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ORIGINAL RESEARCH ARTICLE

# Delayed luminance and chromatic contrast sensitivity in infants with spontaneously regressed retinopathy of prematurity

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**Abstract**
*Background* The current study assessed whether contrast sensitivity is affected in preterm infants with a history of spontaneously regressed retinopathy of prematurity (ROP, Stages 1–3). Specifically, we employed luminance (light/dark) and chromatic (red/green) stimuli, which are mediated by the magnocellular (M) and parvocellular (P) subcortical pathways, respectively.
*Methods* Contrast sensitivity (CS) was measured using forced-choice preferential looking testing in 21 infants with a history of ROP and 41 control preterm infants who were born prematurely but did not develop ROP, tested between 8 and 47 weeks (2–11 months) postterm age. Infants were presented with chromatic and luminance drifting sinusoidal gratings, which appeared randomly on the left or right side of the monitor in each trial. The contrast of the stimuli varied across trials and was defined in terms of root mean squared cone contrast for long- and medium-wavelength cones.
*Results* Between 8 and 25 weeks postterm, ROP infants had significantly worse CS, and there was a trend for greater impairment for luminance than chromatic CS. This delay was not seen at older ages between 26 and 47 weeks postterm.
*Conclusions* These findings are consistent with the concept that early maturation of the M pathway is vulnerable to biological insult, as in the case of ROP, to a greater extent than in the P pathway.

**Keywords** Premature · Infant · Retinopathy of prematurity · Chromatic · Luminance · Contrast sensitivity

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## Introduction

With recent technological and scientific advances in neonatal medicine, the survival rate of infants who are born prematurely is on the rise, as is the number of infants who are at risk for retinopathy of prematurity (ROP). ROP is an ocular disorder that occurs when premature birth of an infant leads to a biochemical chain of events that cause abnormal patterns of blood vessel growth in the retina. It is estimated to occur in approximately 16–19 % of all premature births and in over 50 % of infants weighing less than 1,700 g at birth [1, 2]. ROP affects the development of the structure and function of the peripheral and central retina [3–8], and some of these effects persist into adolescence and early adulthood [5, 6, 9, 10].

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Children who were born very prematurely and had a history of severe ROP have been reported to have deficits in spatial acuity [11–15] and contrast sensitivity [16–20]. It is still not clear whether less severe ROP (stage 1–3), which accounts for approximately 85–90 % of all ROP cases [21, 22], causes specific visual deficits beyond the complications of extreme prematurity. In some studies with older children, acuity and contrast sensitivity are impaired only in severe cases of ROP, which typically coincide with neurological abnormalities, while mild ROP shows no additional impairment beyond prematurity alone; however, contrast sensitivity testing in these studies has been done using the static Pelli-Robson test, which may not be sensitive to changes in visual sensitivity in mild ROP [16, 17, 20, 23, 24].

Whether ROP impairs color vision is more controversial, with a few studies reporting higher incidence of color deficits in children with severe ROP, compared to preterm controls [19, 25, 26] and other studies failing to replicate this finding, even with severe ROP [20, 23, 27, 28]. These studies used pseudoisochromatic plates or hue-matching tests designed as rapid screening tests for inherited cone anomalies (i.e., protanopia and deuteranopia) and are not psychophysical assessments of color sensitivity. One study using computerized psychophysical measurement of contrast thresholds for chromatic red–green and blue–yellow gratings found no evidence of color deficits in children (aged 7–13 years) with a history of mild ROP [29].

In contrast to results from these perceptual studies, electroretinographical recordings have shown that even mild ROP causes cellular dysfunction of both rod and cone responses [7, 30, 31] and have been reviewed in [32]. Multifocal ERG recordings in children show that mild ROP decreases and delays cone photoreceptor response, and this delay was greatest for central fovea and became smaller with increasing eccentricity [6]. Optical coherence tomography studies, which use ultra-high-resolution adaptive optical imaging to study the central retina, have demonstrated subtle abnormalities of the macula, including broader and shallower foveal pits, an abnormal vascular layer over the fovea, and increased inner and outer nuclear layer thickness in patients who had ROP, suggesting that ROP alters the neurovascular development and the redistribution of retinal cells in this region [8]. These neurovascular effects may contribute to subtle visual sensitivity deficits observed in subjects with mild ROP.

The aim of the current study is to address whether or not infants who had mild-to-moderate ROP have impaired contrast sensitivity using psychophysical assessment. We investigated the development of visual contrast sensitivity to luminance (light/dark) and chromatic (red/green) patterns using the forced-choice preferential looking technique [33] in a selected population of infants who were monitored in the neonatal intensive care unit and whose medical reports indicated that the ROP had regressed, not requiring treatment, with no plus disease, macular ectopia, or retinal detachment, and no or only mild brain hemorrhaging at the time of birth. This specific population allowed examination of effects of ROP on visual sensitivity, without the confounding mechanical effects of cellular loss and scarring associated with severe ROP. The utility of our luminance and chromatic stimuli in detecting visual deficits in regressed ROP lies in the fact that our stimuli are designed to differentially tap visual function of the two primary visual retinogeniculate-cortical pathways—the magnocellular (M) and parvocellular (P) pathways. Distinctions between these two primary visual pathways have been supported by anatomical, physiological, and behavioral evidence, with differentiation beginning with distinct retinal ganglion cell types (parasol and midget cells) projecting separately to distinct magnocellular (M) and parvocellular (P) layers in the lateral geniculate nucleus (LGN) and providing relatively segregated input to cortical areas [34–39].[1] The two pathways show marked differences in the relative sensitivities to luminance and chromatic (red/green) contrast. Specifically, M cells are far more sensitive to luminance contrast than the P cells and are not selective for chromatic properties, whereas P cells are far more sensitive to chromatic contrast than the M cells (e.g., [41–43]). Based on these differences, the claim has often been made that magnocellular and parvocellular pathways provide the neural substrate for luminance and chromatic contrast sensitivity, respectively. The current study is the first to investigate whether these

[1] There also exists a third pathway, the "koniocellular" pathway, which originates in the blue-ON bistratified cells of the retina, and is thought to encode "blue/yellow" chromatic information, which is not discussed here (see [40] for a review).

two pathways are differentially affected in infants with regressed ROP.

## Methods

### Subjects

Preterm infants with and without a history of ROP were referred to our laboratory for vision testing through the Neonatal Intensive Care Unit at the University of California San Diego (UCSD) Medical Center and the Ratner Children's Eye Center at UCSD. Preterm infants were also recruited via mass mailings of 3,000–4,000 generic letters sent each month to new parents residing in San Diego County, and parents who were interested called our laboratory to schedule testing. Background information from subjects was obtained from a combination of parental interviews and medical records obtained with parental permission. Appropriate Institutional Review Board approval was obtained. Informed consent was obtained from a parent before testing, and procedures adhered to the tenets of the Declaration of Helsinki (Code of Ethics of the World Medical Association).

The ROP group consisted of 21 preterm infants (12 males and 9 females) who had been diagnosed with stages 1–3 ROP, in zones 2 or 3, which had spontaneously regressed by the time of testing and did not require treatment. They had no form of macular dragging, folds or retinal detachment, based on ophthalmological exams performed by one pediatric ophthalmologist (SLR). The number of infants with stages of ROP was as follows: stage 1 (8), asymmetric stage 1 and stage 2 in each eye (3), stage 2 (5), asymmetric stage 2 and stage 3 in each eye (2), and stage 3 (3), with diagnosis made in accordance with the guidelines of International Classification of Retinopathy of Prematurity. Eight infants with ROP had a history of sepsis. Brain ultrasound results for the infants with ROP were as follows: normal (6), questionable results showing some bleeding and were later cleared or resolved with repeated imaging (4), intraventricular hemorrhaging (IVH) grade 1–2 (5), IVH grade 3 (2), and unconfirmed (2, but parents reported no abnormal brain scans). No consistent pattern of results or statistically significant differences were linked to the degree of ROP or the presence of brain damage in this small sample, and we were unable to compare groups of stages as this was confounded with age differences. The control infants consisted of 41 preterm infants with no brain damage or ROP (21 males and 20 females).

Because we employed red/green isoluminant stimuli, we excluded infants with a greater than 50 % chance of colorblindness, for example, male infants whose maternal grandfather was known to be colorblind. To further ensure that all our infants were generally healthy, we included only infants who, between the time of hospital discharge to the time of testing, had no history of hospitalizations, surgery, congenital or hereditary conditions, convulsions, seizures, illnesses, or cranial/neurological abnormalities.

The means, standard deviations, and ranges of postterm age (age since term), postnatal age (age since birth), gestational age at birth (all in weeks), and birth weights are presented in Table 1. ROP infants in our study were born between 23 and 33 weeks gestational age, with gestational age determined by medical report of due date (in comparison with birth date), typically based on the first ultrasound or on the last menstrual period. Control infants in our sample were born between 30 and 34 weeks gestational age. The mean postterm ages at the time of testing for the ROP and control groups were very closely matched (20.0 vs. 18.8 weeks, respectively), and postnatal age at the time of test was similar, but not identical, for the ROP and control groups (32.9 vs. 26.4 weeks, respectively). It was impossible to match the two groups in both

**Table 1** Mean, standard deviations (SD), and ranges for age, gestational age at birth, and birth weight for each subject group

| | Postterm age (weeks) | | Postnatal age (weeks) | | Gestational age (weeks) | | Birth weight (kilograms) | |
|---|---|---|---|---|---|---|---|---|
| | Mean (SD) | Range | Mean (SD) | Range | Mean (SD) | Range | Mean (SD) | Range |
| ROP ($N = 21$) | 20.0 (7.5) | 8.2–47.4 | 32.9 (8.1) | 16.1–56.3 | 26.9 (2.4) | 23.1–33.1 | 0.9 (0.4) | 0.4–2.0 |
| Controls ($N = 41$) | 18.8 (7.5) | 8.6–37.1 | 26.4 (7.5) | 16.3–43.6 | 32.2 (1.1) | 29.7–33.9 | 1.9 (0.4) | 1.0–2.5 |

Gestational age is calculated using due date from medical records or parent report, based on last menstrual period or the first ultrasound

postterm and postnatal ages because the ROP group was overall more premature, since there is a higher prevalence of ROP with greater prematurity. We chose to compare the two groups at roughly the same range of postterm ages because it was very difficult to get ROP preterms to present for testing at very young postnatal ages. We feel strongly that the greater prematurity in the ROP group is not an issue for two reasons. First, the ranges of gestational age at birth overlapped quite a bit between groups (as did the postnatal and postterm ages). Second, gestational age at birth was not a significant predictor of contrast sensitivity for either ROP or controls (discussed below in *Data Analysis*), and thus, this group difference in prematurity is unlikely to account for impairments in contrast sensitivity we observed in the ROP groups.

## Apparatus and stimuli

Luminance (light/dark) and chromatic (red/green) stimuli were presented on an Iiyama Vision Master Pro 510 monitor (1,024 × 768 pixels, 100 Hertz) generated by a ViSaGe video system (Cambridge Research Systems) and a Dell Dimension XPS computer. The luminance of the monitor was linearized and calibrated using a spectroradiometer (PhotoResearch PR650). Stimuli were horizontally oriented sinusoidal gratings with a spatial frequency of 0.27 cycles/degree moving upward or downward at a temporal frequency of 4.2 Hz. These parameters were chosen because they are near the peak of the spatial and temporal contrast sensitivity functions for young infants [44–47]. The stimuli subtended 11 by 11° and were centered 15° to the left or right of the middle of the video monitor. The mean chromaticity of the gratings and the background was CIE = 0.486, 0.442. The mean luminance of gratings and the background was 21.3 cd/m$^2$. Contrast of stimuli is described in terms of *cone contrast*, i.e., the amount of response modulation produced in the long- and medium-wavelength-selective cones in the eye (see [47] or [48] for methodological details).

### *Determining red/green isoluminance*

The red/green chromatic stimulus in the main experiment was presented at the mean isoluminance value obtained from 18 adults, using standard motion photometry [49–51]. In the motion photometry, adults fixated on a small dot in the center of a moving red/green grating and adjusted the luminance contrast in the grating until the percept of motion was least salient. Each adult subject's isoluminance point was determined from the mean of 25 trials. The stimulus conditions for the motion photometry procedure were identical to those employed in the main experiments (i.e., same size, orientation, spatiotemporal frequency). The justification for using the adult mean isoluminance value in our infant experiments is based on previous experiments demonstrating that infant and adult mean isoluminance points are highly similar to red/green stimuli [51–58]. Moreover, Brown and colleagues argue quantitatively that the variability of isoluminance points across infant subjects is comparable to the variability across adult subjects, when measurement error is taken into account [54]. In previous studies, we have calculated that the amount of luminance error likely to exist in our red/green stimuli is below luminance contrast threshold for infants (see [51] for a discussion).

## Obtaining contrast sensitivities

For each infant, a luminance and chromatic contrast threshold was obtained using the method of constant stimuli and forced-choice preferential looking (FPL) ([33]; see [51, 59] for details). The FPL procedure relies on the fact that infants prefer to look at a patterned stimulus on the one side of a display rather than a blank, homogeneous field on the opposite side. In each trial, a grating stimulus moved randomly either upward or downward and appeared randomly on the left or right side of the video monitor. Testing was conducted binocularly. The experimenter held the infant in front of the monitor at a viewing distance of 38 cm and was unable to see the stimulus (see Fig. 1). The experimenter viewed a video of the infant and used cues such as the infant's head turning and gazing behavior to judge the left versus right location of the stimulus. Because the mean luminance and chromaticity of the stimulus is the same as that of the background, when the contrast in the stimulus is at or below "contrast threshold," it blends into the background and cannot be seen.

Typically, five contrast values (1.25–25 % cone contrast) were presented for each luminance and chromatic condition. Luminance and chromatic conditions, as well as the direction of motion, location of the stimuli, and all contrast levels, were randomized

**Fig. 1** Example of infant testing using forced-choice preferential looking

across trials. Stimuli remained present on the video monitor until the experimenter made the left/right judgment, which was typically less than 2 s. The experimenter's answer was entered into the computer by pressing keys on the keyboard by the parent (who did not view the stimulus). Computer beeps provided feedback as to whether the experimenter's inference of the infant's response was correct. Data from each infant were obtained over the course of 2 days within a 5-day period. The average number of trials for luminance and chromatic conditions, respectively, were 85 (±27) and 87 (±27) for the control infants and 73 (±21) and 76 (±21) for the ROP infants. For each infant, a psychometric curve was fit to the chromatic and luminance data using Weibull functions and maximum likelihood analysis [60, 61]. Threshold was defined as the contrast yielding 75 % correct performance. Contrast sensitivity (CS) was computed as the inverse of threshold times 100 and then logged since log, but not linear, sensitivity data conform to the normal distributions [62].

## Data analyses

In order to inspect raw data and compare developmental trajectories, we plotted all individual log CS values as a function of postterm and postnatal ages (Figs. 2, 3). We then fit linear regression lines separately to log luminance CS and chromatic CS as a function of log postterm and as a function of postnatal age for ROP and control subjects.

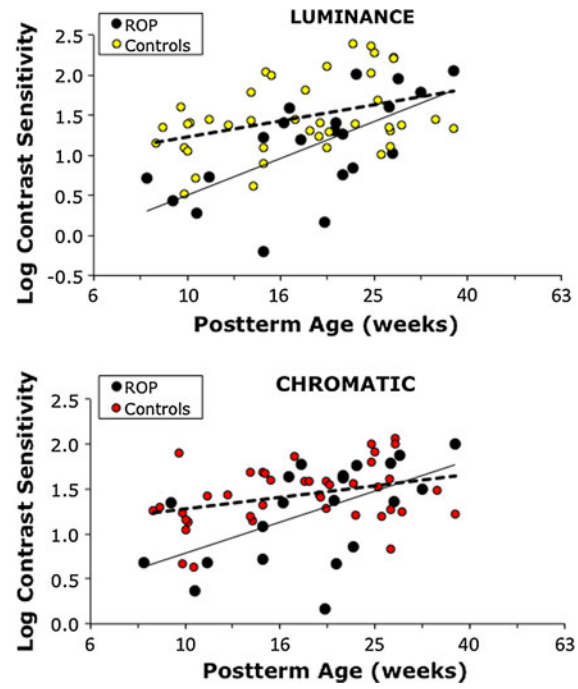


**Fig. 2** Log cone contrast sensitivity as a function of log postterm age for each of the 62 infants. *Top* Luminance CS. *Bottom* Chromatic CS. Regression lines were fit to data from infants with ROP ($N = 21$, *black circles* and *solid lines*) and preterm control infants without ROP ($N = 41$, *light circles* and *dashed lines*). On the *x* axis, log values have been converted into linear equivalents for ease of interpretation

We hypothesized that if contrast sensitivity is impaired due to ROP, then infants with a history ROP should show lower overall performance when compared to controls (i.e., preterms without ROP). To test this hypothesis, we compared the two groups while accounting for variance in our dependent measure due to individual differences in prematurity and log postterm age with a multivariate analysis of covariance. We entered subject group (ROP vs. control) as an independent variable, stimulus type (luminance vs. chromatic) as a repeated subjects variable, and gestational age at birth as well as log postterm age as covariates. Next, we tested the homogeneity-of-slopes assumption, to confirm that the effects of the covariates did not differ for the subject groups. Results of this indicated that the effect of log postterm age on CS was different for the two groups, and this effect was significant ($p = 0.05$; values reported in *Results* below). Hence, we employed a separate-slopes general linear model (GLM), which includes the interaction terms between the covariate and independent variables. Because gestational age at birth

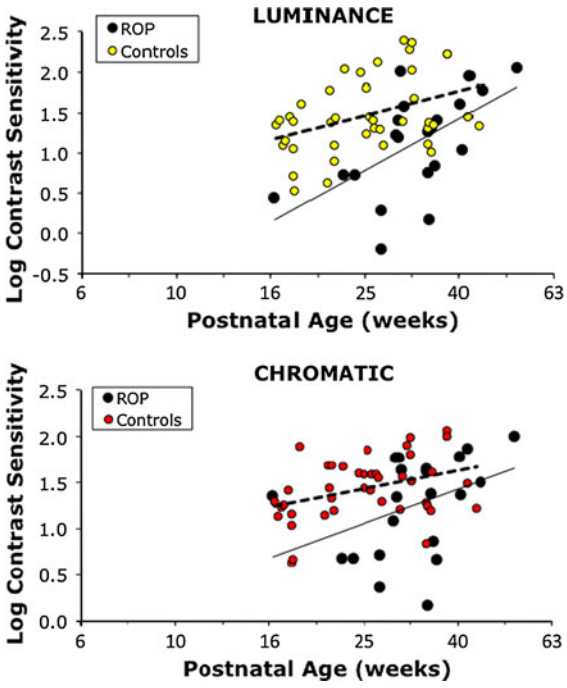


**Fig. 3** As in Fig. 2, log cone contrast sensitivity as a function of log *postnatal* age for each of the 62 infants. *Top* Luminance CS. *Bottom* Chromatic CS. Regression lines were fit to data from infants with ROP ($N = 21$, *black circles* and *solid lines*) and preterm control infants without ROP ($N = 41$, *light circles* and *dashed lines*). On the *x* axis, log values have been converted into linear equivalents for ease of interpretation

was not a significant predictor within our sample ($F(1,58) = 0.16$; $p = 0.69$), nor was it correlated with either luminance CS (ROP: $r = 0.06$; $p = 0.79$, preterm: $r = -0.20$; $p = 0.22$) or chromatic CS (ROP: $r = 0.35$; $p = 0.12$, preterm: $r = -0.29$; $p = 0.07$) based on linear regression, we removed it from the model, retaining the covariate log postterm age in the GLM separate-slopes model. Normality of data, using Kolmogorov–Smirnov tests, and homogeneity of variance, using Levene's test, were verified before statistical analyses. As in our previous studies (e.g., Bosworth and Dobkins [63]), we logged age for data analysis since the development of contrast sensitivity conforms to a linear growth curve when plotted on log-age scale. In our figures, however, we convert the log values into their linear equivalents on the x axis for ease of interpretation.

## Results

### Linear regression

Log luminance and chromatic contrast sensitivities as a function of log postterm age are plotted in Fig. 2, for each infant. Not surprisingly, CS was positively correlated with postterm age for both ROP and controls (correlation coefficients presented in Table 2). The slopes were much steeper for ROP than control infants for both luminance CS (2.29 vs. 1.01 in ROP vs. controls, respectively) and chromatic CS (1.73 vs. 0.64, in ROP vs. controls, respectively). The steeper slopes in ROP infants would suggest an early delay in CS development for ROP infants followed by a later accelerated period that allows them to "catch up" to controls at later ages.

Figure 3 plots log luminance and chromatic contrast sensitivities as a function of log postnatal age. The slopes for postnatal age were slightly steeper than postterm age for three of the four comparisons: luminance CS for both groups and chromatic CS for controls, but not for chromatic CS for the ROP group (comparison of Figs. 2 vs. 3 and see slope values in

**Table 2** Slopes, standard errors, Pearson correlation coefficients, and *p* values are presented for luminance and chromatic CS as a function of postterm and postnatal age (in log weeks) for each subject group

| | Luminance | | | Chromatic | | |
|---|---|---|---|---|---|---|
| | Slope (SE) | *r* | *p* value | Slope (SE) | *r* | *p* value |
| *Postterm age* | | | | | | |
| ROP ($N = 21$) | 2.29 (0.62) | 0.65 | 0.002 | 1.73 (0.57) | 0.57 | 0.007 |
| Controls ($N = 41$) | 1.01 (0.39) | 0.39 | 0.013 | 0.64 (0.28) | 0.35 | 0.027 |
| *Postnatal age* | | | | | | |
| ROP ($N = 21$) | 2.78 (0.85) | 0.58 | 0.004 | 1.39 (0.83) | 0.34 | 0.109 |
| Controls ($N = 41$) | 1.53 (0.56) | 0.40 | 0.009 | 0.99 (0.41) | 0.37 | 0.019 |

*SE* standard error

Table 2). The steeper slopes (i.e., faster rate of development) for postnatal age suggest that earlier birth (and, presumably, extra visual experience) accelerated development. Finally, the plots in Figs. 2 and 3 suggest that the ROP group had overall *lower* contrast sensitivity, particularly between 8 and 25 weeks postterm age, as seen by the downward displacement of regression lines for ROP compared to controls. We explore this group difference with a GLM on mean contrast sensitivities, averaged across infants within each group (*below*).

## GLM results

Subject group means indicated that mean CS was lower in ROP than controls (luminance: 1.12 vs. 1.47 for ROP and controls, respectively; chromatic: 1.25 vs. 1.43 for ROP and controls, respectively). In support of this, the GLM revealed a significant effect of subject group ($F(1, 58) = 5.89$; $p = 0.02$). A separate analysis on the luminance and chromatic CS data showed that this effect was significant for each stimulus type (luminance: $F(1,58) = 5.08$; $p = 0.03$, chromatic: $F(1,58) = 4.81$; $p = 0.03$). There was no main effect of stimulus type ($F(1,58) = 3.61$; $p = 0.06$) and no group × stimulus type interaction ($F(1,58) = 0.432$; $p = 0.51$). Not surprisingly, postterm age was a significant predictor of CS ($F(1,58) = 21.93$; $p < 0.0001$). There was also a significant interaction between postterm age × group ($F(1,58) = 4.12$; $p = 0.05$). This interaction term indicates a different effect of postterm age for the ROP versus the control group upon CS.

As can be seen in Figs. 2 and 3, at younger ages (under ~26 weeks of postterm age), CS in the ROP group was impaired compared to that of controls, while at older ages, the two groups looked very similar. This is also apparent in the steeper slopes of CS development for ROP than controls (slopes in Table 2), suggesting that the younger ROP has lower CS, while the older ROP catch up to perform comparably. To statistically evaluate this post hoc, we split the subjects into two age groups: those ≤25 weeks postterm and those ≥26 weeks postterm age. Mean CS values for these two age groups are shown in Fig. 4. The results of a post hoc ANOVA revealed that at younger ages (8–25 weeks postterm), the ROP group had impaired luminance CS by a factor of 1.6 ($F(1,46) = 14.95$; $p = 0.0004$) and impaired chromatic CS by a factor of only 1.3 ($F(1,46) = 9.48$; $p = 0.003$). The impairment was greater for luminance CS than chromatic CS which is apparent in the left panel of Fig. 4 showing a greater difference in sensitivity between ROP infants and controls in luminance CS than in chromatic CS. No differences were seen for the older group (26–47 weeks postterm), for luminance ($p = 0.63$) or chromatic CS ($p = 0.32$). This null result at the older ages should be viewed with caution, however, since the sample sizes were small for these ages (ROP $N = 5$; control $N = 8$).

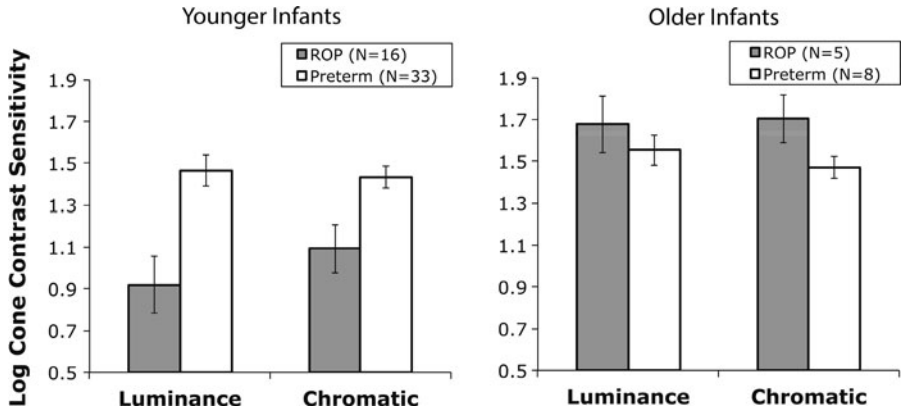


**Fig. 4** Least squared log cone contrast sensitivity means for the ROP group (*dark bars*) and the preterm control group (*white bars*). *Bars* represent group mean; *error bars* denote standard error. *Left panel* Younger infants: 8–25 weeks postterm, adjusted for covariate 15.5 weeks postterm age. *Right panel* Older infants: 26–47 weeks postterm, adjusted for covariate 29.5 weeks postterm age

## Discussion

This study is the first psychophysical examination to determine whether ROP affects luminance and chromatic contrast sensitivities, which are mediated predominantly by the M and P pathways, respectively. The results from this study suggest that between 8 and 25 weeks (2–6 months), ROP infants show an early delay in both pathways with the effect appearing somewhat greater for the M, than P, pathway. In a small sample of older infants, between 26 and 47 weeks (6–11 months) of age, no impairment was seen, which suggests that for the conditions tested in the current study (i.e., low spatial frequencies, mid-range temporal frequency), there is no lasting effect due to ROP. It is possible that we failed to detect smaller deficits at this later age because of our small sample size at the oldest age ($N = 5$ ROP infants) and because age confounds as the postnatal age of the ROP group was somewhat older than that of the controls (43 vs. 37 weeks of age). Given that older infants are expected to have higher CS, the older age of the ROP group could have counteracted any deficits in this group due to ROP. However, this is unlikely because at this older age, the ROP and preterm controls perform similarly to full terms on this measure in a previous study from our laboratory [63].

There are a number of possible explanations for the early delay in contrast sensitivity in ROP patients. It has been recently shown that even *mild* ROP causes long-term structural changes to the retina and deficits in rod and possibly cone, photoreceptor, and postreceptor retinal function that persist long after the acute phase ROP resolves. Fulton et al. [7] found small dysfunction in cone responsivity using multifocal ERG's in patients with mild, regressed ROP that was not treated [6] and greater dysfunction in those who had more severe ROP that required treatment [30], which the authors attribute to cellular dysfunction, rather than cellular loss. ROP has been found to disrupt the formation of the vascular tissue, the foveal pit shape, and the displacement of inner retinal layer cells away from the fovea [3, 8, 30, 64], and these changes are likely to affect or delay the developmental changes in foveal cone density and the postreceptor neurons, which are supported by a rat model of ROP [65]. Any of these abnormalities may cause delays or deficits in acuity or contrast sensitivity by disrupting the light-guiding and pigment absorption properties of the photoreceptors.

Other clinical measures of contrast or acuity, using Teller acuity cards with infants or optotypes in children, have been frequently applied as functional outcome measures in ROP. It is widely accepted that infants and children who had *severe* ROP during the neonatal period, with or without treatment, generally have poor outcomes on these measures [66–68], and there is a positive correlation between the severity of retinal residua of ROP and degree of visual acuity deficits in eyes that had severe ROP during the neonatal period [12]. Typically, studies show children who had spontaneously regressed ROP have mild deficits in peripheral visual field perimetry [69] and spatial acuity [11, 17, 20, 67, 70]. The current study suggests an early delay in contrast sensitivity for low spatial frequencies in infants who had spontaneously regressed ROP (stages 1–3 in zones 2 and 3), and these early delays before 26 weeks of postterm age do not seem to be persistent. This is in line with the finding by Harris et al. [71] that early postreceptor dysfunction in infants with mild ROP also improved with age. They propose that in patients with mild (but not severe) ROP who have photoreceptor damage, there is reorganization of postreceptor retinal circuitry that allows recovery of visual function.

In the current study, we found a trend for greater impairment of luminance than chromatic CS, implying greater M, than P, pathway disruption. We can theorize why the M pathway could be selectively affected to a greater extent than the P pathway due to ROP. It is possible that the failure of the choroid to meet the metabolic demands of photoreceptors will impact larger parasol cells first before the midget retinal ganglion cells, which provide input to the M and P layers of the LGN, respectively. In addition, the vulnerability of the M pathway may be linked to the fact that the ROP damage occurs during a period of critical maturation for the M cells, which happens earlier (and when ROP has the greatest impact) than for P cells. We and others have previously reported earlier development for the M, than P, pathway, for both perceptual studies [44, 55] and EEG studies [72]. Studies of anatomical growth and synapse formation in infant primates also support earlier anatomical and neurophysiological M pathway development [73–82], and this is seen in human infants as well [83].

It is relevant to note that the M pathway provides the bulk of the input to the *dorsal stream*, which is posited to be vulnerable to physical insults and genetic abnormalities (for a review see [84]). Several studies have shown deficits, possibly due to ROP or neurological insult, or both, in extremely preterm children for dorsal stream functions such as local and global motion thresholds [85, 86]; representational momentum [87]; biological motion detection [88]; and motion-based form segmentation [89]. The trend observed in the current study is in line with the notion of magnocellular/dorsal pathway vulnerability that has been noted for other genetic conditions that have biological underpinnings such as autism [90, 91], dyslexia [92], and Williams syndrome [93, 94]. On the other hand, few studies have contrasted M and P pathway functioning, as was done in the current study; thus, more work is needed to see whether the M pathway is indeed more vulnerable to ROP.

Although the current data suggest a trend toward greater effects of ROP on the M than the P pathway, it may be the case that actual impairments in chromatic CS are greater than we observed but were overridden by the fact that the ROP infants were more premature and tested at an older postnatal age than the controls, and we have previously shown that early birth may accelerate the development of the P pathway [63]. Thus, it may be the case that their additional time outside the womb accelerated their visual development, and this counteracted any detrimental effects of ROP at the older ages. Nonetheless, it should be considered based on the current study and our previous work with healthy preterm infants that the M pathway could be relatively more biologically governed, and vulnerable to physical insult, while the P pathway could be relatively more amenable to visual experience.

There are other explanations for the overall CS deficit seen in our sample of infants with spontaneously regressed ROP. First, it is possible that other neurological abnormalities account for the lower CS seen in our sample. None of our subjects had severe brain damage but roughly half of our sample had mild bleeding and mild IVH. These mild cerebral conditions could have caused subtle undetected abnormalities which could explain decreased CS. It has been shown that children with neurological abnormalities at birth have poorer visual acuities later [95–97]. We also cannot rule out that refractive errors account for the decrease in performance in the ROP infants relative to the preterm infants without ROP (the controls). However, it seems unlikely, as the incidence of refractive errors (myopia, high hyperopia, astigmatism, and anisometropia) is high in premature infants with and without ROP [16, 98–100]. In the case of refractive error, chromatic aberrations may cause the chromatic stimuli to contain some luminance error (i.e., and not be isoluminant), which would inflate chromatic contrast sensitivities. Finally, there is also a possibility that the impairment in CS reflects deficits in signals within the rod photoreceptors. The trend for greater impairment in the M, than P, pathway is noteworthy given that electrophysiological and psychophysical studies suggest an important rod input to the subcortical M pathway [43, 101–105].

In sum, results from this study show mild, but significant, contrast sensitivity deficits during young infancy, but these seem to resolve after 10 months of age. These results do not undermine, nor contradict, the need to screen this population since they are at risk for amblyopia, strabismus, refractive error, and cognitive disabilities during early and late childhood (see [106] for a review).

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