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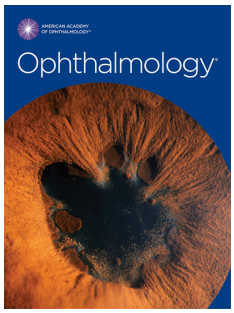

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Relationship between retinal thickness profiles and visual outcomes in young adults born extremely preterm: The EPICure@19 Study

Siva Balasubramanian *[1, 2], Joanne Beckmann *[3], Hemal Mehta [4,5], SriniVas R. Sadda [1, 2], Karntida Chanwimol [1, 2], Marco Nassisi [1, 2], Irena Tsui [1, 2, 6], Neil Marlow [3], Saurabh Jain [4]. *Both authors contributed equally

[1] Doheny Image Reading Center, Doheny Eye Institute, Los Angeles, California, USA

[2] Department of Ophthalmology, David Geffen School of Medicine at UCLA, Los Angeles, California, USA

[3] Academic Neonatology, UCL Elizabeth Garrett Anderson Institute for Women's Health, University College London, London, UK

[4] Ophthalmology Department, Royal Free London NHS Foundation Trust, London, UK

[5] Macular Research Group, University of Sydney, Sydney, Australia

[6] Stein Eye Institute, University of California Los Angeles, Los Angeles, California, USA

Short title: Retinal structure and visual function in adults born extremely preterm

Corresponding Author:

Hemal Mehta MA FRCOphth

Consultant Ophthalmologist

Royal Free London NHS Foundation Trust

Royal Free Hospital, Pond Street, London NW3 2QG

Email: HM@cantab.net

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Keywords: preterm, retinopathy of prematurity, retinal layers, optical coherence tomography

Summary Statement: The retinal layer thickness profiles investigated by optical coherence tomography were altered in young adults born extremely preterm with associated impaired visual function.

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Abstract

Purpose: To quantify inner and outer retinal layer thicknesses and understand their relevance to visual function among young adults born extremely preterm (EP).

Design: Prospective observational study with 19 years follow-up

Participants: A total of 354 eyes (226 eyes of former EP infants and 128 age-matched full-term control eyes) from 177 young adults were evaluated. Among EP participants, 50% of eyes (112/226) were not previously diagnosed with neonatal retinopathy of prematurity (ROP), 38% of eyes (84) had ROP not deemed to require treatment in the neonatal period and 13% (30) had neonatal cryotherapy or laser ablation for ROP.

Methods: Subjects underwent eye examinations including best corrected visual acuity (BCVA) and Heidelberg Spectralis macular spectral domain optical coherence tomography (SD-OCT) imaging. Retinal layers were auto-segmented and thickness profiles were computed at the fovea by the instrument software.

Main outcome measure: Correlation between retinal sublayer thickness and BCVA.

Results: Compared with control eyes, the inner and outer retinal layers of EP eyes were significantly thicker and BCVA was significantly reduced. Retinal layer thicknesses and BCVA were similar for untreated EP eyes and those without neonatal ROP. In contrast, treated eyes had increased inner and outer retinal layer thickness and decreased vision. Inner retinal layer thickness was moderately correlated with worse BCVA ($r = 0.30$, $p < 0.001$) but outer retinal layer thickness was not ($r = -0.01$, $p = 0.80$). Multivariate regression indicated ganglion cell layer thickness was a significant independent predictor of BCVA.

Conclusions: Extremely premature birth influences maturation of the fovea and visual outcomes into early adult life. Increased ganglion cell layer thickness was

associated with worse BCVA. Eyes requiring neonatal treatment for ROP had associated worse BCVA at the age of 19 years.

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Introduction

Children born preterm are at increased risk of developing a range of ocular and vision disorders later in life including refractive errors, amblyopia, strabismus, cataracts, glaucoma and retinal detachment. [1–5] Retinopathy of prematurity (ROP) is a vasoproliferative disorder affecting the preterm retina, and remains the leading cause of childhood blindness following preterm birth accounting for between 6 and 18% of cases in developed countries [6] with rates as high as 40% in developing countries. [7] The development of ROP is related to fetal growth and oxygen exposure in the period after preterm birth and is commonest among the most immature births. [8,9]

The lack of a foveal reflex in premature infants was reported by Isenberg in 1986 based on clinical ophthalmoscopic exam. [10] With the advent of spectral domain optical coherence tomography (SD-OCT), several studies have reported morphological changes following preterm birth among subjects aged 2 years to 18 years, including abnormal foveal contour, absence of a foveal depression, retention of inner retinal layers at the foveal centre and macular oedema. [11,12]

SD-OCT is a fast, non-invasive imaging technique which provides visualization of the retina and choroid. In addition, SD-OCT images also help to quantify changes in the individual retinal thickness profiles using recent advances in automated segmentation algorithms. Although previous studies have investigated the retinal morphological changes in preterm children with or without ROP, [13–15] to the best of our knowledge the association between individual retinal layers and visual outcomes has not previously been established.

The purpose of this study was to correlate visual function with retinal thickness profiles in a large well-characterized cohort of young adults who were born

before 26 weeks of gestation (extremely preterm (EP)) and full-term born controls. This could be helpful to better understand the pathophysiologic mechanisms involved in prematurity, as well as to identify potential SD-OCT biomarkers to monitor disease progression and identify additional new targets for pharmacologic treatment. We hypothesize that abnormalities in the retinal thickness parameters due to EP births are related to reduced visual function.

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Methods

Ethics

The study was conducted according to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) good clinical practice (GCP) Guidelines, the applicable regulatory requirements, and the current Declaration of Helsinki and are in compliance with the Health Insurance Portability and Accountability Act (HIPAA). Ethical approval was granted by the National Research Ethics Service South Central Committee - Hampshire (Reference: 13/SC/0514), and all subjects gave informed consent or assent was sought from a parent (for those lacking capacity to consent) before enrollment.

Subjects and Data Collection

All the data were obtained from the EPICure study (www.epicure.ac.uk), a large well-characterized study on young adults born before 26 weeks of gestation, as part of a long-term follow-up study called the EPICure@19 study. [16] Briefly, all the participants who are now adults underwent complete ophthalmic examination including best corrected visual acuity (BCVA) and spectral domain optical coherence tomography (SD-OCT) imaging on both eyes, as part of a comprehensive clinical and psychological assessment carried out in the NIHR University College London Hospital Clinical Research Facility.

In this prospective longitudinal study, EP participants between 18 - 20 years of age and a full-term born age-matched comparison group attended for assessment. The EP group comprised individuals with and without neonatal ROP, and among the ROP group those with spontaneous resolution and those who received either cryotherapy or laser ablation in the neonatal period.

The comparison group comprised healthy volunteers with no evidence of ocular pathology in both eyes. All study participants underwent a complete ophthalmologic examination, which included BCVA, anterior segment examinations, dilated posterior segment examinations, assessment of their refractive status and ocular motility. The Snellen BCVA for each eye was converted to the logarithm of the minimum angle of resolution (logMAR) and refractive error was represented as spherical equivalent for statistical analysis.

Exclusion criteria

Subjects with suboptimal quality SD-OCT scans due to poor fixation, limited compliance or significant media opacity were excluded.

SD-OCT imaging

SD-OCT scans were acquired using the Spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany). A 20º x 20º (6.1 mm x 6.1 mm) scan pattern consisting of 25 B-scans with an inter-scan distance of 253 µm was centred over the fovea. A single experienced investigator performed all of the SD-OCT imaging without pharmacologic mydriasis.

Image analysis

Retinal layers were auto-segmented (Figure 1) from 25 central horizontal B-scans on a 6 x 6 mm scan pattern using Heidelberg Eye Explorer (version 1.9.13.0; Heidelberg Engineering, Heidelberg, Germany). The individual retinal layer thickness profiles including retinal nerve fibre layer, ganglion cell layer, inner plexiform layer, inner nuclear layer, outer plexiform layer, outer nuclear layer, photoreceptor and retinal pigment epithelium were computed at the fovea corresponding to the central 1 mm circle of Early Treatment Diabetic Retinopathy Scale (ETDRS) by the instrument software.

Statistical analysis

All quantitative measurements were expressed as mean ± standard deviation (range). Differences in age, BCVA, spherical component of refractive error and retinal thickness parameters between EP and comparison eyes were compared using the Mann-Whitney U test. We used the Kruskal-Wallis test to evaluate parameters across the EP groups, i.e. no neonatal ROP, ROP without and ROP with treatment.

The correlation between logMAR BCVA and retinal layers was assessed using bivariate Pearson correlation. Multiple linear regression analysis was used to determine the relationship between logMAR BCVA (dependent variable) and thickness of individual retinal layers.

All statistical analyses were performed using IBM® SPSS® software, version 20, and a *p* value of < 0.05 was considered statistically significant.

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Results

A total of 354 eyes (226 eyes from 113 EP young adults and 128 eyes from 64 age-matched controls) from 177 young adults were enrolled. Among the EP group, 112/226 eyes (50%) had no previously diagnosed neonatal ROP (EP-No-ROP), 84/226 eyes (37%) had ROP not deemed to require treatment in the neonatal period (EP-ROP-NT), and 30/226 eyes (13%) had ROP treated previously with cryotherapy or laser (EP-ROP-T). A total of 208 eyes from 101 EP young adults were analysed after excluding 18 eyes from 12 EP young adults because of insufficient image quality (ten eyes from six EP-No-ROP adults, seven eyes from five EP-ROP-NT adults and one eye from an individual in the EP-ROP-T group).

Participants were evaluated at similar ages and the spherical equivalent of refractive error was not significantly different between EP and comparison eyes (Table 1). The logMAR equivalent BCVA was significantly worse in the EP group (Table 1). The inner retinal layers were thicker overall in the EP group ($p<0.001$) as was each component layer ($p<0.001$ for each; Table 1). Overall, the outer retinal layers were similarly thicker in the EP group ($p<0.001$), but component thickness was only significantly increased in the outer plexiform layer and outer nuclear layers.

Within the EP group, gestational age at birth varied marginally between groups: EP-ROP-T group: 24.7 ± 0.8 weeks, EP-ROP-NT: 25.1 ± 0.7 weeks, EP-No ROP: 25.0 ± 0.9 weeks ($p=0.02$). Again, refractive error was similar when grouped by neonatal ROP status, but logMAR BCVA varied across the three groups ($p = 0.006$), being highest in the EP-ROP-T group, in whom it was significantly higher compared with EP-No ROP ($p = 0.005$; Table 2). Among the EP eyes, IRL thickness varied between groups ($p = 0.04$) and was thickest in EP-ROP-T eyes, again significantly greater than in EP-No ROP eyes ($p = 0.03$). Of the component internal

layers only, the ganglion cell layer differed between EP eyes by ROP status. Overall the outer retinal layers varied by ROP status (p=0.006) and were thicker in EP-ROP-T eyes compared with EP-ROP-NT (p=0.005) and EP-No ROP eyes (p=0.02). The outer plexiform and outer nuclear layers mirrored these differences but retinal pigment layer was lowest in the EP-ROP-T eyes (Table 2).

There was a modest positive correlation between inner retinal layer thickness and logMAR BCVA ($r = 0.30$, $p < 0.001$) meaning thicker inner retinal layer was associated with decreased vision, but there was no significant correlation between outer layer thickness and logMAR BCVA ($r = - 0.01$, $p = 0.80$).

Multiple linear regression model analysis demonstrated ganglion cell layer as an independent predictor of logMAR BCVA ($p < 0.001$). Following ganglion cell layer, a combination of both ganglion cell layer and retinal pigment epithelium was also a significant predictor of logMAR BCVA ($p < 0.001$).

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Discussion

In a cohort of young adults who were born before 26 weeks of gestation, we have identified overall worse visual acuity compared with term born eyes. Among EP eyes, SD-OCT has identified that inner and outer retinal layers were thicker compared with term born eyes and this was most marked in eyes that had been treated for ROP, with laser ablation or cryotherapy. Thicker inner retinal layers were moderately correlated with worse visual acuity independent of refractive status. In particular, thicker ganglion cell layer was independently, and thinner retinal pigment epithelium along with thicker ganglion cell layer were codependently associated with reduced visual acuity.

Previous studies have reported preserved inner and outer retinal thickness in preterm births, [12,17] but to our knowledge its relevance to visual function has not been established. We hypothesize the increase in IRL thickness is a reflection of preserved inner retinal layers at the central fovea in preterm children. [18,19] Previous studies correlating OCT with histologic studies have shown that development of the fovea begins at around 30-32 weeks postmenstrual age and continues until after birth. [18–20] Histological analysis revealed centrifugal displacement of inner retinal layers and centripetal migration of outer retinal layers at the fovea during development. [19] The process of foveal maturation may be slowed or arrested after extremely preterm birth, leaving eyes with thicker retinal layers. Since the visual acuity was specifically correlated with internal layer thickness, but not outer layers, the development of the internal retinal layers may be important in the study of foveal morphological changes following preterm birth. The results from our study also support several histological studies that have identified a disrupted foveal anatomy in preterm infants compared with full-term controls. [18,21,22]

We quantified the component layers within both internal and outer retinal layers. The RPE layer was the only layer which was thinner in EP eyes and was independently associated with visual acuity. Most other layers were relatively thicker in EP eyes with the exception of the photoreceptor layer, which appeared similar within the comparator and EP eyes. Formation or maturation of photoreceptors might be completed during early second trimester or may be more resistant to changes leading to maturational arrest in other layers, resulting in a comparable thickness between EP and full-term born eyes.

Several SD-OCT studies have investigated the retinal layer thickness profiles in preterm children, [18,23,24] but the association between individual retinal layers and visual function has been unclear. We report the novel finding that increased ganglion cell layer was an independent predictor of visual function compared with other retinal layers. A combination of both thinner retinal pigment epithelial layer thickness and thicker ganglion cell layer was also associated with worse visual acuity.

The cells in the ganglion cell layer are usually apparent at around 9 – 12 weeks of gestation. [25] In addition to ganglion cells, it consists of displaced amacrine cells and large number of glial cells. [26] The maturation of the ganglion cell layer occurs throughout late stages of the gestational period and continues during the neonatal period. In this layer, the cells are uniformly distributed during early gestation with highest densities at about 18 to 30 weeks of gestation. [27] Density declines throughout the remainder of the gestation period, particularly rapidly towards the end of gestation. The reduction in ganglion cell layer thickness has been linked to naturally occurring neuronal death, which is an important developmental process in the maturation of retina. [27] The process of centrifugal retinal migration resulting in the maturation of the ganglion cell layer along with other retinal layers, could arrest

following extremely preterm birth, leaving their eyes with a thicker inner layer, particularly affecting the ganglion cell layer, that persists into young adult life, affecting visual acuity.

A histological study investigating the retinal pigment layer in post-mortem eyes, from 24 weeks of gestation to 6 years postpartum, reported a gradual increase in cell density at the macula. [28] Cell density increased steadily in the macular area through the last trimester of gestation before reaching a stable level 6 months after birth. [28] The increase in retinal pigment layer cell density at the macula appears to be due to the centripetal migration of the retinal pigment layer cells. Centripetal migration of epithelial cells could be slowed or halted following extremely preterm birth, leaving a thinner retinal pigment layer extending into adult life and affecting vision. However, future histological studies are required to confirm the retinal pigment layer changes seen in the present study. The photoreceptor layer was the only retinal layer similar across the control and EP groups, and a possible explanation could be that this layer might be one of the earliest to develop during intrauterine life.

The retinal layer thickness profiles were measured at the fovea corresponding to the central 1 mm circle of ETDRS grid so that its association with visual acuity could be established. Future studies are required to investigate the retinal layers outside 1 mm circle i.e., at the parafoveal (1 – 3 mm ETDRS circle) and perifoveal regions (3 – 6 mm ETDRS circle). Analyzing the parafoveal and perifoveal changes in premature infants could be applicable to rodent models, where a fovea is absent, to explore the pathophysiology and potential therapeutic options for ROP. [29,30]

Of note, preterm children are also at an increased risk of developing cortical or cerebral visual impairment (CVI). [31] The CVI is impaired vision without primary ocular pathology and it is one of the leading causes of poor visual acuity among EP

births. [31] The vision impairment usually ranges from severe to complete blindness. CVI could explain the cause of low visual acuity among preterm children with little or no significant change in retinal layers investigated by SD-OCT.

The difference in refractive error was not significant between the groups. Our study population may have had less myopia than other pre-term cohorts. Axial length measurements were not recorded in this analysis and it would be necessary to include this parameter in future studies.

Our study is also limited by its cross-sectional nature. Longitudinal data is required to investigate changes in the retinal layers and visual acuity over time. Other measures of visual function including contrast sensitivity and vision-related quality of life could be included in future studies. Treatment modalities for ROP have also evolved over time. Of note, longitudinal studies are also crucial to determine the postnatal age where the increase in retinal ganglion layer thickness halts. This information would be invaluable for future clinical trials using age-specific retinal thickness profiles as clinical trial endpoints to predict visual acuity changes in ROP.

Nevertheless, our study also has several strengths including its prospective design over 19 years with a large well-characterized cohort, the use of standardized image acquisition protocols, and the inclusion of age-matched controls.

In conclusion, young adults born extremely preterm exhibited significant structural changes at the fovea. Increased ganglion cell layer thickness was associated with worse BCVA. Retinal layer thickness and BCVA were most profoundly affected in those eyes requiring treatment for ROP. These findings provide insight into the pathophysiologic mechanisms following preterm birth that are relevant to the maturation of the human fovea.

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Table 1: Characteristics of visual and retinal layer findings among 101 young adults born before 26 weeks of gestation and 64 age matched term born participants.

Table 2: The individual IRL and ORL thickness layer profiles within the EP group; EP-ROP-NT, EP-ROP-T and EP-No ROP.

Figure 1: A. Raw unsegmented SD-OCT B-scan image generated by Heidelberg Spectralis. B. SD-OCT B-scan image after automated segmentation of individual retinal layers on Heidelberg Spectralis.

RNFL: Retinal nerve fibre layer; GCL: Ganglion cell layer; IPL: Inner plexiform layer; INL: Inner nuclear layer; OPL: Outer plexiform layer; ONL: Outer nuclear layer; PR: Photoreceptor; RPE: Retinal pigment epithelium; BM: Bruch's membrane

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Table 1: Characteristics of visual and retinal layer findings among 101 young adults born before 26 weeks of gestation and 64 age matched term born participants.

		Full term births	Extremely preterm births	Difference in means (95%CI)	Mann Whitney U: 'p' value
Age, years		19.2 ± 0.5 (18 – 20)	19.3 ± 0.5 (18 – 20)	- 0.20 to 0.03	0.22
Refractive error, dioptres		- 1.33 ± 1.79 (- 5.85 – 2)	- 0.48 ± 3.66 (- 7.88 – 10.25)	- 2.05 to 0.36	0.32
LogMAR BCVA		- 0.06 ± 0.15 (- 0.30 – 0.70)	0.15 ± 0.50 (- 0.22 – 2.70)	- 0.30 to - 0.14	< 0.001*
IRL, µm		72.4 ± 14.8 (47 – 125)	103.8 ± 19.9 (50 – 178)	- 35.09 to - 27.62	< 0.001*
ORL, µm		206 ± 10.5 (169 – 228)	218.5 ± 14.5 (150 – 254)	- 15.15 to – 9.77	< 0.001*
IRL, µm	RNFL	13.4 ± 1.9 (8 – 18)	16.4 ± 4.7 (10 – 58)	- 3.73 to - 2.29	< 0.001*
	GCL	17.7 ± 5.3 (10 – 38)	27.3 ± 7.6 (10 – 59)	- 11.04 to - 8.27	< 0.001*
	IPL	22.4 ± 3.9 (16 – 36)	29.66 ± 5.3 (14 – 49)	- 8.25 to - 6.28	< 0.001*
	INL	19 ± 5.2 (7 – 34)	30.4 ± 7.4 (13 – 64)	- 12.79 to - 10.07	< 0.001*
ORL, µm	OPL	26 ± 6 (14 – 64)	31.8 ± 5.5 (15 – 52)	- 7.15 to - 4.58	< 0.001*

	ONL	88 ± 9.6 (55 – 113)	95.7 ± 11.9 (52 – 129)	- 10.12 to - 5.47	< 0.001*
	PR	74.5 ± 4.2 (66 – 86)	73.9 ± 4.6 (63 – 86)	- 0.38 to 1.55	0.33
	RPE	17.7 ± 2.1 (13 – 28)	17.1 ± 2.2 (10 – 25)	0.13 to 1.09	0.015*

Results are expressed as mean ± SD (range).
* Significant levels comparing the groups.
Snellen best corrected visual acuity (BCVA) equivalent: Full term births (20/15 ± 20/30); extremely preterm births (20/30 ± 20/70)

IRL: Inner retinal layer; ORL: Outer retinal layer; ILM: Internal limiting membrane; RNFL: Retinal nerve fibre layer; GCL: Ganglion cell layer; INL: Inner nuclear layer; IPL: Inner plexiform layer; OPL: Outer plexiform layer; ONL: Outer nuclear layer; ELM: External limiting membrane; PR: Photoreceptor; RPE: Retinal pigment epithelium; BM: Bruch's membrane.

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1 Table 2: The individual IRL and ORL thickness layer profiles within the EP group;

2 EP-ROP-NT, EP-ROP-T and EP-No ROP.

Groups		EP			Kruskall Wallis 'p' value
		EP-ROP-T	EP-ROP-NT	EP-No ROP	
Age, years		19.1 ± 0.5 (18.4 – 20.0)	19.3 ± 0.6 (18.4 – 20.5)	19.3 ± 0.5 (18.4 – 20.3)	0.25
Gestational age, weeks		24.7 ± 0.8 (23 – 26)	25.1 ± 0.7 (23 – 26)	25 ± 0.9 (22 – 26)	0.02*
Refractive error, dioptres		- 0.81 ± 2.79 (- 5.13 – 4.87)	-1.47 ± 3.16 (- 6.88 – 5.25)	0.32 ± 4.06 (- 7.88 – 10.25)	0.22
LogMAR BCVA		0.41 ± 0.80 (- 0.08 – 2.70)	0.15 ± 0.45 (- 0.17 – 2.70)	0.09 ± 0.39 (- 0.22 – 2.70)	0.006*
IRL, µm		112.9 ± 25.8 (63 – 157)	103.2 ± 19.6 (50 – 178)	101.7 ± 17.6 (57 – 140)	0.04*
ORL, µm		224.3 ± 20.4 (150 – 248)	216.9 ± 11.8 (171 – 254)	218.1 ± 14.1 (179 – 254)	0.006*
IRL, µm	RNFL	17.1 ± 6.9 (10 – 8)	15.9 ± 1.9 (12 – 20)	16.3 ± 4.2 (12 – 33)	0.72
	GCL	32.7 ± 11.6 (14 – 59)	26.6 ± 6 (10 – 46)	26.3 ± 6.7 (10 – 46)	0.01*
	IPL	32.1 ± 7.2 (20 – 49)	29.2 ± 4.5 (14 – 41)	29.3 ± 5.2 14 – 40)	0.12
	INL	31.7 ± 7.7 (15 – 43)	30.2 ± 8 (13 – 64)	30.2 ± 7 (16 – 48)	0.36

ORL, µm	OPL	34.9 ± 6.2 (23 – 47)	31.2 ± 5.7 (15 – 52)	31.5 ± 4.9 (22 – 52)	0.007*
	ONL	99.7 ± 14.6 (52 – 116)	94.7 ± 10.4 (67 – 129)	95.3 ± 11.9 (71 – 129)	0.01*
	PR	73.7 ± 4.7 (63 – 86)	73.6 ± 4.6 (65 – 86)	74.2 ± 4.5 (63 – 85)	0.45
	RPE	16.0 ± 2.4 (10 – 21)	17.4 ± 2.1 (12 – 25)	17.1 ± 2.1 (11 – 23)	0.03*

Results are expressed as mean ± SD (range).
* Significant levels comparing the groups.
Extremely premature (EP); EP with retinopathy of prematurity treated previously (EP-ROP-T), EP with ROP not treated previously (EP-ROP-NT) and EP only without any signs of ROP (EP-No ROP).
Snellen best corrected visual acuity (BCVA) equivalent: EP-ROP-T (20/50 ± 20/100), EP-ROP-NT (20/30 ± 20/50), EP- No ROP (20/25 ± 20/50).
IRL: Inner retinal layer; ORL: Outer retinal layer; RNFL: Retinal nerve fibre layer; GCL: Ganglion cell layer; INL: Inner nuclear layer; IPL: Inner plexiform layer; OPL: Outer plexiform layer; ONL: Outer nuclear layer; PR: Photoreceptor; RPE: Retinal pigment epithelium.

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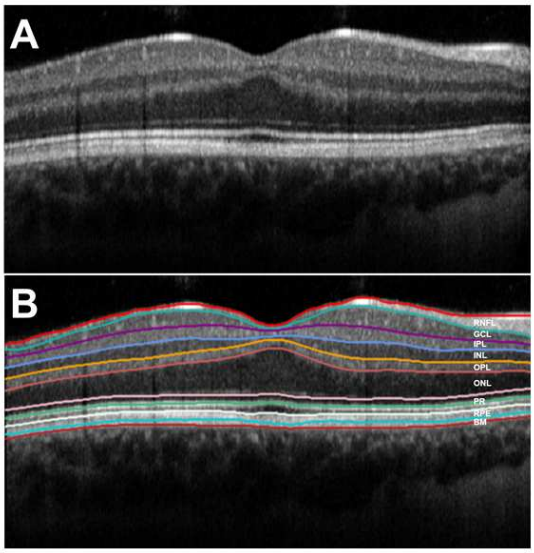

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Highlights

The retinal layer thickness profiles investigated by optical coherence tomography were altered in young adults born extremely preterm with associated impaired visual function. In particular, increased ganglion cell layer thickness was associated with worse visual acuity.

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