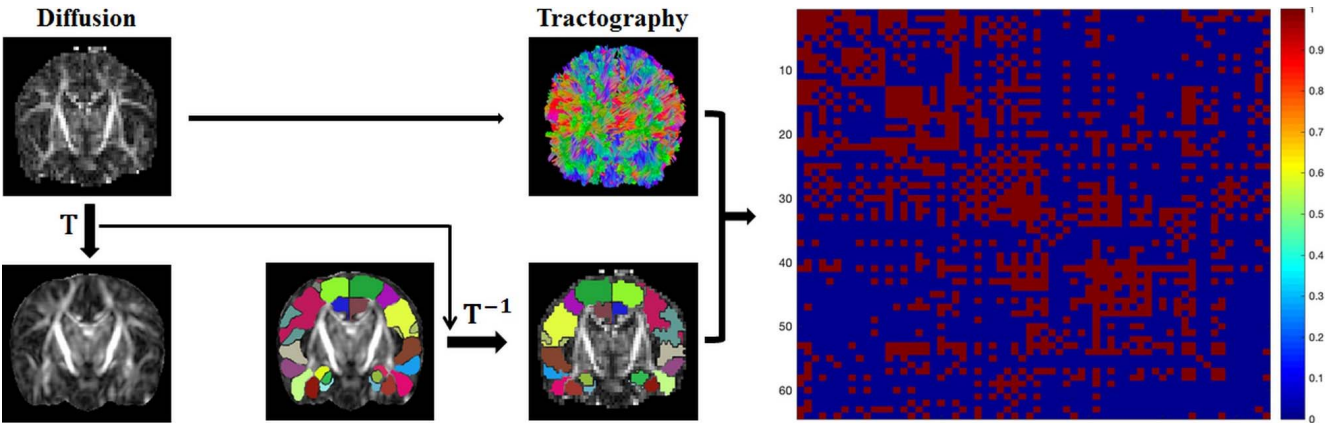


FIGURE 2. Schematic of the processes for obtaining the connectivity matrix. Each diffusion tensor image in its native space was registered to the single-subject template in the JHU atlas via a transformation (*T*). The JHU atlas labels were inversely transferred (*T*⁻¹) to the native space with delineation of network edges and nodes.

TABLE 1. Demographic and Clinical Characteristics of Preterm Neonates With and Without ROP and Full-Term Infants

Parameter	Preterm With ROP (<i>n</i> = 38)	Preterm Without ROP (<i>n</i> = 44)	Full-Term (<i>n</i> = 34)	<i>P</i> Value Among 3 Groups*	<i>P</i> Value (With vs. Without ROP)†
Gestational age, wk	26.8 ± 1.7	30.3 ± 2.6	38.0 ± 1.2	<0.001	<0.001
Birth weight, g	952.2 ± 265.7	1387.5 ± 348.2	3001.8 ± 506.5	<0.001	<0.001
Age at MRI scan, wk	37.0 ± 1.9	36.7 ± 1.5	39.2 ± 1.3	<0.001	0.330
Maternal age, y	34.4 ± 4.7	34.0 ± 4.0	33.3 ± 3.9	0.584	0.660
Length, cm	35.0 ± 4.4	40.0 ± 4.0	49.8 ± 2.1	<0.001	<0.001
Head circumference, cm	25.1 ± 2.3	28.2 ± 2.6	33.5 ± 2.5	<0.001	<0.001
Apgar score at 1 min	2.8 ± 1.6	3.8 ± 1.6	7.8 ± 1.6	<0.001	0.006
Apgar score at 5 min	5.8 ± 1.3	6.6 ± 1.1	9.0 ± 1.1	<0.001	0.004
Days of mechanical ventilation	28.7 ± 28.6	8.5 ± 7.9	0	<0.001	<0.001
Days of O ₂ therapy	50.4 ± 28.5	21.5 ± 21.8	0	<0.001	<0.001
Sex, M:F	18:20	17:27	22:12	0.072	0.425
Intrauterine growth restriction	9	11	0	0.002	0.890
In vitro fertilization	12	9	0	<0.001	0.250
Gestational diabetes mellitus	2	3	3	0.901	1.0
Pregnancy-induced hypertension	8	4	0	0.009	0.209
Premature rupture of membrane	14	16	1	<0.001	0.964
Placenta previa	2	0	0	0.190	0.212
Cesarean section	31	34	15	0.001	0.632
Respiratory distress syndrome	37	33	0	<0.001	0.004
Bronchopulmonary dysplasia	32	16	0	<0.001	<0.001
Necrotizing colitis	8	7	0	0.008	0.548
IVH, grade 1	12	6	0	<0.001	0.050
Clinical sepsis	27	17	0	<0.001	0.003

Data are presented as mean ± standard deviation (SD). Values in bold indicate statistical significance ($P < 0.05$). GA, gestational age; IVH, intraventricular hemorrhage.

* ANOVA or Fisher's exact or χ^2 test was used for comparison among groups.

† Unpaired *t*-test or Fisher's exact or χ^2 test was used for comparison between preterm infants with and without ROP.

RESULTS

Clinical Characteristics

Table 1 presents the clinical characteristics of all participants. In total, 82 preterm and 34 full-term infants were included in this study. There were significant differences in several characteristics such as GA, body weight at birth, GA at the time of MRI, body length, head circumference, Apgar scores at 1 and 5 minutes, and premature rupture of membranes (all $P < 0.05$). Preterm infants had more frequent respiratory distress syndrome, intrauterine growth restriction, bronchopulmonary dysplasia, necrotizing enterocolitis, IVH, patent ductus arteriosus, and sepsis (all $P < 0.05$). All the preterm infants with ROP and 40 of 44 preterm infants without ROP received oxygen therapy.

Table 1 also summarizes the results of the comparison between preterm infants with and without ROP. Both groups

exhibited significant differences in GA, body weight at birth, body length, head circumference, days of oxygen therapy, and bronchopulmonary dysplasia. Detailed clinical characteristics and treatment details of ROP are presented in Table 2. Among 38 infants with ROP, 17, 6, and 15 had maximal stage 1, 2, and 3, respectively. Nine and four infants received bevacizumab injection and laser photocoagulation for treatment-requiring ROP, respectively (Table 2). All the infants with ROP showed regression of ROP, either spontaneously or after treatment.

Comparison of DTI Parameters and ROP-Related Parameters

Table 3 depicts the results of the comparison of FA and MD values among preterm infants with and without ROP and full-term infants. Among the 23 FA values covering multiple brain

TABLE 2. Clinical Characteristics and Treatment Details in the Included Infants With ROP and Those With Severe ROP

Parameter	ROP (<i>n</i> = 38)	Severe ROP (<i>n</i> = 15)
Gestational age, wk	26.8 ± 1.7	26.4 ± 1.5
Birth weight, g	952.2 ± 265.7	877.3 ± 264.1
Extremely low birth weight (<1000 g; %)	20 (52.6)	10 (66.7)
Maximal stage of ROP, 1:2:3 (%)	17:6:15	0:0:15
Zone at the maximal stage, I:II:III	4:34:0	2:13:0
Aggressive posterior retinopathy of prematurity	3	3
Oxygen therapy (%)	38 (100)	15 (100)
Intrauterine growth restriction (%)	9 (23.1)	5 (33.3)
Sepsis (%)	27 (71.1)	12 (80)
Treatment details		
Bevacizumab therapy:laser photocoagulation		9:4
Age at treatment, wk		36.8 ± 2.2

Data are presented as mean ± SD.

TABLE 3. Mean FA and MD Values in Preterm and Full-Term Infants

ROI	FA					MD (mm ² /s)				
	Preterm With ROP (Group 1, n = 38)	Preterm Without ROP (Group 2, n = 44)	Full-Term (Group 3, n = 34)	P Value Among 3 Groups*	Adjusted P (Group 1 vs. 2)†	Group 1 (n = 38)	Group 2 (n = 44)	Group 3 (n = 34)	P Value Among 3 Groups*	Adjusted P†
Corpus callosum genu	0.231 ± 0.064	0.245 ± 0.044	0.268 ± 0.073	0.039	0.746	1.51×10 ⁻³ ± 1.63×10 ⁻⁴	1.53×10 ⁻³ ± 1.14×10 ⁻⁴	1.42×10 ⁻³ ± 1.55×10 ⁻⁴	0.003	0.991
Anterior limb of internal capsule	0.195 ± 0.047	0.196 ± 0.026	0.220 ± 0.056	0.030	0.719	1.43×10 ⁻³ ± 2.79×10 ⁻⁴	1.35×10 ⁻³ ± 1.88×10 ⁻⁴	1.33×10 ⁻³ ± 2.71×10 ⁻⁴	0.217	0.609
Posterior limb of internal capsule	0.342 ± 0.053	0.333 ± 0.036	0.363 ± 0.057	0.030	0.210	1.07×10 ⁻³ ± 9.81×10 ⁻⁵	1.10×10 ⁻³ ± 6.92×10 ⁻⁵	1.04×10 ⁻³ ± 7.91×10 ⁻⁵	0.021	0.274
Anterior corona radiata	0.166 ± 0.044	0.156 ± 0.021	0.190 ± 0.069	0.008	0.898	1.45×10 ⁻³ ± 1.69×10 ⁻⁴	1.51×10 ⁻³ ± 1.30×10 ⁻⁴	1.34×10 ⁻³ ± 1.82×10 ⁻⁴	<0.001	0.064
Superior corona radiata	0.187 ± 0.042	0.174 ± 0.031	0.211 ± 0.060	0.002	0.279	1.52×10 ⁻³ ± 2.05×10 ⁻⁴	1.52×10 ⁻³ ± 1.46×10 ⁻⁴	1.38×10 ⁻³ ± 1.85×10 ⁻⁴	0.002	0.885
Posterior corona radiata	0.214 ± 0.050	0.204 ± 0.031	0.246 ± 0.054	<0.001	0.583	1.43×10 ⁻³ ± 1.76×10 ⁻⁴	1.46×10 ⁻³ ± 1.33×10 ⁻⁴	1.30×10 ⁻³ ± 1.57×10 ⁻⁴	<0.001	0.714
Cingulum, cingular part	0.169 ± 0.046	0.171 ± 0.029	0.178 ± 0.053	0.613	0.726	1.29×10 ⁻³ ± 1.34×10 ⁻⁴	1.30×10 ⁻³ ± 7.17×10 ⁻⁵	1.24×10 ⁻³ ± 1.33×10 ⁻⁴	0.062	0.760
Cingulum, hippocampal part	0.170 ± 0.040	0.170 ± 0.033	0.189 ± 0.042	0.055	0.717	1.35×10 ⁻³ ± 1.73×10 ⁻⁴	1.33×10 ⁻³ ± 8.90×10 ⁻⁵	1.29×10 ⁻³ ± 1.21×10 ⁻⁴	0.183	0.252
Fornix	0.192 ± 0.038	0.207 ± 0.038	0.219 ± 0.048	0.031	0.355	1.53×10 ⁻³ ± 2.23×10 ⁻⁴	1.56×10 ⁻³ ± 1.31×10 ⁻⁴	1.48×10 ⁻³ ± 2.26×10 ⁻⁴	0.179	0.969
Stria terminalis	0.202 ± 0.049	0.212 ± 0.035	0.225 ± 0.067	0.167	0.697	1.32×10 ⁻³ ± 1.55×10 ⁻⁴	1.34×10 ⁻³ ± 1.40×10 ⁻⁴	1.22×10 ⁻³ ± 1.30×10 ⁻⁴	0.002	0.369
Corpus callosum splenium	0.181 ± 0.054	0.175 ± 0.042	0.211 ± 0.067	0.013	0.394	1.52×10 ⁻³ ± 2.37×10 ⁻⁴	1.66×10 ⁻³ ± 2.80×10 ⁻⁴	1.41×10 ⁻³ ± 2.38×10 ⁻⁴	<0.001	0.544
Superior longitudinal fasciculus	0.156 ± 0.044	0.146 ± 0.032	0.171 ± 0.039	0.026	0.666	1.32×10 ⁻³ ± 1.60×10 ⁻⁴	1.45×10 ⁻³ ± 1.52×10 ⁻⁴	1.30×10 ⁻³ ± 1.51×10 ⁻⁴	<0.001	0.030
External capsule	0.196 ± 0.036	0.186 ± 0.022	0.211 ± 0.038	0.005	0.672	1.32×10 ⁻³ ± 1.29×10 ⁻⁴	1.33×10 ⁻³ ± 9.22×10 ⁻⁵	1.23×10 ⁻³ ± 1.33×10 ⁻⁴	0.001	0.441
Posterior thalamic radiation	0.194 ± 0.063	0.196 ± 0.039	0.222 ± 0.067	0.067	0.821	1.38×10 ⁻³ ± 1.48×10 ⁻⁴	1.44×10 ⁻³ ± 1.39×10 ⁻⁴	1.30×10 ⁻³ ± 1.29×10 ⁻⁴	<0.001	0.533
Sagittal stratum	0.207 ± 0.056	0.202 ± 0.029	0.234 ± 0.069	0.024	0.711	1.34×10 ⁻³ ± 1.44×10 ⁻⁴	1.42×10 ⁻³ ± 1.42×10 ⁻⁴	1.27×10 ⁻³ ± 1.12×10 ⁻⁴	<0.001	0.251
Thalamus	0.204 ± 0.034	0.187 ± 0.020	0.208 ± 0.047	0.016	0.293	1.25×10 ⁻³ ± 1.38×10 ⁻⁴	1.20×10 ⁻³ ± 9.31×10 ⁻⁵	1.17×10 ⁻³ ± 1.35×10 ⁻⁴	0.024	0.133
Putamen	0.212 ± 0.044	0.176 ± 0.046	0.207 ± 0.043	0.001	0.091	1.37×10 ⁻³ ± 2.44×10 ⁻⁴	1.34×10 ⁻³ ± 2.14×10 ⁻⁴	1.31×10 ⁻³ ± 2.62×10 ⁻⁴	0.511	0.509
Globus pallidus	0.217 ± 0.038	0.189 ± 0.037	0.218 ± 0.051	0.002	0.205	1.26×10 ⁻³ ± 2.35×10 ⁻⁴	1.20×10 ⁻³ ± 1.49×10 ⁻⁴	1.21×10 ⁻³ ± 2.10×10 ⁻⁴	0.323	0.355
Caudate nucleus	0.150 ± 0.035	0.138 ± 0.024	0.165 ± 0.054	0.012	0.680	1.70×10 ⁻³ ± 3.52×10 ⁻⁴	1.68×10 ⁻³ ± 1.95×10 ⁻⁴	1.62×10 ⁻³ ± 3.51×10 ⁻⁴	0.481	0.541
Cerebral peduncle	0.264 ± 0.069	0.261 ± 0.035	0.279 ± 0.076	0.434	0.696	1.24×10 ⁻³ ± 1.59×10 ⁻⁴	1.33×10 ⁻³ ± 1.32×10 ⁻⁴	1.25×10 ⁻³ ± 1.62×10 ⁻⁴	0.012	0.005
Superior frontooccipital fasciculus	0.172 ± 0.037	0.160 ± 0.027	0.194 ± 0.068	0.007	0.322	1.78×10 ⁻³ ± 3.62×10 ⁻⁴	1.63×10 ⁻³ ± 2.38×10 ⁻⁴	1.58×10 ⁻³ ± 3.29×10 ⁻⁴	0.018	0.318
Inferior frontooccipital fasciculus	0.214 ± 0.049	0.210 ± 0.027	0.244 ± 0.055	0.003	0.478	1.42×10 ⁻³ ± 1.78×10 ⁻⁴	1.39×10 ⁻³ ± 1.63×10 ⁻⁴	1.30×10 ⁻³ ± 1.87×10 ⁻⁴	0.013	0.606
Corticospinal tract	0.206 ± 0.070	0.216 ± 0.042	0.212 ± 0.082	0.808	0.450	1.31×10 ⁻³ ± 4.12×10 ⁻⁴	1.27×10 ⁻³ ± 2.98×10 ⁻³	1.28×10 ⁻³ ± 5.23×10 ⁻⁴	0.904	0.944

Data are presented as mean ± SD. Values in bold indicate statistical significance ($P < 0.05$).

* Obtained by ANOVA.

† A general linear model was used to confirm the association of each of ROI with ROP using clinical variables such as GA, age at MRI scan, and IVH as covariates, as these exhibited significant association in the univariate regression analyses, among preterm infants.

TABLE 4. Mean FA and MD Values in Preterm Infants With and Without Severe (Stage 3 or Worse) ROP

ROI	FA			MD (mm ² /s)		
	Preterm With Severe ROP (n = 15)	Preterm Without Severe ROP (n = 67)	Adjusted P*	Preterm With Severe ROP (n = 15)	Preterm Without Severe ROP (n = 67)	Adjusted P*
Corpus callosum genu	0.238 ± 0.039	0.239 ± 0.058	0.524	1.52×10 ⁻³ ± 9.38×10 ⁻⁵	1.52×10 ⁻³ ± 1.47×10 ⁻⁴	0.808
Anterior limb of internal capsule	0.209 ± 0.036	0.193 ± 0.037	0.049	1.37×10 ⁻³ ± 2.16×10 ⁻⁴	1.39×10 ⁻³ ± 2.42×10 ⁻⁴	0.245
Posterior limb of internal capsule	0.351 ± 0.037	0.334 ± 0.046	0.125	1.10×10 ⁻³ ± 8.43×10 ⁻⁵	1.08×10 ⁻³ ± 8.45×10 ⁻⁵	0.459
Anterior corona radiata	0.174 ± 0.049	0.158 ± 0.030	0.437	1.44×10 ⁻³ ± 1.21×10 ⁻⁴	1.49×10 ⁻³ ± 1.57×10 ⁻⁴	0.257
Superior corona radiata	0.192 ± 0.023	0.178 ± 0.039	0.317	1.52×10 ⁻³ ± 1.65×10 ⁻⁴	1.52×10 ⁻³ ± 1.78×10 ⁻⁴	0.933
Posterior corona radiata	0.224 ± 0.033	0.206 ± 0.042	0.185	1.44×10 ⁻³ ± 1.21×10 ⁻⁴	1.45×10 ⁻³ ± 1.61×10 ⁻⁴	1.0
Cingulum, cingular part	0.179 ± 0.043	0.168 ± 0.036	0.182	1.31×10 ⁻³ ± 1.29×10 ⁻³	1.30×10 ⁻³ ± 9.98×10 ⁻⁵	0.572
Cingulum, hippocampal part	0.185 ± 0.031	0.167 ± 0.037	0.051	1.38×10 ⁻³ ± 1.81×10 ⁻⁴	1.33×10 ⁻³ ± 1.22×10 ⁻⁴	0.195
Fornix	0.207 ± 0.037	0.199 ± 0.039	0.128	1.56×10 ⁻³ ± 1.99×10 ⁻⁴	1.55×10 ⁻³ ± 1.76×10 ⁻⁴	0.432
Stria terminalis	0.219 ± 0.051	0.205 ± 0.040	0.083	1.37×10 ⁻³ ± 1.58×10 ⁻⁴	1.32×10 ⁻³ ± 1.44×10 ⁻⁴	0.035
Corpus callosum splenium	0.189 ± 0.035	0.175 ± 0.050	0.223	1.63×10 ⁻³ ± 2.42×10 ⁻⁴	1.59×10 ⁻³ ± 2.75×10 ⁻⁴	0.065
Superior longitudinal fasciculus	0.168 ± 0.039	0.147 ± 0.038	0.158	1.38×10 ⁻³ ± 1.14×10 ⁻⁴	1.40×10 ⁻³ ± 1.78×10 ⁻⁴	0.367
External capsule	0.202 ± 0.039	0.188 ± 0.026	0.417	1.34×10 ⁻³ ± 1.12×10 ⁻⁴	1.32×10 ⁻³ ± 1.10×10 ⁻⁴	1.0
Posterior thalamic radiation	0.211 ± 0.047	0.192 ± 0.051	0.084	1.42×10 ⁻³ ± 9.50×10 ⁻⁵	1.41×10 ⁻³ ± 1.55×10 ⁻⁴	0.181
Sagittal stratum	0.214 ± 0.046	0.202 ± 0.043	0.439	1.39×10 ⁻³ ± 1.16×10 ⁻⁴	1.39×10 ⁻³ ± 1.54×10 ⁻⁴	0.198
Thalamus	0.209 ± 0.039	0.191 ± 0.025	0.402	1.28×10 ⁻³ ± 1.83×10 ⁻⁴	1.21×10 ⁻³ ± 9.69×10 ⁻⁵	0.114
Putamen	0.207 ± 0.046	0.190 ± 0.048	0.781	1.33×10 ⁻³ ± 1.99×10 ⁻⁴	1.36×10 ⁻³ ± 2.34×10 ⁻⁴	0.105
Globus pallidus	0.219 ± 0.043	0.198 ± 0.039	0.907	1.23×10 ⁻³ ± 1.13×10 ⁻⁴	1.23×10 ⁻³ ± 2.09×10 ⁻⁴	0.531
Caudate nucleus	0.164 ± 0.041	0.140 ± 0.026	0.059	1.68×10 ⁻³ ± 2.94×10 ⁻⁴	1.69×10 ⁻³ ± 2.75×10 ⁻⁴	0.943
Cerebral peduncle	0.278 ± 0.051	0.259 ± 0.053	0.212	1.26×10 ⁻³ ± 1.44×10 ⁻⁴	1.29×10 ⁻³ ± 1.53×10 ⁻⁴	0.571
Superior frontooccipital fasciculus	0.184 ± 0.030	0.162 ± 0.032	0.072	1.72×10 ⁻³ ± 3.56×10 ⁻⁴	1.70×10 ⁻³ ± 3.02×10 ⁻⁴	0.366
Inferior frontooccipital fasciculus	0.212 ± 0.035	0.212 ± 0.039	0.997	1.41×10 ⁻³ ± 1.71×10 ⁻⁴	1.40×10 ⁻³ ± 1.71×10 ⁻⁴	0.391
Corticospinal tract	0.198 ± 0.060	0.214 ± 0.056	0.377	1.48×10 ⁻³ ± 5.31×10 ⁻⁴	1.25×10 ⁻³ ± 3.04×10 ⁻⁴	0.076

Data are presented as mean ± SD. Boldface indicates statistical significance ($P < 0.05$).

* A general linear model was used to confirm the association of each of ROI with severe ROP using clinical variables such as GA, age at MRI scan, and IVH as covariates, as these exhibited significant association in the univariate regression analyses.

areas, significant differences were observed among the groups in 17 (73.9%) regions, including the following: anterior, superior, and posterior corona radiata; superior and inferior frontooccipital fasciculus; putamen; globus pallidus; and caudate nucleus. Mean FA values in the preterm groups were lower than those in the full-term group. Table 3 also presents the comparison of MD values among the groups. MD values in 15 of 23 areas (65.2%) were significantly different among the groups ($P < 0.05$).

In contrast to the comparison among the three groups, significant differences in DTI parameters were observed in only few areas in the analyses between the preterm infants with and without ROP. When adjusting for other covariates such as GA, age at scan, and IVH, we observed significant associations between ROP and MD values in the superior longitudinal fasciculus ($P = 0.030$) and cerebral peduncle ($P = 0.005$).

The preterm infants with and without severe ROP were also compared in terms of DTI parameters (Table 4). The general linear model revealed statistically significant associations between severe ROP and FA values in the anterior limb of the internal capsule ($P = 0.049$) and between severe ROP and MD values in the stria terminalis ($P = 0.035$). However, subgroup analyses revealed no significant association between

DTI parameters and bevacizumab therapy (all $P > 0.05$; Supplementary Table S1).

Supplementary Table S2 lists the DTI parameters associated with ROP after adjusting for GA, GA at the time of MRI, and IVH. Multiple regression analyses revealed significant associations between ROP and MD values in the superior longitudinal fasciculus ($r = -9.78 \times 10^{-5}$, $P = 0.030$) and cerebral peduncle ($r = -1.20 \times 10^{-4}$, $P = 0.005$). Most of the regression coefficients for FA values were greater than 0, indicating that FA values and ROP exhibited a positive correlation, whereas those for MD values were less than 0, suggestive of an inverse relationship between MD values and ROP after adjusting for GA at birth, GA at the time of MRI, and IVH. We also observed significant associations between severe ROP and FA values in the anterior limb of the internal capsule and MD values in the stria terminalis (Supplementary Table S3).

Differences in Global Network Connectivity Among the Infant Groups

Nodal strength, path length, the small-world index, and modularity were comparable among preterm infants with and without ROP and full-term infants (all $P > 0.05$). Among preterm infants, there was no significant association between

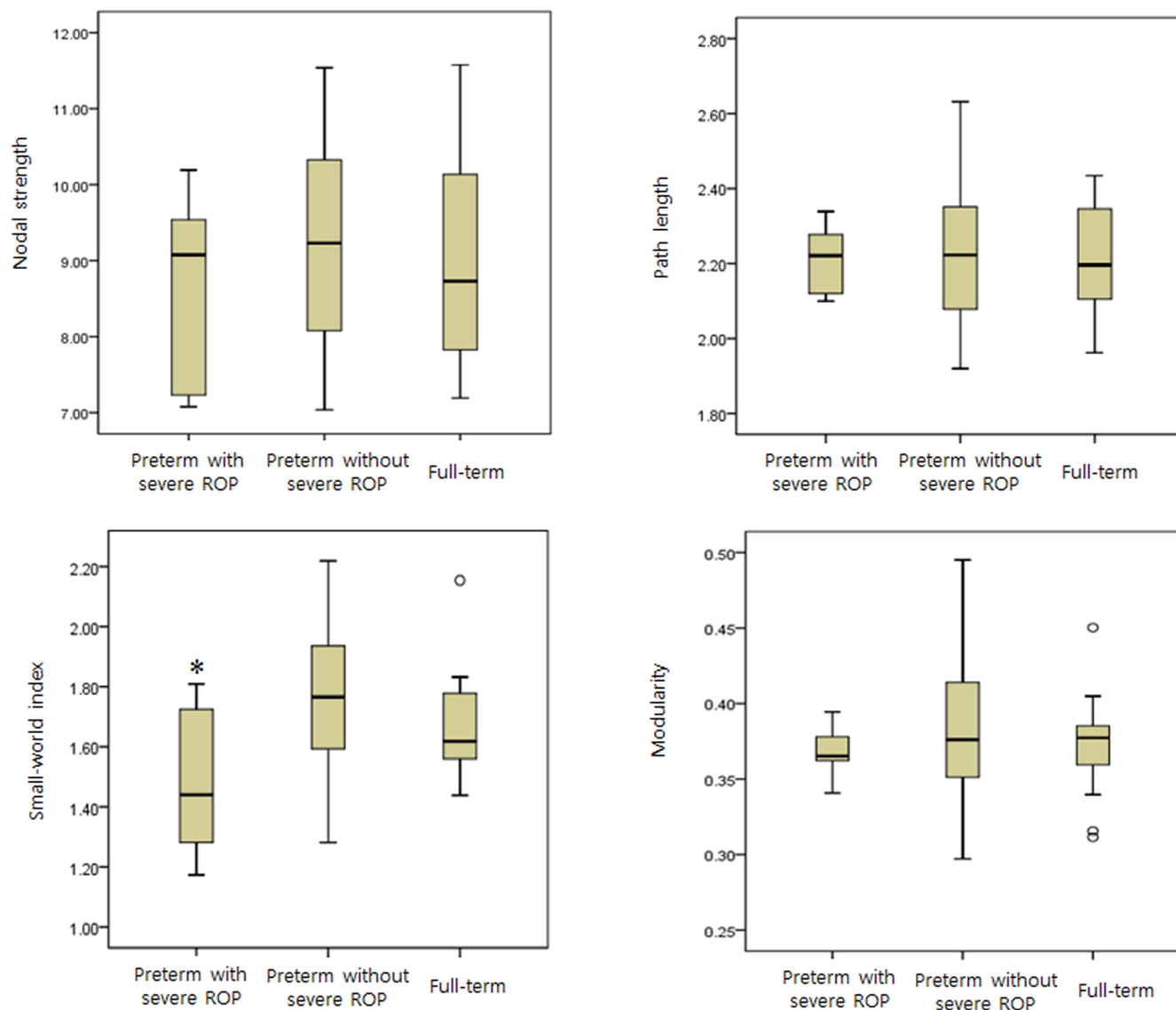


FIGURE 3. Box plots of global structural brain network characteristics (i.e., nodal strength, path length, modularity, and small-world index) among preterm infants with and without severe ROP and full-term control groups. In these plots, the lower and upper margins of each box represent quartiles (i.e., the 25th and 75th percentiles, respectively), whiskers represent the 10th and 90th percentiles, and the circles beyond the whiskers represent outliers. An *asterisk* indicates statistical significance.

ROP and any index from the general linear model analyses. However, preterm infants with severe ROP exhibited lower small-world index values than those without severe ROP (1.477 ± 0.261 and 1.645 ± 0.351 , $P = 0.011$), independent of GA at birth, GA at the time of MRI, and IVH (Fig. 3).

DISCUSSION

In this study, we used DTI parameters to evaluate the association between white matter maturation and ROP. We found significant differences in the DTI parameters of several white matter regions among the preterm and full-term infants, but we observed fewer differences between preterm infants with and without ROP from our analyses. Structural network analyses revealed a significant difference in small-world index values between those with and without severe ROP. Our results may indicate maturational delay of the specific white matter regions in infants with ROP and the reorganized structural brain network after birth in infants with severe ROP.

As previous studies have reported the association between white matter maturation delay and cognitive outcomes in children born preterm,^{12,29} our findings may provide functional implications in preterm infants with ROP. Clinical outcomes of ROP have improved greatly since the introduction of laser and anti-vascular endothelial growth factor therapy for severe retinopathy. Therefore, in infants with ROP, clinicians or parents might believe that the condition is no longer associated with childhood visual or nonvisual impairments, in cases of regression or successful treatment. However, our results on white matter maturation in infants with ROP indicate that these infants may retain an increased risk of cognitive or motor impairment. Mechanistically, our results might also suggest a possible association between ROP and white matter maturation in certain areas of the brain. However, as motor and cognitive outcomes were not assessed in this cross-sectional study, further studies are required to validate the clinical and mechanistic implications our study.

Hellstrom et al.² suggested ROP as a window into the postnatal development of the brain, and because ROP is associated with neurologic dysfunction and poor brain growth. White matter analyses in our study suggest that white matter injury can occur as a comorbidity of the CNS system in infants with ROP and should be considered carefully. However, we used two control groups (full-term and preterm controls) and a general linear model to discriminate the effects of ROP/severe ROP from those of GA (preterm birth). The results indicated that the microstructural integrity of the white matter significantly differed among the groups in several areas, but relatively fewer differences were observed between preterm infants with and without ROP. These findings suggest that preterm birth may exert a greater effect on white matter microstructural development than ROP does.

However, previous studies have reported an association between delays in microstructural development of the white matter and ROP.⁷ Thompson et al.²³ observed an association between severe ROP and microscopic alterations in the optic radiations in very preterm children. Additional studies have revealed that FA values in the posterior limb of the internal capsule, external capsule, and optic radiations are decreased in infants with severe ROP.²⁹ Functionally, these differences, in addition to the ocular complications of ROP, may lead to visual impairment.^{2,12,30} In the present study, we analyzed microstructural integrity in a greater number of white matter areas ($n = 23$), adjusting our analyses for GA, GA at the time of MRI, and IVH. ROP was significantly associated with MD values in the superior longitudinal fasciculus, an association fiber tract that synapses on neurons in the occipital lobe and cerebral peduncle, which refines motor movements and uses proprioceptive information to maintain balance and posture. Furthermore, infants with and without severe ROP exhibited significant differences in FA values within the anterior limb of the internal capsule, which contains thalamic fibers that project to the cingulate and prefrontal cortex. These patients also exhibited significant differences in MD values within the stria terminalis, a band of fibers running along the ventricular surface of the thalamus serving as a major output pathway of the amygdala.

There are two distinct pathways of neural processing of vision: the dorsal and ventral pathways. The ventral visual pathway carries information about perceptual features, allowing the creation of long-term representations necessary to identify and recognize objects, whereas the dorsal pathway processes information about objects and their locations in a moment-to-moment manner and mediates the visual control of skilled actions. Among the areas investigated in this study, the inferior frontooccipital fasciculus is the white matter region consisting of the ventral stream of the visual pathway, whereas superior longitudinal fasciculus and superior frontooccipital fasciculus are the regions consisting of the dorsal pathway. In these white matter regions, preterm infants with and without ROP exhibit nonsignificant differences in DTI parameters. In contrast, there were remarkable differences in FA and MD values among preterm infants with and without ROP and full-term infants. This suggests maturational delay of the dorsal and ventral pathways in infants with ROP might be attributed to preterm birth, rather than ROP. The maturation of the two pathways and associated functional deficits in infants with ROP should be investigated further, as these pathways are important for visual perceptual function in infants with ROP.

Changes in DTI parameters may reflect alterations in white matter fiber diameter/density, myelination, or membrane permeability.³¹ Therefore, our results may indicate differences in white matter maturation between preterm and full-term infants and between infants with and without severe ROP. The observed associations between altered white matter micro-

structure and preterm birth/ROP may reflect common etiologic factors, such as hypoxic-ischemic insult in preterm infants, for both ROP and white matter injury.^{32,33} Furthermore, hyperoxia can activate signaling pathways, resulting in pathologic angiogenesis via reactive oxygen species, the key pathogenesis of ROP.³⁴ The oxidative stress caused by hyperoxia may also be relevant to white matter injury in premature infants as it also induces apoptosis in the brain, leading to white matter injury in the neonatal brain.³⁵ In addition, we detected differences in structural connectivity alterations between preterm infants with and without severe ROP, supporting our findings regarding differences in DTI parameters between these groups. The brain networks of patients with severe ROP exhibited significant decreases in small-worldness, suggesting that severe ROP exerts an impact on the development of integrated and segregated networks. Our results are in concordance with recent findings that early developmental connectivity is altered by preterm birth and adverse neonatal conditions.^{36,37} As these significant associations between connectivity and ROP may be predictive of behavioral performance and cognitive capacity later in life,³⁸ infants with severe ROP may be at risk for poorer behavioral and cognitive outcomes. However, our cross-sectional data do not reveal the precise effect of ROP or severe ROP on white matter development during the post-term period, so further studies are necessary.

Currently, anti-vascular endothelial growth factor treatment is widely performed in cases of severe ROP, such as zone I or zone II posterior stage 3 with plus disease.³⁹ Due to the possibility of its systemic antiangiogenic effect, it is very important to assess systemic side effects of the therapy. As antiangiogenic effects can be detrimental to brain development, it might anatomically affect the brain microstructure and functionally result in adverse motor, sensory, or cognitive outcomes. However, its effect has been debated and not been extensively studied for brain white matter. In our subgroup comparison between the preterm infants with and without bevacizumab therapy, there was no parameter showing a statistically significant difference between the two groups. This comparison might indicate that the short-term effect of bevacizumab therapy at term equivalent ages is minimal in terms of brain white matter integrity; however, due to the limitation of the small number of patients who underwent this therapy, its long-term effect on the brain should be evaluated further.

The present study possesses several limitations of note. First, our study used a cross-sectional design, and we were, thus, unable to determine the causal relationship between ROP and white matter maturation. Although we controlled for important confounding variables such as GA, age at MRI, and mild IVH, significant differences in clinical characteristics among the groups may have affected our results. Furthermore, our evaluations of the effect of ROP on postnatal development were somewhat limited, as we assessed DTI parameters obtained at term-equivalent ages. Further studies using data obtained at greater ages are required to provide more conclusive data regarding post-term white matter development. Additionally, the subgroup comparison of the DTI parameters between the infants treated with and without bevacizumab therapy involved a small number of treated infants, particularly those who received bevacizumab therapy; thus, this comparison might not have sufficient power to show statistical significance. Furthermore, as visual outcomes could not be assessed at term-equivalent ages, we were unable to evaluate the relationship between white matter abnormalities and visual function. Future studies should examine the associations between various cognitive functions and white matter abnormalities at later time points in infants with ROP, as

these associations may elucidate ROP's effects on brain structure and cognition.

In conclusion, our findings demonstrated that white matter microstructural abnormalities were associated with preterm birth in multiple areas of the brain and with ROP in a few areas at term-equivalent ages. Our results suggest that preterm birth exerts a greater effect on white matter maturation than ROP up to the point of term-equivalent ages. Future studies should investigate the association between ROP and CNS development in further detail by evaluating post-term neural development.

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