

Special Issue

OCT-Based Macular Structure–Function Correlation in Dependence on Birth Weight and Gestational Age—the Giessen Long-Term ROP Study

Wadim Bowl, Knut Stieger, Magdalena Bokun, Silke Schweinfurth, Kerstin Holve, Monika Andrassi-Darida, and Birgit Lorenz

Department of Ophthalmology, Justus-Liebig-University, Giessen, Germany

Correspondence: Birgit Lorenz, Department of Ophthalmology, Friedrichstrasse 18, Justus-Liebig-University, 35392 Giessen, Germany; birgit.lorenz@uniklinikum-giessen.de.

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PURPOSE. To compare retinal layer thicknesses in preterm and term-born children using spectral-domain optical coherence tomography (SD-OCT) and to correlate structure with retinal function.

METHODS. We performed SD-OCT single and volume scans in the foveal region of premature children aged 6 to 13 years without ROP (no-ROP, $n = 100$) and with spontaneously regressed ROP (sr-ROP, $n = 50$) documented with wide-angle digital imaging during routine screening for acute ROP, and 30 age-matched term-born children. Retinal layer segmentation and analysis was performed with custom-made software in single and volume-scans using an Early Treatment of Diabetic Retinopathy Study grid-based method, and compared to light increment sensitivity (LIS) data obtained with a microperimeter at eccentricity points of 0° , 2.8° , and 8° , as previously described.

RESULTS. Overall, seven children had to be excluded due to poor image quality ($n = 1$ no-ROP; $n = 2$ sr-ROP; $n = 4$ term). Total retina, ganglion cell + inner plexiform layer (GCL+) and outer nuclear layer + external limiting membrane (ONL+) thickness at the foveal center in no-ROP and sr-ROP were significantly higher compared with term children. Gestational age (GA) and birth weight (BW) were inversely correlated with these layer thicknesses. Rod and cone outer segment length did not differ in either group. The ratio of ONL+ to the whole retina at 0° correlated significantly with reduced LIS.

CONCLUSIONS. Increased thicknesses of the entire retina or specific layers at the fovea did not correlate with functional loss; but a thinner ONL in retinæ without foveal pit did. This reduced ONL+ ratio is potentially caused by a reduced foveal cone density and may be the first morphologic functional correlate in prematurity and ROP.

Keywords: retinopathy of prematurity, birth weight, gestational age, spectral-domain optical coherence tomography, fundus-controlled perimetry, long-term functional outcome

Premature birth interrupts developmental processes, including neuronal differentiation and cell migration in all neurologic tissues.^{1–3} Minor sequelae in prematurely born children and their effects on daily life as they grow up are less well known. The most common retinal defect associated with preterm birth is retinopathy of prematurity (ROP), which can cause serious ocular complications related to neovascularization. We recently published long-term follow-up functional data on prematurely born children showing that the prevalence of subnormal visual acuity and visual central and paracentral light increment sensitivity (LIS) in fundus-controlled perimetry were significantly higher compared with an age-matched control group.⁴ Similar effects on visual acuity (VA) were shown by others.^{5–7}

Vasculogenesis begins in the central retina at 24 to 28 weeks gestational age (GA), and the peripheral retina is vascularized at 40 weeks GA.⁸ Differentiation and maturation of the fovea and macular retinal layers begins at 24 to 27 weeks GA and is not completed until approximate age 3 to 4 years, resulting in an immature fovea even in term-born neonates.^{9–11} Several histologic and optical coherence tomog-

raphy studies have described persistence of inner retinal layers and absence of the foveal curvature in the fetal eye, and subsequent changes in the width and length of photoreceptor structures over time.^{8,10–13} Foveal development such as migration, redistribution, and growth of subcellular structures occur in premature infants ex-utero.^{14,15} Several signs of immaturity have been reported in prematurely born neonates in spectral-domain optical coherence tomography (SD-OCT) measurements when compared with the adult fovea: a shallow foveal pit, persistence of inner retinal layers, and a thin photoreceptor layer, thinnest at the foveal center.^{15–17} Vajzovic et al.¹⁸ hypothesized that photoreceptor development of term-born children is considerably different from that found in preterm infants. It remains unclear how long it lasts until the foveal region of premature children reaches maturity and whether the OCT morphology could be a useful predictor of the resulting visual function.

The aim of the present study was to compare the foveal and perifoveal structure of prematurely born children with spontaneously regressed and without ROP to that of age-matched full-term children using SD-OCT, and to determine whether the



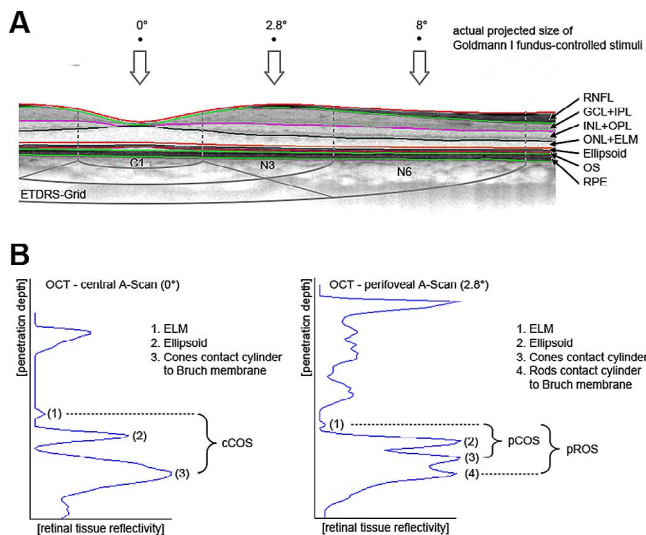


FIGURE 1. Spectral-domain OCT analysis methods. (A) Representative foveolar SD-OCT single scan, automatically segmented with custom software (Justus-Liebig-University).²⁰ A schematic representation of the dimensions of the ETDRS grid is displayed below the scan. Above the scan, three fundus-controlled Goldmann I stimuli are displayed in their actual size as projected on the retina.⁴ (B) Representative central and perifoveal A-scans demonstrating the measurement of COS and ROS.²¹

findings were related to prematurity and ROP, and mirroring recently published visual deficits (VA and fundus-controlled LIS) in the same cohort.

METHODS

The present study followed the tenets of the Declaration of Helsinki and was approved by the ethics committee of the Justus-Liebig-University of Giessen (Az 150/09). Informed consent was obtained from all parents and informed assent from all children participating in the study.

Patients

The present study is a long-term follow-up study of prematurely born participants from a multicenter field study between 2001 and 2007 (Lorenz, 2009). All 150 preterm children included in the present study were imaged at the time of the ROP screening by digital wide-field retinal imaging (RetCam I; Massie Research Laboratories, Inc., Pleasanton, CA, USA), which provides objective documentation of ROP. In the present study, only children without apparent psychological or neuronal disorders, neonatal hypoglycemia, intraventricular hemorrhage, or severe birth asphyxia-related hypoxic-ischemic encephalopathy were included, and all children attended regular schools and showed no significant deficiencies in basic literacy and numeracy. Parents were also specifically asked as to early childhood development and performance at school. All perinatal data and digital fundus images were available from the original field study.¹⁹ Detailed demographic data were recently published.⁴

A total of 30 healthy age-matched term-born children were recruited from the local population who had no history of ocular abnormalities, strabismus, amblyopia, or high refractive errors, and who were capable of performing all tests in this study.

Optical Coherence Tomography

High-resolution SD-OCT was performed using a commercial device (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany). One eye of each participant was analyzed (matching to the eye in which fundus-controlled perimetry was performed—always the better-seeing eye⁴). Results of the left eye were mirrored along the vertical axis to be comparable with the right eye. For analysis of foveal shape and central thickness, only single scans (B-scan, >80 averaged scans) with best resolution and best foveal centration were taken into account. For analysis of the average retinal thickness, volume scans (C-scan, 16 averaged scans) were used. Images were exported into a custom-made automated layer segmentation software (DiOCTA²⁰; copyright by Justus-Liebig-University, Giessen, Germany), and the thicknesses of the described retinal layers were measured automatically. The central foveal pit was selected manually by an experienced examiner. All segmentations in every scan in all quadrants were reviewed and, if necessary, corrected manually in order to achieve the most accurate segmentation outcome possible by an experienced operator. On average, 10.3% of all scans had to be corrected manually at least in one layer.

Layer Segmentation

The thicknesses of eight retinal layers were quantified automatically from OCT images. We measured the following: retinal nerve fiber layer (RNFL); ganglion cell layer plus inner plexiform layer (GCL+); inner nuclear layer plus outer plexiform layer (INL + OPL); outer nuclear layer plus external limiting membrane (ONL+); inner segment (IS); inner ellipsoid segment of the photoreceptor layer (ellipsoid); outer segment of the photoreceptor layer (OS), and RPE (Fig. 1A).

Central foveal thickness was defined as the thickness of the entire retina from the inner aspect of the inner limiting membrane (ILM) to the inner aspect of the RPE at the foveal center. The inner retina layers included all retinal tissue from the inner aspect of the ILM to the outer border of the INL.

Layer Thickness Analysis

We used two different methods in layer thickness analysis for OCT morphology description and structure-function analysis. First, we measured a single point (A-scan) at the respective position (0°, 2.8°, and 8°) nasal to the fovea. Second, the average retinal thickness and the average thickness of the different OCT layers were calculated with custom software (Justus-Liebig-University) and presented as numeric values for nine Early Treatment of Diabetic Retinopathy Study (ETDRS) fields. The total area measured had a diameter of 6 mm around the foveal center and was divided into three concentric regions. The central region was 1 mm in diameter (C1), and the inner and outer circles were divided in four quadrants each (3 mm inferior, superior, nasal, and temporal: I3, S3, N3, and T3, respectively; 6 mm inferior, superior, nasal, and temporal: I6, S6, N6, and T6, respectively; Fig. 1A).

Outer photoreceptor regions were analyzed as described by Spaide et al.²¹ Two defined spots were selected at the central fovea and at 2.8° toward the optic nerve head (Fig. 1B). They largely corresponded with the fundus-controlled testing pattern used in our recent publication.⁴ The analysis was performed on three A-scans next to each other surrounding the 0° and the 2.8° point. On the basis of the exported A-scans, the median of three measurements was taken: length of central fovea cone outer segments (cCOS); length of perifoveal cone outer segments (pCOS); and length of perifoveal rod outer segments (pROS; Fig. 1B).

TABLE 1. Light Increment Sensitivity and VA in Prematures Compared With Term-Born Children⁴

	<i>N</i>	LIS 0°, decibel; mean ± SD	LIS Nasal 2.8°, decibel; mean ± SD	LIS Nasal 8°, decibel; mean ± SD	VA, logMAR; mean ± SD
Term	30	14 ± 1.7	13 ± 1.4	10 ± 1.8	−0.07 ± 0.05
no-ROP	100	12 ± 2.2	12.2 ± 1.7	9 ± 1.9	0.00 ± 0.09
sr-ROP	50	12 ± 1.9	11.6 ± 1.0	9 ± 2.2	0.00 ± 0.11

Structure-Function Correlation

The thus-defined OCT parameters were correlated with our recently published data on VA and LIS at 0°, 2.8°, and 8° with fundus-controlled perimetry in the same cohort of children.⁴ In particular, fundus-controlled data allowed precise allocation to the structural OCT maps (Fig. 1A).

Visual acuity was assessed with ETDRS letters. Fundus-controlled perimetry was performed with a microperimeter (MP1; Nidek Technologies, Tokyo, Japan) at 17 positions at the posterior pole of a customized pattern (1 stimulus at 0°, 8 stimuli at 2.8°, and 8 stimuli at 8°). The examination started always with Goldmann III stimuli, followed by a second examination with Goldmann I stimuli.⁴ Only Goldmann I stimuli provided reliable LIS thresholds.⁴ Results of the left eye were mirrored along the vertical axis to be comparable with those of the right eye. For precise alignment of the structure-function correlation, only the three stimuli nasal to the fovea were taken into account (Fig. 1A). The single LIS parameters at each eccentricity (2.8° and 8°) were within the standard deviation of all eight stimuli tested. The analysis between the nasal, temporal, superior, or inferior parts of the different eccentricities did not show any statistically significant differences among the participants.⁴

Statistical Analysis

Statistical analysis was conducted with commercial software (Sigma Plot 12.0; Systat Software GmbH, Erkrath, Germany). Normal distribution was tested with the Shapiro-Wilk normality test. Kruskal-Wallis 1-way ANOVA on ranks was applied to test for significant differences among the different premature groups and term-born controls. Multiple comparison tests (Holm-Sidak or Dunn's method) were applied when testing for statistical differences between the groups and sectors (BW, GA, or stage). The linear regression model and Pearson correlation were used to test for bivariate correlations when comparing VA, LIS, and retinal layer thickness. Statistical significance was assumed at $P < 0.05$.

RESULTS

The study included 100 preterm children without ROP (no-ROP), 50 preterm children with spontaneously resolved ROP documented with digital wide-field retinal imaging, and 30 children born at term. Of the 50 children, maximum stage 1 was detected in 21 children (zone 2: $n = 16$; zone 3: $n = 5$); another 21 children had stage 2 (zone 2: $n = 17$; zone 3: $n = 4$); and 8 children had stage 3 (zone 2: $n = 7$; zone 3: $n = 1$). All children from both groups were also further divided into sectors according to BW (<1000, 1000–1500, and >1500 g) and GA (<28, 28–32, and >32 weeks). Seven children (no-ROP: $n = 1$; sr-ROP: $n = 2$; term: $n = 4$) were excluded because of poor scan image quality. The study groups' descriptive characteristics, including gestational age, birth weight, actual age, and sex have been published previously.⁴ Table 1 summarizes the functional outcome in LIS and VA in the study

groups at stimulus positions relevant for this study.⁴ Statistically significant differences were observed for LIS and VA at the foveal center (at 0°) within all three groups, and for LIS at 2.8° between term and sr-ROP.

The mean values of foveal (0°), perifoveal (2.8°), and peripheral (8°) thicknesses of the whole retina are shown in Figure 2A for all three groups. The mean values of the foveal minimum were highest in the sr-ROP group, intermediate in the no-ROP group, and lowest in the term-born group. These differences were statistically significant among all three groups in the foveal center (0°; $P = 0.011$) and between sr-ROP and term in the perifoveal measuring point (2.8°; $P = 0.032$). These data were confirmed by the ETDRS-based layer analysis, in which the C1 sector, representing the fovea, was significantly thicker in the no-ROP and sr-ROP groups compared with term. (Supplementary Fig. S1).

The impact of the ROP stage on retinal thickness is shown in Figure 2B. Retinal thickness was higher in all three subgroups (stage 1, 2, and 3) compared with term-born children, but no significant differences were observed among each other ($P = 0.012$). In the prematurely born children, low GA and BW correlated significantly with a thicker central fovea (Figs. 2C, 2D; GA: $P = 0.026$; BW: $P = 0.037$). Multiple regression analysis, including GA, BW, ROP (spontaneously regressed/without) showed that low GA was the only significant risk factor.

We observed significantly higher values of the mean thickness of the GCL+ layer for the sr-ROP group in relation to the no-ROP and term groups at 0° eccentricity (Fig. 3A; $P = 0.014$). The layer ONL+ was significantly thicker in the no-ROP and sr-ROP groups compared with term (Fig. 3B; $P = 0.022$). Again, these data were confirmed by the ETDRS grid-based layer analysis, in which C1, but no other sector, was significantly increased for both layers (Supplementary Figs. S2, S3; $P = 0.045$). Similar to GCL+ and ONL+ thickness analysis, the INL+ thickness was significantly increased in C1 ($P = 0.048$). All other sectors did not show any significantly changed layers within the groups (Supplementary Fig. S4). The analysis of RNFL thickness demonstrated no significant differences in the ETDRS grid layer analysis (Supplementary Fig. S5).

Measurements of cCOS, pCOS, and pROS did not reveal statistically significant changes between term and preterm children, independent of the presence or absence of ROP (cCOS: $P = 0.601$; pCOS: $P = 0.979$; pROS: $P = 0.573$; Fig. 4).

When correlating whole retina thickness, GCL+, ONL+, RNFL, or INL+ with LIS or VA data, no correlation was found (data not shown), indicating that a thickened retina (often along with a shallow foveal pit or its complete absence) alone is not the reason for reduced LIS and VA in preterm children.

When analyzing the individual thickness profiles of all children, a subset of preterm children differed in their distribution of individual layers above IS (Fig. 5A). The retinal ratio analysis between different layers described in Table 2 was initiated after the single layer analysis did not result in conclusive data, although it was particularly noticeable that several children had abnormal foveae. When looking at the ratio of the ONL+ to the entire retinal thickness at the foveal

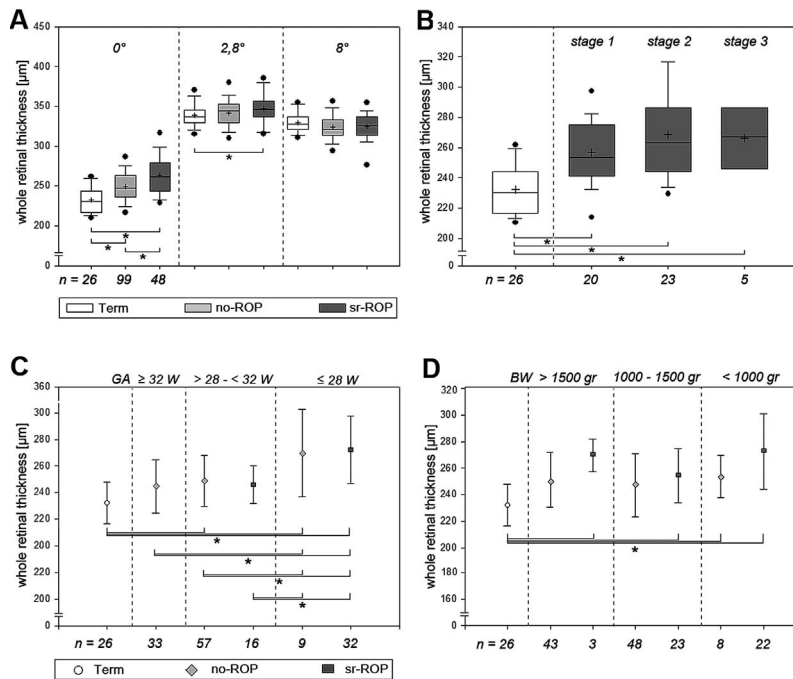


FIGURE 2. Whole retinal thickness analysis. **(A)** Spectral-domain OCT single-scan layer thicknesses of the whole retina displayed for the measuring points 0, 2.8, and 8° in sr-ROP and no-ROP children compared with term-born children. **(B)** Central whole retinal thicknesses in sr-ROP divided according to stage and compared with term. **(C)** Central foveal thickness divided by GA for no-ROP and sr-ROP groups compared with term. **(D)** Central foveal thickness divided by BW for no-ROP and sr-ROP groups compared with term. Significant differences ($P < 0.05$) are represented with square brackets with asterisks. All other combinations are not significant.

minimum (foveal center at 0°), 29.3% of the no-ROP group (29/99 children), compared with 39.6% of the sr-ROP (19/48 children) had a ratio of ONL+ to whole retinal thickness (“retina”) below 45%, which is below the limit (complete range of measurements) of what was found in term-born children (Figs. 5A, 5B). The ratio of ONL+ to the sum of inner retinal layers (NFL + GCL + IPL + INL + OPL = IRL) and the ratio of IRL to whole retinal thickness differed significantly in the same subgroups (ANOVA $P = 0.043$; Fig. 5B, Table 2). The impact of this morphologic anomaly, which we defined as macular developmental arrest (MDA), on LIS was significant (Fig. 5C). Children with significantly differing ratios had significantly lower LIS values compared with term-born children or children with normal ratios, whether they belonged to the no-ROP or the sr-ROP group ($P = 0.009$). No correlation was found between VA values and the calculated retinal ratios (Supplementary Fig. S6).

DISCUSSION

In the present study, the effect of prematurity on foveal thickness was evaluated in 147 preterm children with and without ROP and 26 term-born children aged 6 to 13 years. None of the children showed any apparent psychological or neuronal disorders, neonatal hypoglycemia, or intraventricular hemorrhage, allowing concentration on the impact of ROP, gestational age, and birth weight on OCT morphology and functional outcome. To the best of our knowledge, this is the first OCT-based comparison of foveal morphology and LIS from fundus-controlled perimetry in a cohort of prematures. Furthermore, our study is the largest of prematures with analyzed foveal structure and function, and with documented retinal status at the time of screening for acute ROP^{1,15,17,18,22–26}

Our analysis of retinal thickness confirms an increased central foveal thickness (0° and C1) in preterm children

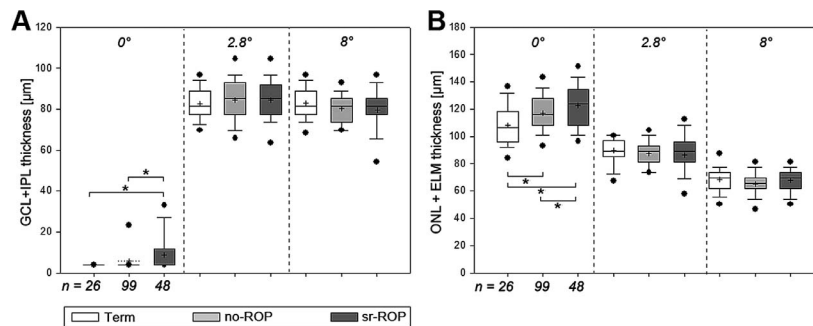


FIGURE 3. Thickness analysis of GCL + IPL. **(A)** Spectral-domain OCT single scan layer thicknesses of the GCL + IPL layers displayed for the eccentricities 0, 2.8, and 8° in sr-ROP and no-ROP children compared with term-born children. **(B)** Spectral-domain OCT single-scan layer thicknesses of the ONL + ELM layers of the no-ROP and sr-ROP groups, compared with Term. Significant differences ($P < 0.05$) are represented with square brackets with asterisks. All other combinations are not significant.

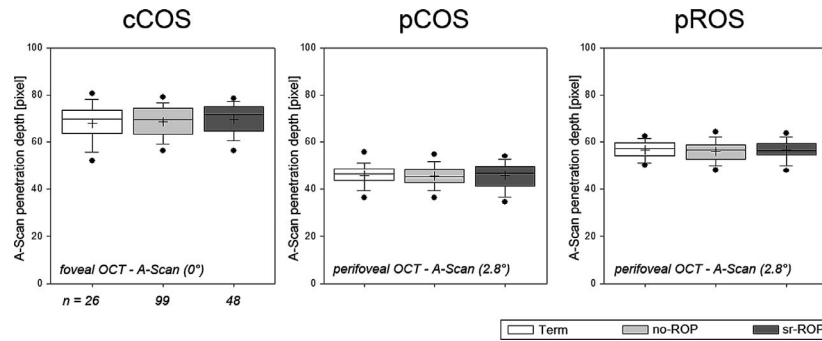


FIGURE 4. Photoreceptor outer segments analysis. Measurements of cCOS, pCOS, and pROS in sr-ROP and no-ROP patients compared with age-matched term-born children. Significant differences ($P < 0.05$) are represented with *square brackets with asterisks*. All displayed combinations are not significant.

compared with that of full-term children reported in a number of recent studies,^{17,22–26} and counteracts the study of Pueyo et al.¹ We observed thicker absolute GCL+ and ONL+ layers in preterm children in agreement with previous reports,^{16,22} and confirm that other retinal layers were not significantly different as reported by the same authors.

Multiple comparison analysis of our data showed that foveal, GCL+, and ONL+ thickness strongly depended on GA, and less on BW. These parameters were inversely correlated with GA and BW, which is supported by Akerblom et al.¹⁷ and Park et al.²² Preterm birth between 24 and 28 weeks GA has been proposed as a critical period associated with a failure of the normal migration on inner retinal layers away from the fovea, resulting in increased foveal thickness.^{13,17,22} In contrast, stage of ROP appeared to have no impact on the degree of abnormal foveal development.

While the absolute thicknesses of the GCL+, ONL+, and INL+ layers were significantly higher in prematures than in term-born controls, we found that the absolute layer thicknesses did not show a positive correlation to LIS or VA. A shallow foveal pit itself has been shown not to necessarily impede VA²⁷ or LIS, as shown in the present study. However, layer-specific OCT analysis disclosed a previously undescribed peculiarity in foveal morphology in a high number of premature children. One third of all prematures showed a disproportion of the ONL+ to whole retinal thickness ratio. This discrepancy emerged especially—but not exclusively—in prematures with higher central retinal thickness and independent of the groups, no-ROP or sr-ROP, which we defined as MDA. In previous studies, this morphology was often described as “shallow foveal pit,”²⁴ “foveal hypoplasia,”^{24,25} or “fovea with overlying layers of neural cells.”²³ We suggest

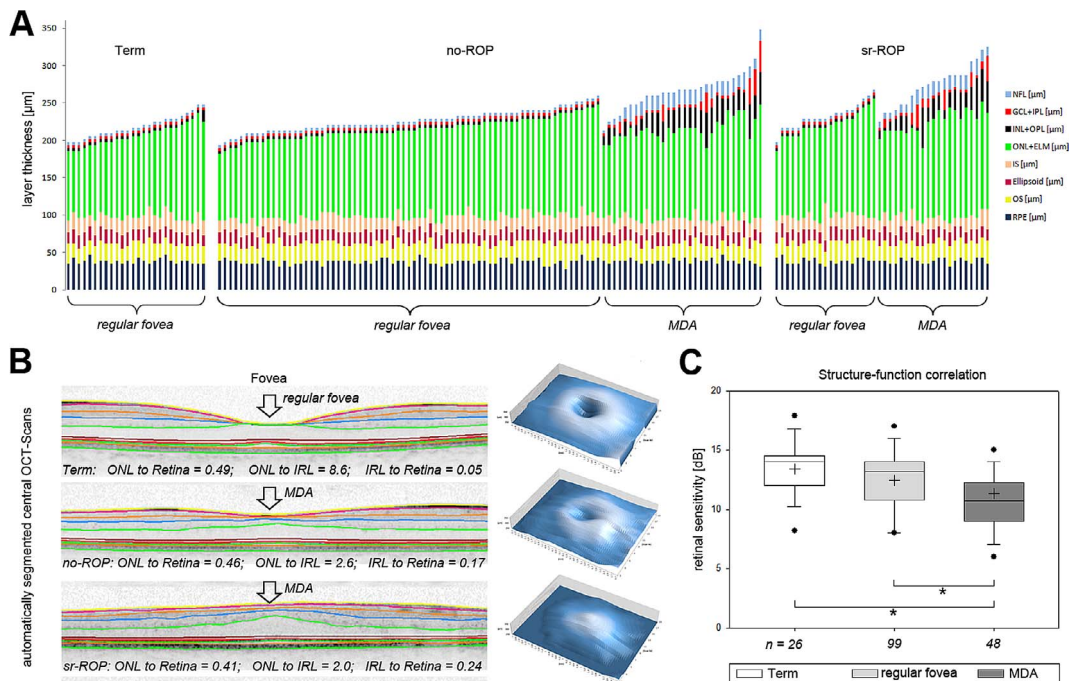


FIGURE 5. Structure-function correlation of MDA as seen in SD-OCT. **(A)** Central thicknesses of retinal layers measured with SD-OCT, segmented with DiOCTA,²⁰ and plotted into the diagram. Every box represents one eye of one child, sorted by affiliation to their groups. Within the group, the children are sorted primarily by the whole retinal thickness and secondly by the sum of NFL + GCL + INL, described as MDA. **(B)** Automatically segmented SD-OCT-scans with marked fovea and associated ratio of “ONL+ to retina,” “ONL to IRL,” “IRL to retina,” and 3D-reconstruction of their foveal shape. **(C)** Preterms divided by ratio of “IRL to retina” compared with term (term, regular fovea, and MDA). Significant differences ($P < 0.05$) are represented with *square brackets with asterisks*. All other combinations are not significant.

TABLE 2. Comparison of Three Different Mathematical Ratios Between ONL+, IRL, and Whole Retinal Thickness to Describe Retinal Morphology

	Ratio of ONL+ to Whole Retinal Thickness, mean (SD)	Ratio of ONL+ to IRL, mean (SD)	Ratio of IRL to Whole Retinal Thickness, mean (SD)
Term	0.499 (± 0.02)	9.176 (± 1.43)	0.055 (± 0.008)
no-ROP, regular fovea	0.515 (± 0.02)	10.062 (± 1.12)	0.052 (± 0.003)
no-ROP, MDA	0.441 (± 0.03)	2.386 (± 0.67)	0.197 (± 0.04)
sr-ROP, regular fovea	0.521 (± 0.04)	10.463 (± 1.5)	0.050 (± 0.003)
sr-ROP, MDA	0.452 (± 0.04)	2.522 (± 0.68)	0.191 (± 0.04)

that MDA describes best the underlying pathophysiology, resulting in a shallower foveal pit, significantly increased GCL+ and INL+ thickness, and simultaneous reduction of ONL+ thickness. Macular developmental arrest revealed a highly positive correlation to LIS measured with fundus-controlled perimetry.

In line with our photopic retinal sensitivity measurements, Menghini et al.²⁸ stated that in normal eyes, ONL thickness and cone density were significantly correlated. The relationship between ONL thickness and cone density was strongest at locations between 0.5 and 1.5° eccentricity, where cones dominate the ONL.²⁸ Their findings—observed with OCT and adaptive optics scanning laser ophthalmoscope (AOSLO) without the contribution from Henle fiber layer (HFL)^{28,29}—compared favorably to similar results reported by others, where HFL measurements were included.³⁰ Although it remains still challenging to predict cone density from ONL thickness, our results show that prematures without ROP and with spontaneously regressed ROP have significantly reduced photopic retinal function on fundus-controlled perimetry, and that a likely explanation could be reduced cone density in the foveal center.

Interestingly, we did not find a reduced length of cone outer segments at 0 and 2.8° (cCOS, pCOS). This COS band, described by Spaide et al.,²¹ was recently defined as the cone outer segment enclosed by apical processes of the RPE, and was reported to be absent at birth in prematures.^{12,18} Recently published data on adaptive optics measurements of extrafoveal cone density and packing geometry in preterm eyes stated that there was no evidence of cone loss or changed thickness of photoreceptor laminae in children with treated ROP.³¹ It was claimed that photoreceptors have at least a delayed maturation at the time of critical visual system development, and that this could be responsible for a reduced visual function.¹⁸ So far, no longitudinal studies are available that have evaluated the development of retinal layers as seen with OCT over several years after birth. Evaluation of the cCOS, pCOS, and pROS thicknesses in our cohort is in agreement with ongoing maturation of photoreceptors into school age in prematures without ROP and with spontaneously regressed ROP, as suggested by Vajzovic et al.¹⁸

In conclusion, we found that the ratio of ONL+ to whole retinal thickness and IRL indicates a correlation between foveal morphology and LIS in former prematures without ROP and with spontaneously regressed ROP. As the reduced ONL+ ratio could indicate a reduced foveal cone density, further studies including AOSLO should follow to confirm our findings and further investigate the correlation between impaired retinal function and structural changes.

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