

Cone-Mediated Function Correlates to Altered Foveal Morphology in Preterm-Born Children at School Age

Wadim Bowl,* Sinan Raoof, Birgit Lorenz, Kerstin Holve, Silke Schweinfurth, Knut Stieger, and Monika Andrassi-Darida

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

Correspondence: Monika Andrassi-Darida, Department of Ophthalmology, Justus-Liebig-University, Friedrichstrasse 18, Giessen 35392, Germany; monika.andrassi-darida@augen.med.uni-giessen.de.

Current affiliation: *Department of Nuclear Medicine, Justus-Liebig-University Giessen, Giessen, Germany.

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PURPOSE. To correlate cone- and rod-mediated function with morphology of the macula in preterm-born children without and with spontaneously regressed retinopathy of prematurity (ROP).

METHODS. We performed spectral-domain optical coherence tomography (SD-OCT) single scans in the macular center of preterm-born children aged 6 to 12 years (mean \pm SD, 7.4 ± 1.8) without ROP (noROP; $n = 59$) and with spontaneously regressed ROP (srROP; $n = 34$), documented with wide-angle digital imaging during routine screening for acute ROP, and compared the data from 14 age-matched term-born children. SD-OCT data were compared to functional cone- and rod-mediated results of scotopic and photopic chromatic pupillometry (cP) and two-color fundus-controlled perimetry (2C-FCP).

RESULTS. SD-OCT showed a shallowed foveal pit with significantly reduced outer nuclear layer to inner retinal layer ratio, indicating macular developmental arrest (MDA). MDA was present in 44% of the srROP and 27% of the noROP children. Pupil reaction to photopic red stimuli on blue background showed significantly lower values in all preterm-born children with MDA. In accordance, photopic light increment sensitivity (LIS) to red stimuli in the foveal center on the 2C-FCP was also significantly reduced in children with MDA. Under scotopic conditions, no significant differences were apparent in both pupil reaction with cP and LIS with 2C-FCP.

CONCLUSIONS. Both objective pupillary response to cone-mediated photopic red stimuli and subjective central cone-mediated results in fundus-controlled perimetry were reduced in preterm-born children with MDA. MDA was present in a significant number of patients with srROP, but also without ROP.

Keywords: chromatic pupillometry, two-color perimetry, optical coherence tomography, prematurity, retinopathy of prematurity, macular developmental arrest

Retinal maturation begins in the early prenatal period and by mid-gestation all retinal cell types are present but still not fully mature.^{1,2} Differentiation of cell types, centrifugal and centripetal migration, and apoptosis are continuing in part not only until full-term birth but also until several years after birth.^{3,4} Healthy, full-term infants have a more immature full-field electroretinogram (ffERG) response from rods than from cones when measured at birth, indicating a slower rod maturation process.^{5,6} Rapid development of ffERG responses takes place in the first few months after birth.⁷ Prematurely born infants show immature responses from both rods and cones.^{8,9} Even if these responses seem to adapt to the responses of full-term infants at 40 weeks of gestational age, they are maturing more slowly in subsequent childhood development.^{10,11} The impact of immaturity and retinopathy of prematurity (ROP) in preterm-born children on the structural and functional development of the retina is still not fully explored. Several studies^{12–15} have shown increased macular thickness with a shallow fovea and persistent inner retinal layers (IRLs) in preterm-born children. These morphologic changes coexist with various visual dysfunctions when tested at school age, such as decreased best-corrected visual acuity,

altered foveal light increment sensitivity (LIS), and reduced multifocal ERG responses (mfERG).^{12,16–19}

Reduced cone photoreceptor function under photopic lighting conditions in the foveal and parafoveal area^{12,16,18,19} has been accurately evaluated with fundus-controlled perimetry.¹² Unfortunately, dark-adapted perimetry, as a practical diagnostic tool, is hampered by long test duration, high patient burden, and lack of accurate fixation control. Scotopic protocols require up to 60 or more minutes, and typically, more than 100 threshold estimates are made. The long duration and a high number of threshold measurements can fatigue patients and affect reliability and reproducibility.²⁰

We previously have developed a fundus-controlled method to measure central LIS under scotopic conditions with minimal fixation inaccuracy and good sensitivity and specificity.¹² The present study aimed at correlating the precisely located values of photopic and scotopic responses to scotopic and photopic stimuli in former preterm children with or without spontaneously regressed ROP (srROP) by using scotopic and photopic chromatic pupillometry (cP). This approach is suited to young children with minimum compliance required. In parallel, we evaluated morphologic changes of the fovea as seen by spectral-domain optical coherence tomography (SD-OCT).



TABLE 1. Demographic Data and SD-OCT Parameters for Groups Divided Into Children With srROP and noROP in Comparison to nChild

Parameter	srROP	noROP	nChild	ANOVA, <i>P</i> Values
Patients = eyes	34	59	14	-
Age, mean ± SD, y	7.3 ± 1.6	7.5 ± 1.5	6.8 ± 1.8	>0.05
Sex				-
Male	29	29	5	
Female	15	30	9	
Stage, 1/2/3		-	-	-
1	8			
2	24			
3	2			
GA, mean ± SD, wk	28.4 ± 1.7	31.2 ± 2.1	40.2 ± 0.9	<0.001
BW, mean ± SD, g	1081 ± 316	1488 ± 326	3654 ± 505	<0.001
BCVA, mean ± SD, logMAR	0.00 ± 0.07	-0.02 ± 0.05	-0.06 ± 0.04	-
Foveal SD-OCT analysis				
Whole retinal thickness, μm	260 ± 22	251 ± 23	230 ± 14	>0.05
IRL thickness, μm	23 ± 14	18 ± 12	7 ± 3	>0.05
ONL+ELM thickness, μm	112 ± 16	118 ± 14	109 ± 14	>0.05
ONL+/IRL index	4.9 ± 3.1	5.3 ± 3.4	10.0 ± 0.8	>0.05

BCVA, best-corrected visual acuity; BW, birth weight; GA, gestational age.

METHODS

Subjects

The present investigation was performed as a part of a long-term follow-up study of preterm-born participants from a prospective multicenter field study conducted between 2001 and 2007.²¹ Research followed the tenets of the Declaration of Helsinki. Ethical approval was obtained from the local institutional ethics committee (Az 150/1). A total of 107 subjects were included in the study: 93 preterm-born children and 14 healthy age-matched term-born controls.

All 93 preterm children were imaged at the time of the prospective ROP screening study by using digital wide-field retinal imaging (RetCam I; Massie Research Laboratories, Inc., Pleasanton, CA, USA), which provided reliable documentation of ROP.²¹ 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 specifically asked as to early childhood development and performance at school. All perinatal data were available from the original field study. Demographic data and group formation are displayed in Tables 1 and 2.

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

All analyses described below were performed in the groups of preterm-born children with srROP (*n* = 34), preterm-born children without ROP (noROP; *n* = 59), and age-matched term-born children (nChild; *n* = 14) (Table 1).

Optical Coherence Tomography and Layer Segmentation

High-resolution SD-OCT was performed with a Spectralis-OCT (HRA+OCT; Heidelberg Eng, Heidelberg, Germany). One eye of each participant was analyzed, matching to the eye in which fundus-controlled scotopic and photopic perimetry was performed. This was always the better-seeing eye in case of interocular asymmetry, and the dominant eye in participants

with symmetric performance. Left eye results were mirrored along the vertical axis to be comparable with the right eye. To evaluate the fovea, only single scans (B-scans, >80 averaged scans) with best resolution and best foveal centration were analyzed. Images were exported into a custom automated layer segmentation software²² (DiOCTA; copyright by Justus-Liebig-University, Giessen, Germany), and the thicknesses of six defined retinal layers were measured automatically.

We defined the following layers: retinal nerve fiber layer (NFL); ganglion cell layer plus inner plexiform layer (GCL+IPL); inner nuclear layer plus outer plexiform layer (INL+OPL); outer nuclear layer plus external limiting membrane (ONL+ELM); inner segment plus inner ellipsoid segment of the photoreceptor layer plus outer segment of the photoreceptor layer (Ellipsoid + OS), and retinal pigment epithelium (RPE). The ratio of ONL+ELM (in short ONL+) to the sum of IRLs (IRL = NFL+GCL+IPL+INL+OPL) overlying the foveal center was calculated, as described in our recent publications^{12,19} (Figs.

TABLE 2. Demographic Data and SD-OCT Parameters for Groups Divided Into Children With MDA and noMDA

Parameter	MDA (<i>n</i> = 31)	noMDA (<i>n</i> = 62)	ANOVA, <i>P</i> Values
Patients = eyes	31	62	-
Age, mean ± SD, y	7.5 ± 1.3	7.4 ± 1.6	>0.05
Sex			-
Male	18	30	
Female	13	32	
No ROP	16/31	43/62	
Stage			-
1	8	9	
2	4	10	
3	2*	0	
GA, mean ± SD, wk	29.8 ± 2.7	30.3 ± 2.0	>0.05
BW, mean ± SD, g	1264 ± 454	1377 ± 315	>0.05
BCVA, mean ± SD, logMAR	0.02 ± 0.05	-0.018 ± 0.05	>0.05
Foveal SD-OCT analysis			
Whole retinal thickness, μm	273 ± 23	245 ± 15	<0.001
IRL thickness, μm	31 ± 15	8 ± 1	<0.001
ONL+ thickness, μm	119 ± 15	119 ± 19	>0.05
ONL+/IRL index	4.5 ± 1.7	15 ± 2	<0.001

* Stage and zone was not recorded for one child.

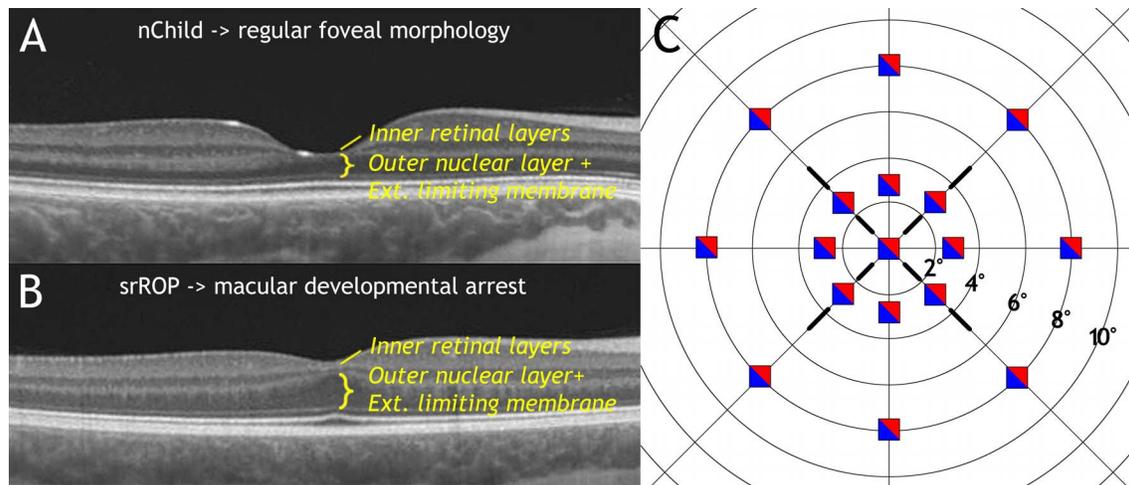


FIGURE 1. (A, B) Examples of OCT single scans with measure marks that demonstrate the outer nuclear layer with the external limiting membrane (ONL+) and the sum of inner retinal layers overlying the ONL+ in the center of the fovea. (C) Stimulus pattern used in scotopic and photopic fundus-controlled perimetry.

1A, 1B). To elucidate the impact of pathologically changed foveal morphology, the groups were redistributed into groups with an ONL+/IRL ratio ≤ 6.5 (with macular developmental arrest [MDA]) and at least seven with normal foveal morphology (noMDA). Corresponding values were evaluated in our previous publications.^{12,19}

Chromatic Pupillometry

The pupil reaction to chromatic stimuli was recorded with a modified f2D Pupillometer (Bino1; AMTech, Dossenheim, Germany). The pupillometer is a goggle-based device with two inbuilt infrared-cameras for simultaneous recording of both pupil reactions (Fig. 2A). The frame speed was set to 25 Hz, according to the manufacturer's instructions. Stimulus projection was achieved with a time-triggered Espion Ganzfeld ColorDome Stimulator (Espion E²; Diagnosys LLC, Lowell, MA, USA).

Based on the protocols described by Park et al.,²³ Kardon et al.,²⁴ Kawasaki et al.,²⁵ and Lisowska et al.,²⁶ blue and red stimuli were displayed with a duration of 1 second under dark and light-adapted conditions. All preterm-born and term-born children were tested with a protocol containing three repeats

of fixed illuminances (0.01 cd/m² blue stimuli at a wavelength of 460 nm and 100 cd/m² red stimuli at a wavelength of 640 nm). Dark-adapted testing was performed after 20 minutes in the dark. Dark-adapted protocols were performed with blue stimuli on black background in a darkroom. Light-adapted protocols were performed with red stimuli on blue background (0.78 cd/m²) under room light conditions, with 3 minutes' adaptation time to the blue background before the test (Fig. 2B).

The direct pupil reaction to the short stimulus was recorded as the maximum pupil constriction amplitude. The pupil reaction was evaluated as the maximum constriction relative to the baseline of the dark- or light-adapted pupil diameter, and maximum pupil constriction amplitude was defined as the delta from a corrected baseline to the maximum deflection of the wave height.

Fundus-Controlled Chromatic Perimetry (2C-FCP)

A commercially available Microperimeter MP1 (Nidek Technologies, Padova, Italy) was modified for the purpose of two-color scotopic and photopic perimetry as described in our previous publication.²⁷ Stimuli were presented at 17 positions

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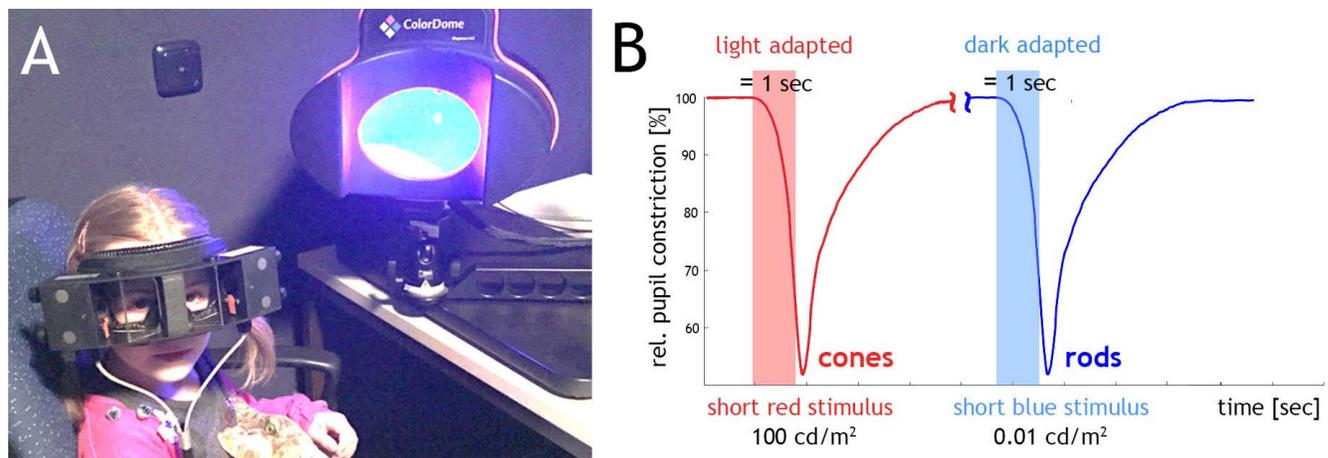


FIGURE 2. (A) Child wearing the chromatic pupillometry goggles in front of the Ganzfeld stimulator. (B) Chromatic pupillometry examples for pupillary response measurement under scotopic and photopic conditions.

TABLE 3. Objective Scotopic and Photopic Chromatic Pupillometry and Subjective Scotopic Two-Color Fundus-Controlled Functional Data Grouped According to the Presence of ROP or of MDA

Examination Method	srROP (n = 34)	noROP (n = 59)	nChild (n = 14)	ANOVA
cP: scotopic blue, mean ± SD, %	32.3 ± 5.5	32.2 ± 4.7	31.8 ± 3.0	P = 0.980
2C-FCP: scotopic 8° blue, mean ± SD, dB	13.3 ± 3.5	12.9 ± 3.2	14.2 ± 2.2	P = 0.275
cP: photopic red, mean ± SD, %	32.2 ± 4.9	32.6 ± 4.7	36.1 ± 3.2	P = 0.005
2C-FCP: scotopic 0° red; mean ± SD, dB	6.9 ± 2.3	6.8 ± 2.2	7.2 ± 0.8	P = 0.876
2C-FP: photopic 0° red, mean ± SD, dB	12.4 ± 1.9	12.8 ± 2.3	13.4 ± 1.6	P = 0.285
	MDA (n = 31)	noMDA (n = 62)	nChild (n = 14)	ANOVA
cP: scotopic blue, mean ± SD, %	32.2 ± 3.4	32.3 ± 5.6	31.8 ± 3.0	P = 0.979
2C-FCP: scotopic 8° blue, mean ± SD, dB	13.3 ± 3.4	12.9 ± 3.2	14.2 ± 2.2	P = 0.396
cP: photopic red, mean ± SD, %	29.3 ± 3.5	34.1 ± 4.6	36.1 ± 3.2	P < 0.001
2C-FCP: scotopic 0° red, mean ± SD, dB	4.5 ± 1.7	7.9 ± 1.5	7.2 ± 0.8	P < 0.001
2C-FP: photopic 0° red, mean ± SD, dB	10.8 ± 1.5	13.6 ± 1.9	13.4 ± 1.6	P < 0.001

noMDA, regular foveal morphology on OCT.

of a customized pattern on the posterior pole of the retina up to 8° eccentricity. Light output of the MP1 was reduced by a Schott (Mainz, Germany) longpass filter RG780 (>50% transmission above 716 nm) and a Schott bandpass filter BG3 (>50% transmission from 250–435 nm) outside the instrument to create the stimulus colors red and blue. Goldmann size III blue and red stimuli were presented on a background of 0.16 cd/m² under dark-adapted conditions. Additionally, red stimuli were presented on a background of 1.27 cd/m² under light-adapted conditions, preset by the manufacturer. The rod-mediated light increment sensitivity measured with the blue stimuli was taken from the averaged results of 8 stimuli placed at 8° eccentricity (Fig. 1C).

Statistical Analysis

Statistical analysis was conducted by using Sigma Plot 12.0 (Systat Software, San Jose, CA, USA) and MS Excel 2013 (Microsoft, Redmond, WA, USA). Normality test was conducted 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 children to test for statistical differences between the groups. The Holm-Sidak test for multiple comparison was applied as a post hoc test for pairwise comparison. An overall significance level of $P = 0.05$ was set. To take into account the fact that there were multiple comparisons on three groups, the Bonferroni correction was used.

RESULTS

Morphologic Analysis of OCT Data

SD-OCT showed a shallowed foveal pit coupled with significantly reduced ONL+IRL ratio ($P < 0.001$) in 15 patients of the srROP group and 16 patients of the noROP groups compared to nChild. Mean retinal thicknesses in the foveal center were significantly greater in the srROP ($P < 0.001$) and noROP ($P < 0.001$) groups. Accordingly, mean thicknesses of the sum of IRLs were significantly thicker in both preterm-born groups (srROP and noROP) than in age-matched term-born controls ($P = 0.011$). However, the ONL+ELM thicknesses showed no significant differences between the three groups ($P = 0.288$).

In a previous analysis of structural and functional data from premature children, we have defined a cutoff value with regard to the ONL+IRL ratio as measured on SD-OCT images, which

separates subjects with a shallow foveal pit and presence of IRL at the fovea from those with a healthy foveal pit and no IRL (Figs. 2A, 2B).¹² We termed the first condition as “macular developmental arrest.” In the current study, MDA was present in 16 preterm children without ROP (27% of noROP) and 15 preterm children with srROP (44% of srROP), while noMDA was observed in 43 preterm children without ROP (73% of noROP) and 19 children with srROP (56% of srROP) (Table 2). The children with MDA displayed a significantly thicker IRL and whole retina thickness at the foveal minimum ($P < 0.01$, Table 2).

Photopic Results

Under photopic conditions, the pupil reaction to red stimuli on blue background showed significantly lower values in both srROP and noROP groups compared to age-matched term-born controls ($P = 0.005$) (Table 3). The significance level was set at $P = 0.005$ owing to the Bonferroni correction. LIS measurements to red stimuli in the modified fundus-controlled perimeter showed no such significances for the srROP, noROP, and nChild groups ($P = 0.285$). Taking into account the results of the foveal morphologic analysis and redistributed preterm-born groups, the MDA group showed significantly reduced pupillary reaction to photopic red stimuli ($P < 0.001$) (Fig. 3A), and photopic LIS to red Goldmann III stimuli at 0° and 2.8° on the 2C-FCP ($P < 0.001$) (Fig. 4A; Table 3).

Scotopic Results

Under scotopic conditions, all groups (srROP, noROP, nChild) showed no significant differences on both objectively measured pupil reaction to blue stimuli in cP and subjectively measured LIS to blue stimuli in 2C-FCP (P values in Table 3; Figs. 4B, 4C). Even after redistributing the groups of srROP and noROP according to MDA or noMDA, no significant differences were seen for scotopic reactions to blue stimuli in cP (Fig. 3B), or with regard to LIS regardless of eccentricity tested (Figs. 3D, 4). In contrast, MDA was associated with significantly reduced scotopic LIS to red Goldmann III stimuli at 0° and 2.8° on the 2C-FCP ($P < 0.001$) (Figs. 3C, 4B; Table 3).

DISCUSSION

The present study adds to the previously reported results that MDA in preterm children has an effect on the central sensitivity under conditions that induce cone-mediated results. We and

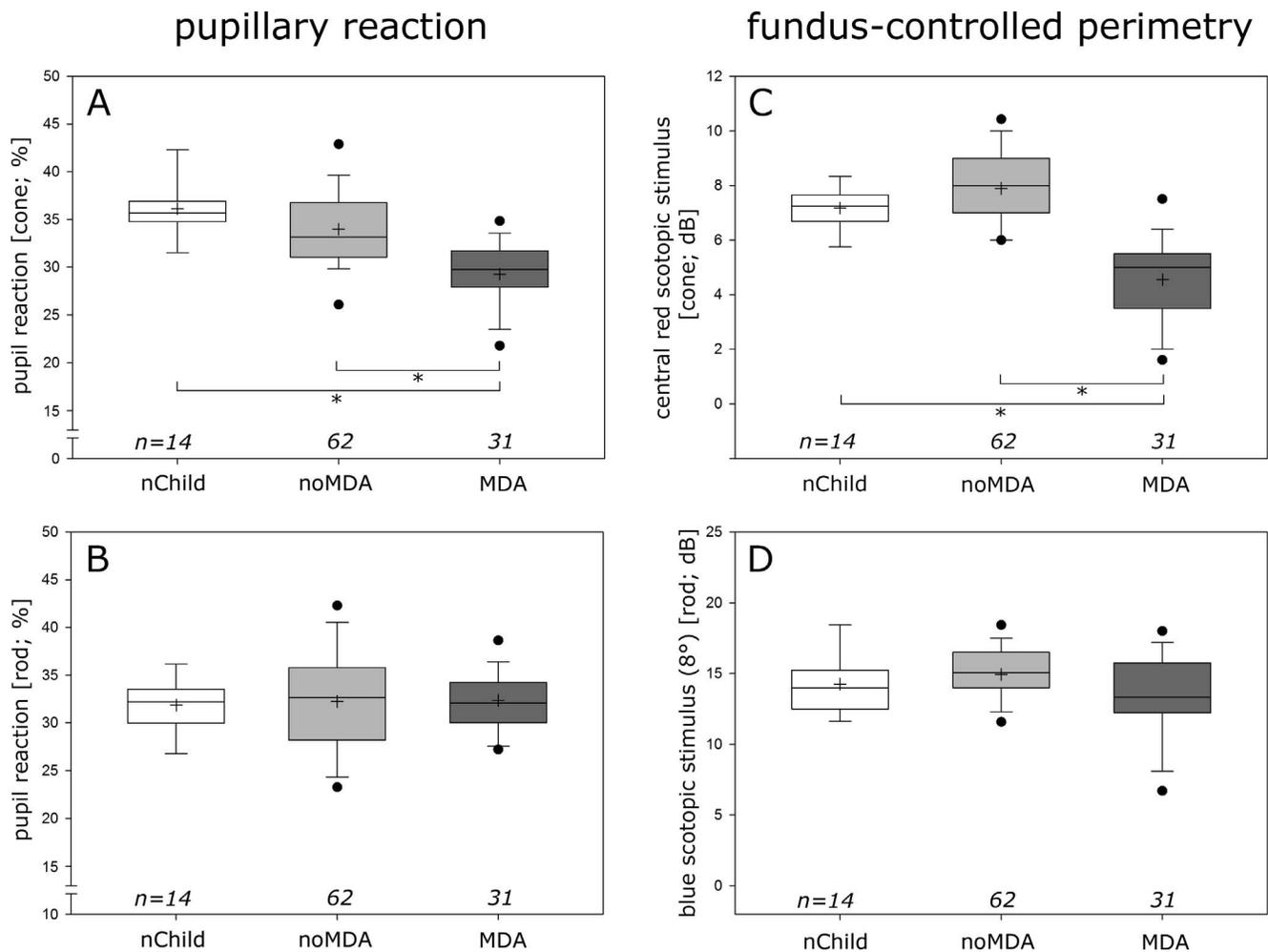


FIGURE 3. Data of chromatic pupillometry (A, B) and fundus-controlled perimetry (C, D), and patients and probands grouped according to the presence or absence of MDA. (A) Pupil reaction to red stimuli, showing the cone responses in the test, demonstrates a significantly reduced reaction in the MDA group, both when compared to noMDA or nChild. (B) Pupil reaction to blue stimuli, showing the rod responses in the test, demonstrates no differences between groups. (C) LIS values for the central red stimulus under scotopic conditions show a significantly reduced threshold in the MDA group compared to both the noMDA and nChild group. (D) LIS values for the blue stimuli under scotopic conditions show no significant differences between groups. * $P = 0.05$.

others^{12,28–30} have shown previously a higher incidence of foveal abnormalities with SD-OCT in infants and children with a history of ROP. A current explanation is that IRLs have failed or not completed their centrifugal migration. Also, at the same time, cone photoreceptors have completed their centripetal migration after preterm birth.^{4,28,29} One assumption is that the morphologic and functional changes in the central fovea go along with parafoveal changes and impairments of photoreceptors before and on the rod ring at approximately 18° eccentricity.²⁸ In our previous study,¹² preterm-born children show significantly reduced cone-mediated LIS to photopic red stimuli in the foveal center. We now showed that preterm-born children with MDA also had a significantly lower pupillary reaction to red, that is, cone-mediated stimuli with cP. The pathology was only evident in cones, as rod-mediated pupillary reaction was similar in all three groups. Pupillometry is an objective functional test requiring minimal cooperation and could therefore enable evaluation of central cone function even at a much younger age.

In previous reports, rod and cone photoreceptor function has been assessed in premature children with a history of ROP by ffERG and mfERG.^{10,11,16–19,31} While scotopic ffERG allows

assessment of rod photoreceptor function, photopic ffERG describes cone function. Both ffERG methods measure the summation response of all photoreceptors, similar to the response of all rod or cone photoreceptors to blue or red cP. Interestingly, in the present study we observed reduced cone function but no alteration to the rod-mediated response in cP. Earlier studies using ffERG have described loss of rod function,¹¹ but no cone function loss.¹⁷ However, in those studies, persistent rod function loss is only seen in children with severe ROP, whereas in children with milder forms of ROP, rod function is only reduced in infancy but is normal in school children. The data are therefore in line with our results obtained with cP, because we only assessed patients with mild spontaneously regressed or no ROP history.

MfERG is a way to document functional deficits of foveal cones.^{10,16,18,19,31} The mfERG response is a complex waveform that combines contributions from the cone photoreceptors and potentials from cone ON and OFF bipolar cells of the postreceptor retina.^{32,33} The spatial resolution of the mfERG enables assessment of local areas within the retina, similar to the data obtained with 2C-FCP. Again, mfERG data from patients with a history of severe ROP display reduced cone

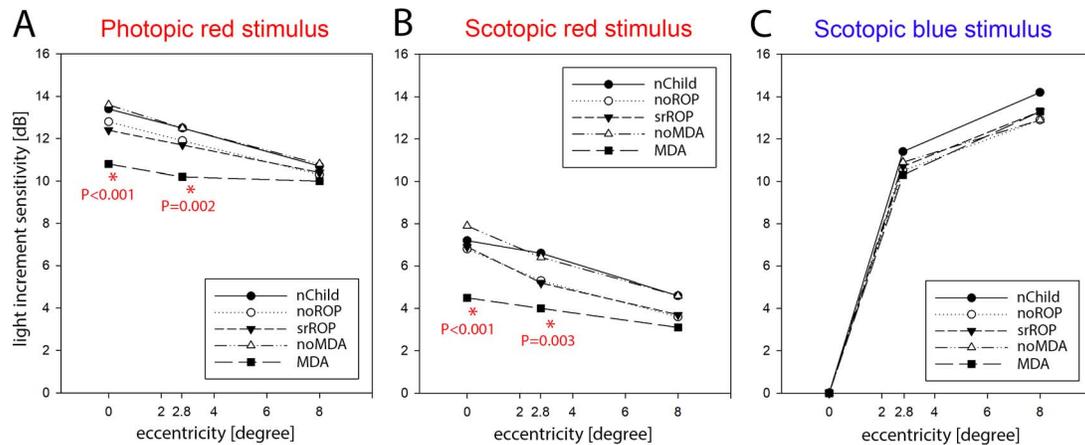


FIGURE 4. Data of fundus-controlled perimetry with spatial resolution. (A) LIS values to photopic red stimuli at 0°, 2.8°, and 8° eccentricity. (B) LIS values to scotopic red stimuli at 0°, 2.8°, and 8° eccentricity. (C) LIS values to scotopic blue stimuli at 0°, 2.8°, and 8° eccentricity.

function, while milder forms of ROP or no ROP at all are not associated with cone function loss.³¹ This correlation with severity of ROP is in line with the data obtained with 2C-FCP, where we assessed premature children with mild or no ROP.

Functional diagnostic tools for quantitative evaluation of retinal function of patients are valuable across patients with different retinal diseases.^{34–38} Throughout all procedures, specific narrowband stimuli are used to determine rod- or cone-mediated reaction across the retina. Every procedure asks for active cooperation of the patient, except cP, where the response of the retina is estimated through the assessment of the pupil size. In the simplest form, cP is conducted by sequentially displaying a series of individual red or blue full-field stimuli in a specialized full-field-stimulator, while an infrared camera scans the pupil size of both eyes. The patient does not need to actively respond to the presented stimuli because the pupil reacts on a subconscious, autonomic level. In contrast to other diagnostic methods, like full-field stimulus test,³⁹ dark-adapted two-color threshold perimetry,⁴⁰ and fundus-controlled two-color threshold adaptometry,²⁸ cP examinations provide fully objective data on retinal function, but without spatial resolution. To our knowledge, this is the first study on premature-born children that provides cone- and rod-mediated responses measured with cP. The value of such objective functional data is supported by significantly correlated results from subjective fundus-controlled scotopic and photopic perimetry in the same cohort, providing exact spatially resolved information. The point in favor of the cP technique is its usability in children before school age, when cooperation in subjective functional tests is limited or absent as is in infants.

In conclusion, we showed for the first time a decreased objective cone-mediated pupillary response to photopic red stimuli that correlated to reduced central cone-mediated results in fundus-controlled perimetry in young preterm-born children with MDA. The functional deficits are measurable in premature children with and without ROP when MDA is present. This would indicate that prematurity itself is the main risk factor for MDA and resulting functional deficits.

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