


ORIGINAL ARTICLE

Peripapillary retinal nerve fibre layer thickness and macular ganglion cell layer volume in association with motor and cognitive outcomes in 11-year-old children born very preterm

Tuomo Lehtonen^{1,2}  | Eija Vesti^{1,2} | Leena Haataja³ | Anna Nyman⁴ |
 Karoliina Uusitalo^{2,5} | Markku T. Leinonen⁶ | Sirkku Setänen^{2,5} |
 on behalf of the PIPARI Study Group

¹Department of Ophthalmology, University of Turku, Turku, Finland

²Turku University Hospital, Turku, Finland

³Department of Pediatric Neurology, University of Helsinki, and Pediatric Research Center, Helsinki University Hospital, Helsinki, Finland

⁴Department of Psychology, University of Turku, Turku, Finland

⁵Department of Pediatric Neurology, University of Turku, Turku, Finland

⁶Ocusweep (Ocuspecto Oy), Turku, Finland

Correspondence

Tuomo Lehtonen, Department of Ophthalmology, Turku University Hospital, Kiinamyllynkatu 4-8, 20521 Turku, Finland.
 Email: tuomo.lehtonen@tyks.fi

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Abstract

Purpose: The purpose of the study was to study the association between retinal parameters and motor and cognitive outcomes in children born very preterm.

Methods: This study is part of a prospective cohort study of very preterm infants (birth weight \leq 1500 grams/gestational age $<$ 32 weeks). At 11 years of age, the ophthalmological assessment included a retinal optical coherence tomography (OCT) examination of the peripapillary retinal nerve fibre layer (PRNFL) and the macular ganglion cell layer (GCL). The motor performance was assessed with the Movement Assessment Battery for Children—Second Edition (Movement ABC-2), and the cognitive outcome with the Wechsler Intelligence Scale for Children—Fourth Edition (WISC-IV).

Results: A total of 141 children were included. The mean (SD) average PRNFL was 95 μ m (10.2 μ m). The mean (SD) macular GCL volume was 0.34 mm³ (0.03 mm³). Higher PRNFL thickness associated with higher percentiles for total scores in the motor assessment ($b = 0.5$, 95% CI 0.1–0.8, $p = 0.01$) and higher macular GCL volume with higher scores in the cognitive assessment ($b = 1.4$, 95% CI 0.5–2.3, $p = 0.002$), also when adjusted for gender, birth weight z-score (birth weight in relation to gestational age) and major brain pathology at term.

Conclusion: The associations between higher average PRNFL thickness and better motor performance as well as higher macular GCL volume and better cognitive performance refer to more generalized changes in the brain of 11-year-old children born very preterm. Retinal OCT examinations might provide a deeper insight than mere eyesight in long-term neurodevelopmental follow-up of children born very preterm.

KEYWORDS

ganglion cell layer, long-term neurodevelopment, movement assessment battery for children second edition, optical coherence tomography, peripapillary retinal nerve fibre layer, Wechsler intelligence scale for children fourth edition

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1 | INTRODUCTION

Prematurity is associated with altered retinal thickness. Most of the studies investigating peripapillary retinal nerve fibre layer (PRNFL) describe decreased thickness in the global average value or limited to one or more quadrants of the PRNFL (Fieß, Christian, et al., 2017; Park & Oh, 2015; Rothman et al., 2015; Ruberto et al., 2014; Tariq et al., 2011; Wang et al., 2012). The clinical significance of PRNFL alterations in prematurity is unclear. A lesser PRNFL thickness has been associated with decreased visual acuity (Fieß, Christian, et al., 2017) while other studies have not found an association with visual function (Åkerblom et al., 2012; Oros et al., 2014; Ruberto et al., 2014). Prematurity-related brain lesions are known to reduce PRNFL thickness, probably via retrograde trans-synaptic degeneration, and relate to visual field defects (Lennartsson et al., 2014). However, reduced PRNFL thickness is observed not only in those with brain pathology (Åkerblom et al., 2012). Children born preterm have increased retinal thickness in the macula (Balasubramanian et al., 2019; Fieß, Janz, et al., 2017; Park & Oh, 2012; Rosén et al., 2020; Ruberto et al., 2014; Tariq et al., 2011). These changes are speculated to be caused by abnormal cell migration during foveal development. A thickened fovea seems to associate with lower visual acuity (Balasubramanian et al., 2019; Fieß, Janz, et al., 2017).

Preterm birth increases risk for motor and cognitive impairments (Böhm et al., 2002; Evensen et al., 2004). We have previously shown that better motor performance was associated with better cognitive performance in 11-year-old children born very preterm (Nyman et al., 2017; Setänen et al., 2016). As the retina is an extension of the central nervous system, prematurity-related brain changes and alterations in retinal thickness might share a common origin or be causally related. Retinal changes might thus reflect motor and cognitive performance. In fact, PRNFL thinning has previously been reported to associate with lower cognitive and motor outcomes in children born very preterm at 18–24 months of age (Rothman et al., 2015).

The present study aimed to evaluate the association of average PRNFL thickness and macular GCL volume with motor and cognitive outcomes in 11-year-old children born very preterm. We hypothesized that a higher average PRNFL and a higher macular GCL volume would associate with better motor and cognitive outcomes in early adolescence.

2 | METHODS

2.1 | Participants

This prospective regional cohort study is part of the multidisciplinary PIPARI Study (The Development and Functioning of Very Low Birth Weight Infants from Infancy to School Age) of infants born very preterm. The participants were born between January 2001 and December 2006 to Finnish or Swedish speaking families in Turku University Hospital, Finland. From 2001

to 2003 the inclusion criteria were birth weight ≤ 1500 g and prematurity (<37 gestational weeks). From 2004, the inclusion criteria were extended to all infants born <32 weeks of gestational age irrespective of birth weight. A total of 34 infants died and 9 parents refused to participate. The exclusion criteria were severe congenital anomalies or diagnosed syndromes affecting development ($n = 25$). A total of 221 infants were eligible.

For the present study, children with ophthalmological, motor and cognitive assessment at 11 years of age were included. Two children died during the follow-up, and 51 did not participate. We excluded children with prior retinopathy of prematurity (ROP) of stage 2 or higher ($n = 6$). The decision of exclusion was based on prior observations of severe ROP affecting retinal layers (Åkerblom et al., 2012; Park & Oh, 2015; Pueyo et al., 2015). Children with myopia of 5 dioptres or more in either eye were excluded ($n = 2$). There were no children with a major eye pathology in the final study population. In OCT examinations, the exclusion criteria were a signal-to-noise ratio of 15 dB or less or improper scan alignment ($n = 11$) due to lack of co-operation or other technical reason. Only the results of the right eye of each participant were used in the analyses. Children with cerebral palsy ($n = 8$) were excluded. The final number of children assessed was 141. The flow chart of the participants is shown in Figure 1.

The study followed the tenets of the Declaration of Helsinki. The Ethics Review Committee of the Hospital District of South-West Finland approved the study protocol in 2000 and in 2012. Written informed consent was provided by the parents and children.

2.2 | Ophthalmological assessment at 11 years

Ophthalmological assessment was performed by one ophthalmologist (T.L.). Best corrected distance visual acuity was measured with numerical logMAR charts at a distance of 3 or 4 meters. Near visual acuity was measured at 30 cm. Low-contrast visual acuity was measured using optotypes of 2.5% of contrast level at 3 or 4 m. Crowded optotype visual acuity test at 30 cm had 25% optotype interspacing. Both eyes underwent refraction after instillation of 1% cyclopentolate eye drops. OCT scans were acquired with Heidelberg Spectralis OCT (Heidelberg Engineering GmbH). The global average thickness of the PRNFL was measured using the standard circular OCT scan of 12 degrees centred at the optic nerve head. GCL volume was measured within the 3 mm ETDRS circle in the centre of the macula. Nerve fibre layer and GCL segmentation was performed automatically by the default device software. All results were manually checked for correct segmentation and adequate quality. Eye biometry was acquired with Carl Zeiss IOLMaster (Carl Zeiss Meditec AG). For each child, a history of ROP and its subtype was searched for in the medical records. Intraocular pressure was measured in cases of suspicious optic disc cupping. Confrontation perimetry by quadrant finger counting was performed to rule out the most prominent defects in visual fields.

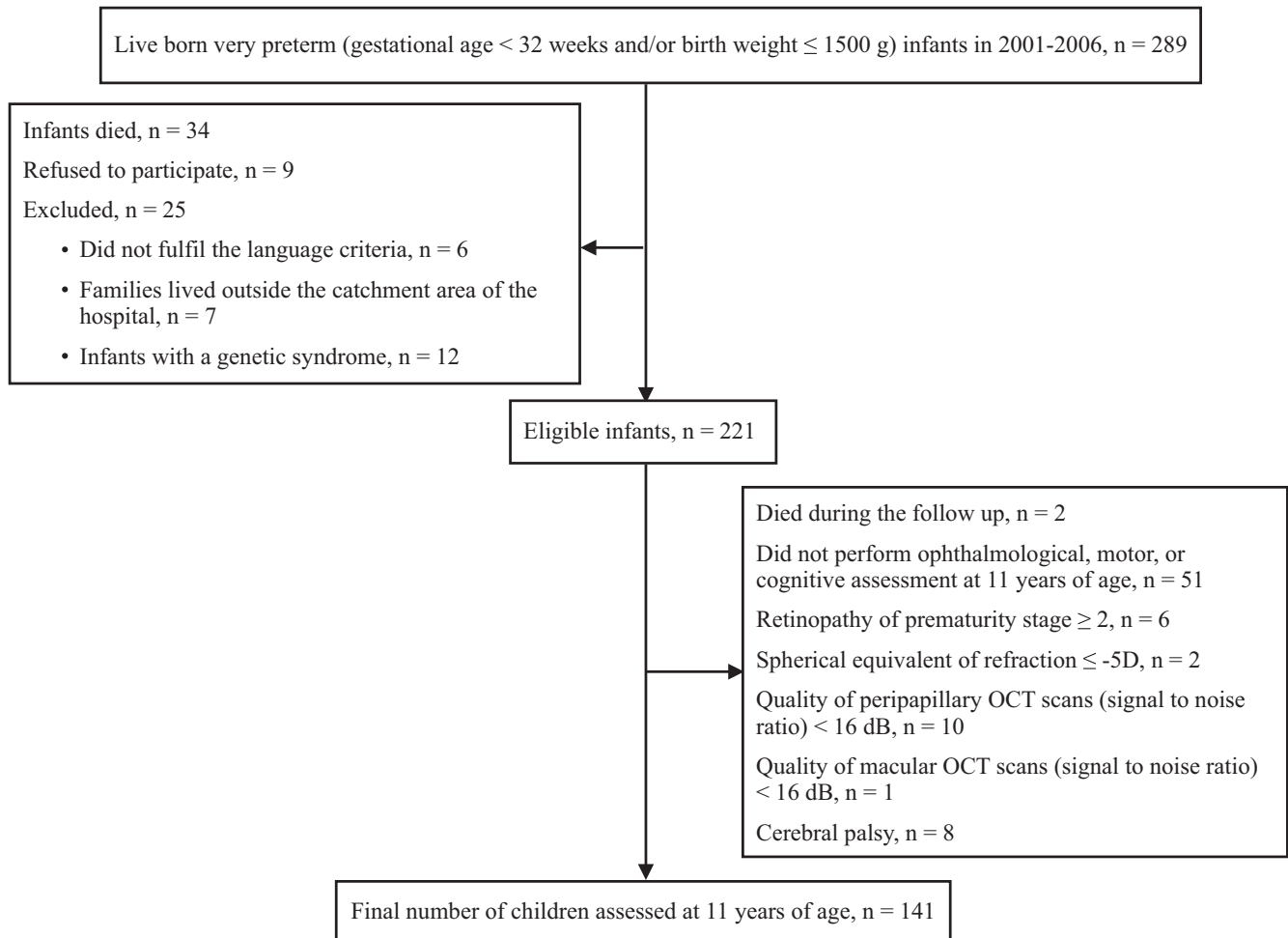


FIGURE 1 Flow chart of the study children. OCT, optical coherence tomography.

2.3 | Motor assessment at 11 years

The motor outcome was assessed with the Movement Assessment Battery for Children - Second Edition (Movement ABC-2) (Setänen et al., 2016) performed by one of three physicians. It includes three subscales: manual dexterity, aiming and catching and balance. The raw scores of the subscales were converted into total standard scores and percentiles according to the test manual (Setänen et al., 2016), using age band 3 (11–16 years) and the norms for 11-year-old-children. A higher percentile indicates a better outcome. Percentiles for total scores were used as a continuous variable in the analyses.

2.4 | Cognitive assessment at 11 years

The cognitive outcome was assessed with the Wechsler Intelligence Scale for Children—Fourth Edition (WISC-IV), Finnish translation (Nyman et al., 2017). The assessment was performed in Finnish or Swedish according to child's native language. Finnish assessments were performed by one of two Finnish-speaking psychologists and the Swedish assessments by a native Swedish-speaking psychologist. General intelligence was measured with a full-scale intelligence quotient (IQ), which consists of four indexes: verbal comprehension, perceptual reasoning, working memory and processing

speed. Based on the test manual (Nyman et al., 2017), a full-scale IQ <70 (<−2 SD) was classified as severe cognitive impairment.

2.5 | Magnetic resonance imaging of the brain

The brain magnetic resonance imaging (MRI) was performed at term age. One neuroradiologist analysed the images and manually performed volume measurements blinded to the clinical information of the infant. Axial T2-weighted images, coronal three-dimensional T1-weighted images and coronal T2-weighted images of the entire brain were obtained using the MRI equipment of an open 0.23 Tesla Outlook GP (Philips Medical) equipped with a multipurpose flexible coil fitting the head of the infant. All of the sequences were optimized for the imaging of a term infant brain. The infants were categorized into three groups based on the structural MRI findings: (i) normal findings consisted of normal brain anatomy (cortex, basal ganglia and thalami, posterior limb of internal capsule, white matter, germinal matrix, corpus callosum, and posterior fossa structures), width of extracerebral space <5 mm, ventricular/brain (V/B) ratio <0.35, (ii) Minor pathologies consisted of consequences of intraventricular haemorrhages grade 1 and 2, caudothalamic cysts, width of the extracerebral space of 5 mm and V/B ratio of 0.35 and (iii) major pathologies

consisted of consequences of intraventricular haemorrhages grade 3 and 4, injury in cortex, basal ganglia, thalamus or internal capsule, with injury of corpus callosum, cerebellar injury, white matter injury, increased width of extracerebral space >5 mm, V/B ratio >0.35, ventriculitis or other major brain pathology (infarcts) (Setänen et al., 2014).

2.6 | Statistical analysis

The distribution of continuous variables was checked, and the descriptive statistics are presented in mean (SD) when the data were normally distributed and in median (min, max) when not. Differences in continuous background characteristics between participating children ($n = 141$) and dropouts ($n = 80$) were studied using the independent samples t -test (Table 1). For the categorical background characteristics, Chi-square test or Fisher's exact test was used. Differences in the average PRNFL thickness and macular GCL volume according to the findings of the brain magnetic resonance imaging at term (normal findings or minor pathologies and major pathologies), small for gestational age status, and ROP status (no ROP, ROP stage 1) were studied using the independent samples t -test. Spearman's rho was used to study the correlations between the average PRNFL thickness as well as macular GCL volume and distance visual acuity, near visual acuity, low-contrast distance visual acuity and crowded optotype near visual acuity. Linear regression analysis was used to study the associations between ophthalmological outcomes (average PRNFL thickness and macular GCL volume) and percentiles for total scores of the Movement ABC-2 and full-scale IQ. The analyses were adjusted for sex, birth weight z-score (birth weight in relation to gestational age), and brain MRI findings at term as these have previously found to be associated with cognition at 11 years in children born very preterm in this cohort (Nyman

et al., 2017). Goodness of fit was reported according to Akaike's information criterion, where information criteria are in smaller-is-better form (Table 3). Residuals were checked to justify the analysis. The following were considered a sign of multicollinearity: a correlation coefficient equal to or greater than 0.8 and/or a tolerance value less than 0.1 and/or a Phi and Cramer's V equal to or greater than 0.8 was considered a sign of multicollinearity. The statistical analyses were performed using an SPSS version 27.0 (IBM SPSS Statistics, IBM Corporation). A two-tailed p -value of <0.05 was considered statistically significant.

3 | RESULTS

A total of 141 children (62 females, 79 males) were included in the study. The background characteristics of the study children and the dropouts ($n = 80$) are shown in Table 1. The study children had a higher gestational age ($p = 0.004$, independent samples t -test) and birth weight ($p = 0.08$) and suffered less often from bronchopulmonary dysplasia ($p = 0.01$, Chi-square test), operated necrotizing enterocolitis ($p = 0.04$, Fisher's Exact Test), and major brain pathologies in magnetic resonance imaging (MRI) at term ($p = 0.002$, Chi-square test); their background was more often that of multiple births ($p = 0.01$) compared with the dropouts. There were 2 (1.4%) children with severe hearing impairment and 12 (8.5%) children with full-scale IQ < 70.

3.1 | Ophthalmological outcome

The mean (SD) average PRNFL was 95 μm (10.2 μm), and the mean (SD) macular GCL volume was 0.34 mm^3 (0.03 mm^3). There was no difference in the average PRNFL thickness or macular GCL volume regarding brain MRI findings at term, small for gestational

TABLE 1 Background characteristics of the study children born very preterm (birth weight ≤ 1500 g or gestational age < 32 weeks) compared with the characteristics of the dropouts (including two children who died).

	Study children, ($n = 141$)	Dropouts, ($n = 80$)	p -Value
Gestational age, mean (SD) [min, max], week	29.4 (2.6) [23.0, 35.9]	28.3 (2.8) [23.4, 35.1]	0.004
Birth weight, mean (SD) [min, max], grams	1172.4 (311.0) [400, 2120]	1008.5 (357.5) [565, 1970]	0.07
Birth weight z-score ^a , mean (SD) [min, max]	-1.5 (1.4) [-4.9, 2.2]	-1.1 (1.5) [-4.7, 3.4]	0.1
Small for gestational age (<-2 SD), n (%)	48 (34.0)	20 (25.0)	0.2
Male, n (%)	79 (56.0)	46 (57.5)	0.8
Caesarean delivery, n (%)	88 (62.4)	46 (57.5)	0.5
Multiple birth, n (%)	51 (36.2)	16 (20.0)	0.01
Bronchopulmonary dysplasia, n (%)	12 (8.5)	16 (20.0)	0.01
Operated necrotizing enterocolitis, n (%)	3/138 (2.2)	7/79 (8.9)	0.04
Sepsis, n (%)	20 (14.2)	17 (21.3)	0.2
Major brain pathologies in magnetic resonance imaging at term age ^b , n (%)	26/136 (19.1)	30/79 (38.0)	0.002

^aBirth weight in relation to gestational age.

^bThe specific imaging protocol and details about the classification of the findings have been described previously (Setänen et al., 2014).

TABLE 2 Descriptive characteristics for visual acuity, refractive errors and eye biometry in children born very preterm ($n = 141$).

Outcome variable	Median (min, max)
Distance visual acuity, logMAR	0.0 (−0.30, 0.22)
Near visual acuity, logMAR	0.0 (−0.2, 0.6)
Crowded near visual acuity, logMAR	0.0 (−0.1, 0.8)
Low-contrast visual acuity, logMAR	0.5 (0.1, 0.9)
Spherical equivalent, D	0.5 (−2.5, 5.0)
Astigmatism, D	0.25 (−0.25, 2.00)
Axial length, mm	22.8 (20.1, 24.8)
Mean corneal curvature, D	44.4 (38.4, 48.2) ^a

^aData missing for one child.

age status or ROP status. The descriptive characteristics for visual acuity, refractive errors and eye biometry are shown in Table 2. A higher average PRNFL thickness correlated with better near visual acuity ($r = -0.2$, $p = 0.04$, Spearman's rho) and with better crowded optotype near visual acuity ($r = -0.2$, $p = 0.04$). There were no statistically significant correlations between the macular GCL volume and visual acuity parameters. There were 127 (90.1%) children without ROP and 14 (9.9%) children with ROP stage 1. The average PRNFL thickness or macular GCL volume did not differ between children without ROP and children with ROP stage 1.

3.2 | Motor outcome

The mean (SD) percentile for total scores of the Movement ABC-2 was 38.4 (23.5). The Movement ABC-2 increased by 0.5 percentiles when the average PRNFL thickness increased by 1 μm ($b = 0.5$, 95% CI 0.1–0.8, $p = 0.01$, Linear regression analysis), also when adjusted for gender, birth weight z-score (birth weight in relation to gestational age), and major brain pathology in MRI at term (Table 3). Similar association was not found between macular GCL volume and percentiles for total test scores of the Movement ABC-2.

3.3 | Cognitive outcome

The mean full-scale IQ was 89.5 (SD 15.8). The full-scale IQ improved by 1.4 points when the macular GCL volume increased by 0.01 mm^3 ($b = 1.4$, 95% CI 0.4–2.3, $p = 0.002$, Linear regression analysis), also when adjusted for gender, birth weight z-score (birth weight in relation to gestational age), and major brain pathology in MRI at term (Table 3). Similar association was not found between the average PRNFL thickness and full-scale IQ.

4 | DISCUSSION

This is the first study to show that retinal parameters associated with motor and cognitive outcomes in 11-year-old children born very preterm. A higher PRNFL thickness associated with better motor performance and a higher macular GCL volume associated with better cognitive

performance. These results were in agreement with our hypothesis that retinal OCT could provide prognostic information on neurodevelopment.

A higher PRNFL thickness associated with better motor performance at 11 years of age even when adjusted for gender, birth weight z-score (birth weight in relation to gestational age) and major pathology in brain MRI at term. Children born very preterm can possess subnormal visual fields (Jacobson et al., 2006; Larsson et al., 2004). Scotomata could then have an impact on the Movement ABC-2 performance in tasks requiring good visuomotor performance such as catching a ball. An example of brain-related PRNFL thinning with visual field defects is prematurity-related white matter injury, which is thought to act via retrograde trans-synaptic degeneration (Lennartsson et al., 2014). White matter damage related to prematurity can also cause defective motion perception (Weinstein et al., 2012). In contrast, we did not find differences in the average PRNFL thickness between children with normal findings or minor pathologies and children with major pathologies in brain MRI at term. Lastly, glaucoma could also cause a reduction in PRNFL thickness, affect visual fields and spare visual acuity. In cases of suspicious optic disc cupping, intraocular pressure was measured to rule out glaucoma. All the study children were also examined with confrontation perimetry to rule out the most evident defects in visual fields. The test, however, is probably not sensitive enough to detect less evident visual field abnormalities that might have an effect in fast-paced visuomotor tests (Pandit et al., 2001).

Rothman et al. have shown that a thinner papillomacular and temporal retinal nerve fibre layer correlated with a poorer cognitive and motor performance in very preterm infants at 18–24 months of corrected age. A thinner papillomacular and temporal retinal nerve fibre layer also correlated with a higher global brain MRI lesion burden index (Rothman et al., 2015). Tong et al. have analysed optic nerve morphology from OCT scans in 44 preterm infants born at ≤ 30 weeks gestational age and 52 term infants born at ≥ 36 weeks gestational age. At 37–42 weeks post-menstrual age, central cupping was found to be greater in the preterm group. In preterm infants, larger cup-to-disc ratio was associated with a lower cognitive performance at the age of 18–22 months corrected age. Periventricular leukomalacia, which is a severe brain pathology related to prematurity, was a contributing factor (Tong et al., 2014). Interestingly, we found no association between PRNFL thickness and cognitive performance in 11-year-old children born very preterm. Direct comparisons between the cohorts are challenging because of differences in inclusion criteria, outcome measures and definitions used.

The thickness of the macular GCL—inner plexiform complex has been reported to associate with cognitive performance and sensorineural function in adults (Merten et al., 2020). This is the first study to evaluate the association between the macular GCL volume and concurrent cognitive performance in 11-year-old children born very preterm.

In contrast to our findings, a previous study of 347 children aged 6–13 years has shown that small for

TABLE 3 Associations between ophthalmological outcomes (average PRNFL thickness and macular GCL volume) and motor and cognitive outcomes.

Percentiles for total scores (the movement assessment battery for children – Second edition)				
	b	95% CI	AIC	p
Average PRNFL thickness (µm)	0.5	0.1 to 0.8	1288.9	0.01
Adjusted ^a	0.5	0.1 to 0.8	1240.8	0.01
Macular GCL volume (1/100 mm ³)	0.8	–0.5 to 2.1	1285.2	0.2
Adjusted ^a	0.6	–0.8 to 1.9	1237.7	0.4
Full-scale intelligence quotient (The Wechsler Intelligence Scale for Children – Fourth Edition)				
	b	95% CI	AIC	p
Average PRNFL thickness (µm)	0.13	–0.1 to 0.4	1181.6	0.3
Adjusted ^a	0.12	–0.1 to 0.8	1142.4	0.4
Macular GCL volume (1/100 mm ³)	1.4	0.5 to 2.3	1166.3	0.002
Adjusted ^a	1.3	0.4 to 2.2	1127.6	0.004

^aAdjusted for sex, birth weight z-score, major brain pathology in magnetic resonance imaging at term since these have previously been found to be associated with cognition at 11 years in children born very preterm in this cohort (Nyman et al., 2017).

Abbreviations: AIC, Akaike's information criterion (in smaller-is-better form); GCL, ganglion cell layer; PRNFL, peripapillary retinal nerve fibre layer.

gestational age status was associated with lower PRNFL thickness. In a subgroup of 112 children aged 6–8 years, the small for gestational age children had lower visuo-motor performance (Oros et al., 2014). There was no difference in the average PRNFL thickness or macular GCL volume according to a small for gestational age status in the present study. This is in line with our previous findings showing similar neurodevelopmental outcomes compared with other children born very preterm in this study population (Leppänen et al., 2014; Lind et al., 2011; Maunu et al., 2011).

A major strength of this study was that all the study children performed an extensive ophthalmological, motor and cognitive assessment with a reasonable attrition rate. The study children were healthier compared with the dropouts regarding perinatal background characteristics. An even higher follow-up rate without dropouts might have strengthened our results. A possible limitation was that we did not exclude stage 1 ROP from the analysis. Every case of stage 1 ROP was limited to zone 3, that is the periphery, so it is unlikely that ROP would have skewed the results obtained from the posterior pole. Moreover, we found no difference in the average PRNFL thickness or macular GCL volume between children without ROP and children with ROP stage 1. This is in agreement with previous literature (Fieß, Christian, et al., 2017; Ulusoy et al., 2020).

In conclusion, the associations between higher average PRNFL thickness and better motor performance as well as a higher macular GCL volume and a better cognitive performance refer to more generalized changes in the brain of children born very preterm still in early adolescence. Retinal OCT examinations might thus provide a deeper insight than mere eyesight in long-term neurodevelopmental follow-up of children born very preterm.

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ORCID

Tuomo Lehtonen  <https://orcid.org/0000-0002-1890-3297>

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