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Development of Scotopic Visual Thresholds in Retinopathy of Prematurity

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Abstract

Purpose—To test the hypothesis that the late-maturing parafoveal rod photoreceptors are more vulnerable than peripheral rods to the effects of retinopathy of prematurity (ROP).

Methods—Twenty-four infants with a history of preterm birth (gestational age at birth ≤31 weeks) participated in a longitudinal study: 12 had mild ROP that resolved without treatment, and 12 had never had ROP. Thresholds for detecting stimuli (2° diameter, 50 ms duration) presented 10° (parafoveal) and 30° (peripheral) from a central fixation target were estimated by using a preferential-looking method. At each visit, thresholds at both sites were obtained in random order. Thresholds of the preterm subjects were compared with those of previously reported term infants.

Results—The course of threshold maturation in subjects with ROP was significantly prolonged ($P \leq 0.01$) compared with those who had never had ROP and with term-born control subjects. On average, parafoveal thresholds in subjects with ROP reached the adult level at a median age of 12 (range, 6–18) months, and peripheral thresholds reached the adult level at 9 (range, 5–12) months. Median thresholds in subjects who had never had ROP reached adult levels at both sites by approximately 7 months.

Conclusions—The slower development of parafoveal compared with peripheral thresholds in subjects with a history of ROP is evidence that the late-maturing parafoveal rods are more affected by the ROP disease process.

In normal development of the visual system, rod photoreceptor differentiation occurs first in the central retina and continues following a central-to-peripheral gradient.[1] Developmental elongation of rod outer segments is delayed, however, in parafoveal relative to peripheral rods.[2–5] The relatively immature parafoveal rod outer segments are shorter,[3] resulting in reduced quantum catch and proportionate elevation of parafoveal relative to peripheral thresholds in normal young infants.[6,7] At age 10 weeks, rod-mediated thresholds in the normal parafoveal retina are ~0.5 log unit higher than in the peripheral retina.[6,7] By age 6 months, thresholds at both parafoveal and peripheral sites have fallen to adult values and have become equal, as they are in adults.[7]

In infants and children with a history of retinopathy of prematurity (ROP),[8] as well as in rat models of ROP,[9,10] abnormalities in rod and rod-driven function have been demonstrated in ERG studies of full-field retinal responses. The full-field studies, however, cannot evaluate specific retinal sites.

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Psychophysical procedures based on preferential-looking paradigms allow quantitative study of retinal function in small, selected retinal sites during development[7] and have been used to monitor the course of retinal diseases.[11,12] In the present study, sites in the parafoveal and peripheral retina (Fig. 1A) were selected and tested by using psychophysical procedures.[6,13] The parafoveal site is within zone I and the peripheral site is within zone II, as defined by the International Classification of ROP.[14] In the preterm infant, active ROP in zone I is associated with high risk of poor outcome.[15] We tested the hypothesis that rods in the late-maturing parafoveal retina are more vulnerable to the effects of ROP. Specifically, we followed the course of development of rod-mediated thresholds at both 10° (parafoveal) and 30° (peripheral) retinal sites in infants who were born prematurely, some of whom had a history of ROP and others who had never had ROP.

Methods

Subjects

Twenty-four infants with a history of preterm birth participated. In the neonatal intensive care unit, serial ophthalmic examinations for ROP followed schedules similar to those used in multicenter treatment trials.[15–17] Twelve subjects never had ROP and 12 had bilateral ROP that resolved without treatment. For the ROP subjects, the maximum severity of ROP[18] in each eye is listed in Table 1. None had zone I or plus disease. ROP was not active during the postterm ages at which subjects were tested. The left eye of subject 11 (Table 1) had a transient retinal detachment localized to zone III; the detachment resolved without treatment before the first test. Seven other infants were recruited for the study, but completed only one ($n = 4$) or two ($n = 3$) sessions. The thresholds obtained from these infants were within the range of those who completed the longitudinal study.

For the 12 infants with ROP, median gestational age at birth was 27 (range, 24–30) weeks; median birth weight was 843 (range, 610–1170) g. For the 12 without ROP, median gestational age was 29 (range, 27–31) weeks; median birth weight was 1335 (range, 992–1945) g. Although there was an overlap of gestational age and birth weight, both differed significantly between groups (gestational age: Mann-Whitney U = 24, $P < 0.01$; birth weight: U = 3, $P < 0.01$).

The median spherical equivalent of subjects with ROP at the last test was +2.13 (range, −2.50 to +5.00) D in the right eye and +1.38 (range, −3.75 to +5.00) D in the left eye. The median spherical equivalent of subjects without ROP was +2.25 (range, −0.38 to +4.50) D in the right eye and +2.25 (range, +0.38 to +6.00) D in the left eye. The median spherical equivalent did not differ significantly in either the right or left eye between subjects with and without ROP. None became high myopes (−5 D or more)[18] during the study. Only three subjects (ROP 11 and 12 and no-ROP 24) had a more than 0.50 D difference in spherical equivalent between eyes.

Threshold measurements were obtained longitudinally in three to nine sessions (median, five sessions). Median corrected age was 10 (range, 8–20) weeks at the first session and 53 (range, 25–189) weeks at the last session. Corrected age equals postnatal age minus the difference between term (40 weeks) and gestational age at birth. For instance, the corrected age of an infant born at 26 weeks gestation and tested at postnatal age 24 weeks is 10 weeks.

Thresholds of the preterm infants were compared with those of healthy full-term infants who participated in a previous study in which the same apparatus and procedures were used.[7]

The study conformed to the tenets of the Declaration of Helsinki and was approved by the Children's Hospital Committee on Clinical Investigation. Written informed consent was obtained from the parents before each session.

Stimuli

Two 500-W tungsten sources (DAY/DAK, 3200° K; Osram Sylvania, Danvers, MA) were used to present 50 ms duration, blue (Wratten 47B, $\lambda < 510$ nm; Eastman Kodak, Rochester, NY), 2° diameter spots on a rear projection screen (Fig. 1B). Stimuli were presented either 10° (parafoveal) or 30° (peripheral) to the right or left of a central, 30-min arc-diameter red fixation light flickering at 1 Hz.[6,7] Stimulus intensity was controlled by calibrated neutral-density filters. Calculation of the retinal illuminance produced by the stimuli was based on luminance measurements made with a calibrated photodiode and scotopic filter (IL 1700; International Light, Newburyport, MA) placed at the position of the subject's eyes. Retinal illuminance varies directly with pupillary diameter and transmissivity of the ocular media and inversely with the square of the posterior nodal distance.[19] The scotopic troland value of the stimulus was calculated, taking into account previously reported infants' pupillary diameter,[20] axial length,[21–24] and media density.[25]

Procedure

Thresholds were determined with a two-alternative, forced-choice, preferential-looking method[26] that incorporated a "fix-and-flash" procedure.[6,7,27,28] After 30 minutes of dark adaptation, the infant was held by a parent 50 cm from the rear projection screen and viewed the screen binocularly. The fixation target attracted the infant's gaze to the center of the screen. A second adult, the observer, used an infrared viewer to watch the infant. When the observer reported that the infant was alert and looking at the center, the experimenter extinguished the fixation light and presented a test flash. The observer was unaware of the right–left position of the test flash. Based on the infant's head and eye movements, the observer reported stimulus location, right or left, and received feedback from the experimenter on every trial. Thresholds were determined with a transformed up–down staircase that estimates the 70.7% correct point of the psychometric function.[29] After completion of threshold measurement at one site, the threshold was obtained at the other site. The flip of a coin determined which site, parafoveal or peripheral, was tested first, and the observer was informed of the site to be tested. The median number of trials per staircase was 34 (range, 25–50), and the median number of reversals (change from incorrect to correct response) was 4 (range, 3–8). The number of trials or number of reversals did not vary significantly with group, age, or test site.

At every session, thresholds were obtained at both test sites. This within-subject, within-session design allows detection of small (fractions of a log unit) differences between parafoveal and peripheral thresholds.[6,7,13,30,31] The difference between thresholds at 10° and 30° was designated "delta 10–30" ($\Delta_{10–30}$). The stimulus conditions were selected such that in healthy, dark-adapted adult subjects, thresholds at both sites are equal[6,32]; that is, $\Delta_{10–30}$ is 0.

Control experiments in adults indicated that the observer could reliably detect a horizontal deviation of 2° or more from the fixation target.[6] Thus, a reliable response to the 10° and 30° stimuli, with no overlap, was expected.

Analyses

Linear regression summarized the course of threshold development in each subject at each site: parafoveal and peripheral. This approach was used in our previous longitudinal study of threshold development in term-born infants.[7] Their thresholds were used to calculate a prediction interval (PI), which gives the range within which 99% of normal thresholds are expected to fall.[33] Each regression included the threshold obtained at the initial session up to

and including the first threshold that fell within the 99% PI for adults. For those subjects with no ROP who had all thresholds within the normal PI for age, each regression included the threshold obtained at the initial visit up to and including that obtained at approximately 6 months. The slope of the fitted line (log scotopic td-s per month) and the age at which the fitted line reached the mean threshold in adults were noted. Results from subjects with and without ROP were compared by using the Mann-Whitney U test. The significance level for all tests was $P < 0.01$.

Results

Thresholds for all ROP subjects ($n = 12$) are plotted as a function of corrected age in Figure 2. Before age 6 months, nearly all thresholds were within the broad PIs for normal. Between ages 6 and 12 months, most of the parafoveal thresholds were above the prediction limit for normal, whereas most of the peripheral thresholds were within the PI, and the differences between parafoveal and peripheral thresholds ($\Delta_{10–30}$) were abnormal in all but one subject. That is, nearly all $\Delta_{10–30}$ values were greater than 0. After 12 months, all threshold values fell within the PI at both sites, and $\Delta_{10–30}$ values became normal. Seven of the 12 ROP subjects had thresholds measured after age 18 months (not shown in Fig. 2). In all seven, thresholds remained normal at both sites. Once a subject's threshold fell within the PI for normal adults, it never became abnormal at a later visit. In a prior report, we found persistent elevation of parafoveal thresholds and abnormal $\Delta_{10–30}$ values in older children and adolescents with a history of mild ROP only if they had become highly myopic (−5 D or more)[18] by age 18 months.[31] None of the subjects in the present study became high myopes.

Figure 3 shows thresholds as a function of corrected age in subjects who had never had ROP ($n = 12$). In 9 of the 12 subjects, all parafoveal and peripheral thresholds, as well as $\Delta_{10–30}$ the values, were within the normal PI. The parafoveal thresholds of subjects 13, 14, and 22 at ages 6 to 9 months were just above the PI, but their peripheral thresholds were within the PI at those ages. We note that the gestational age (27 weeks) of two of these subjects (13 and 14) was the lowest among those who had never had ROP.

The regression analyses for two representative subjects, one with a history of ROP and one without, are illustrated in Figure 4. A linear model provides a reasonable description of the course of threshold development in the former preterm subjects, as it does in term-born infants.[7] The slopes of the regression lines and calculated ages at which threshold reached the mean adult value are shown in Figure 5 for all subjects. Table 2 lists the median regression parameters for the preterm subjects and for previously reported term-born infants.[7] The median proportion of variance accounted for by the regression (r^2) did not differ significantly between the subjects with and without ROP for parafoveal thresholds (medians: ROP = 0.88; no-ROP = 0.94; U = 47, NS), peripheral thresholds (ROP = 0.84; no-ROP = 0.96; U = 57, NS), or $\Delta_{10–30}$ (ROP = 0.79; no-ROP = 0.82, U = 58, NS).

As summarized in Figure 5 (top), the rates of threshold development, estimated by the slope of the regression line (Table 2), overlapped broadly at both sites. The median rate of threshold development did not differ significantly between the ROP and no-ROP groups (parafoveal: U = 37, NS; peripheral: U = 53, NS), despite the slightly slower rate at both sites in the ROP subjects. The median rate of change in $\Delta_{10–30}$ however, was significantly slower in the ROP subjects than in those who had never had ROP (U = 25; $P < 0.01$).

The lower panels of Figure 5 summarize the age at which the adult mean threshold was reached. The regression analysis indicated that at the parafoveal site, ROP subjects reached the adult mean threshold at a median age of 12 (range, 6–18) months, which is, on average, approximately 5 months later than subjects who had never had ROP (U = 19; $P < 0.01$; Table

2). At the peripheral site, subjects with ROP reached the adult threshold value only slightly later than those who had never had ROP. The average difference between the groups was approximately 2 months (U = 30; NS). With two exceptions (subjects 14 and 22), subjects who had never had ROP reached the adult mean threshold at both the parafoveal and peripheral sites at about age 7 months. In term-born infants, parafoveal and peripheral thresholds reach adult levels by age 6 months.[7]

The age at which $\Delta_{10–30}$ reached the adult mean was significantly later in subjects with ROP than in those who had never had ROP (U = 25, $P < 0.01$). One subject in the no-ROP group (subject 13) had normal courses of threshold development at both test sites. Despite this result, the $\Delta_{10–30}$ values were constant (0.3 log unit) at all three sessions. Subject 21, who entered the study at age 4 months, had $\Delta_{10–30}$ values at the adult level at every session. We have not applied the regression analysis to the data of these two subjects who had constant $\Delta_{10–30}$ values.

In this small sample with a limited range of severity of ROP, courses of parafoveal threshold development were similar in those with more severe ROP (for example, subject 3, Table 1) and those with less severe ROP (subject 8). The ROP subject (subject 6) who had only 1 clock hour of disease in zone II had normal courses of threshold development at both sites. The subject (subject 11) with the most severe and asymmetric ROP had regression parameters close to the median for the ROP group. The threshold test is not sensitive to asymmetric disease, because subjects viewed the stimuli binocularly.

Discussion

In the ROP subjects, the course of threshold development was prolonged, more so in the parafoveal than in the peripheral retina. Development of $\Delta_{10–30}$ which is an expression of parafoveal threshold relative to the mildly elevated peripheral threshold, was even more prolonged, with a slower rate (slope) and adult value reached at a later age. Thus, we find evidence that parafoveal rods are more affected by mild ROP than are peripheral rods. In subjects who had never had ROP, the courses of development were only slightly slower than in term-born control subjects.

There are several possible explanations for the slow course of threshold development in ROP subjects. These explanations are not mutually exclusive. In healthy, term-born infants, the development of rod-mediated thresholds is attributable to elongation of rod outer segment length and consequent increased probability of quantum catch (although a postreceptor immaturity cannot be ruled out).[7] Possibly, there is a slower rate of rod outer segment elongation in infants with ROP. Another explanation to consider is a change in the packing density of parafoveal rods with age. Redistribution of rod and cone photoreceptors in the parafovea occurs during simian development.[34] Ordinarily, as the foveal pit develops, cone photoreceptors pack together.[35,36] Development of the foveal pit is delayed in infants with ROP.[37] Perhaps the packing of nearby parafoveal rods is also delayed. A third possibility is disorganization of rod outer segments as has been found in a rat pup model of ROP.[38] Disorganization of rod outer segments is one explanation for the increased retinal noise and elevated thresholds that we found in the increment threshold functions of adolescents with a history of mild ROP.[30] If there were, indeed, rod outer segment abnormalities in the ROP subjects in the present study, we postulate that the abnormalities resolved because thresholds became normal.

The parafoveal stimulus tests retinal sensitivity in zone I, the retinal region associated with high risk ROP.[14,15] Even though none of the subjects ever had zone I disease by clinical examination, the threshold data raise the possibility of subclinical involvement in zone I. The majority of subjects had ROP in zone II, yet the threshold tested by the peripheral stimulus

was comparatively less affected by ROP and had a developmental course that was not significantly different from that of subjects who had never had ROP. Possibly, the greater maturity of the peripheral rods protected them from ROP, or the large peripheral receptive fields masked the effect of ROP on peripheral thresholds.

The prolonged course of scotopic threshold development in subjects with ROP is further evidence that even mild ROP affects development of the neural retina. The slower course at the parafoveal site is evidence that the late-maturing parafoveal rods are particularly vulnerable to the ROP disease process. The underlying mechanisms remain to be defined.

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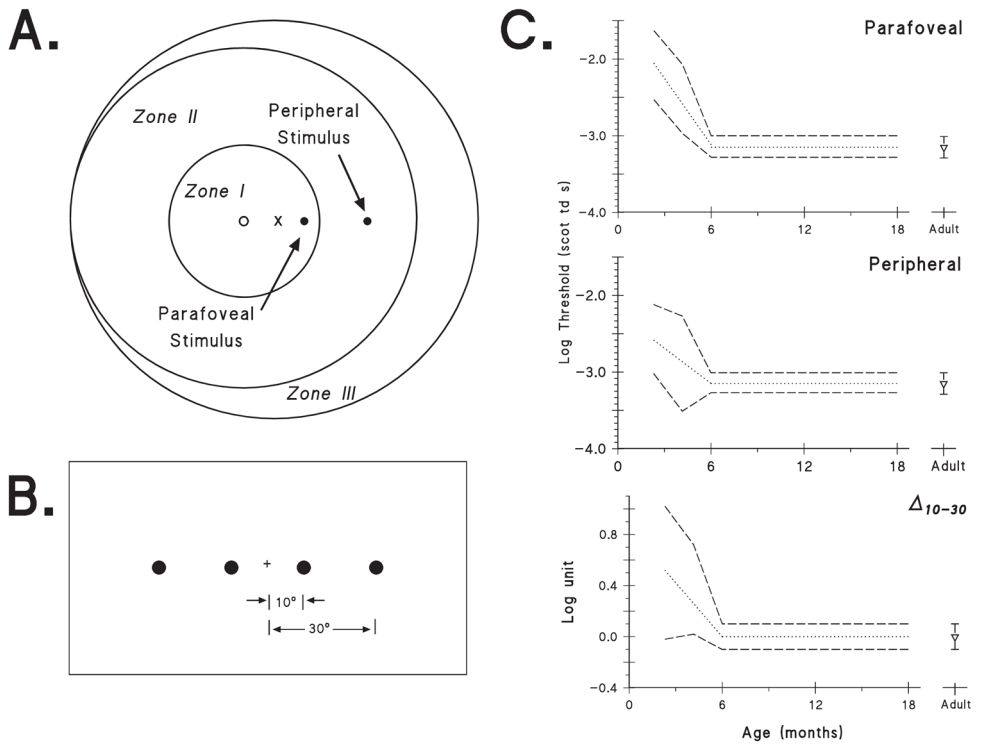

Figure 1.

(**A**) ROP zones and location of stimuli. The position of the parafoveal and peripheral stimuli (●) are superimposed on a diagram of the ROP zones, as defined by the International Classification of ROP.[14] The ROP zones are centered on the optic disc (○). The fovea is indicated by the X. (**B**) The screen and stimuli (not to scale). The 2° diameter stimuli at the parafoveal (10° eccentric) and peripheral (30° eccentric) sites are indicated. + indicates the central fixation display. (**C**) Templates for normal threshold development based on longitudinal data from term-born infants.[7] *Top*: parafoveal threshold as a function of age; *middle*: peripheral threshold; *bottom*: $\Delta_{10–30}$. In each panel, the average course of threshold development for term born infants is represented by the sloping *dotted line* which is the mean regression for threshold data from 2 to 6 months.[7] After 6 months, the *horizontal dotted line* is plotted at the mean adult threshold.[7] By age 6 months, parafoveal and peripheral thresholds in term-born infants are equal to those in adults. The difference between parafoveal and peripheral thresholds ($\Delta_{10–30}$) is 0 by age 6 months, as it is in adults (*bottom*). *Dashed lines* in all panels: the upper and lower limits of the 99% PI for normal. *Triangles* in all panels: adult mean. Error bars, 99% prediction limits in adults.

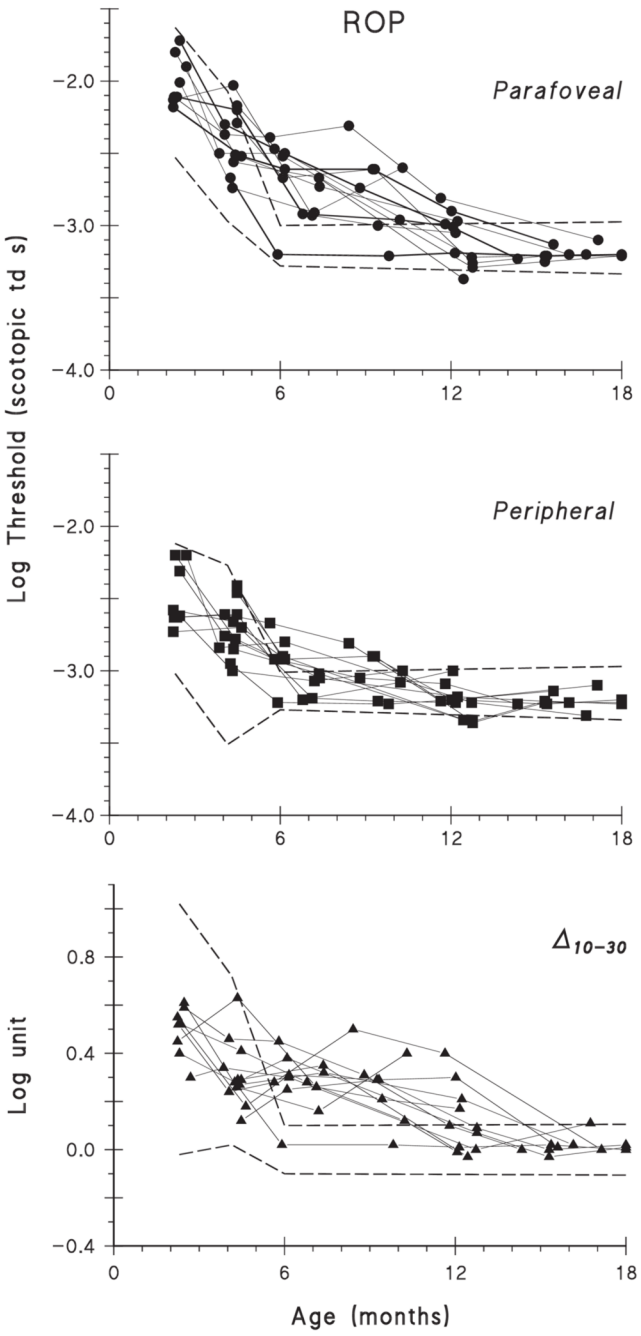

Figure 2.
Parafoveal thresholds, peripheral thresholds, and $\Delta_{10–30}$ of subjects with a history of ROP (*n* = 12) plotted as a function of corrected age. *Dashed lines*: the 99% PI for normal, replotted from Figure 1C.

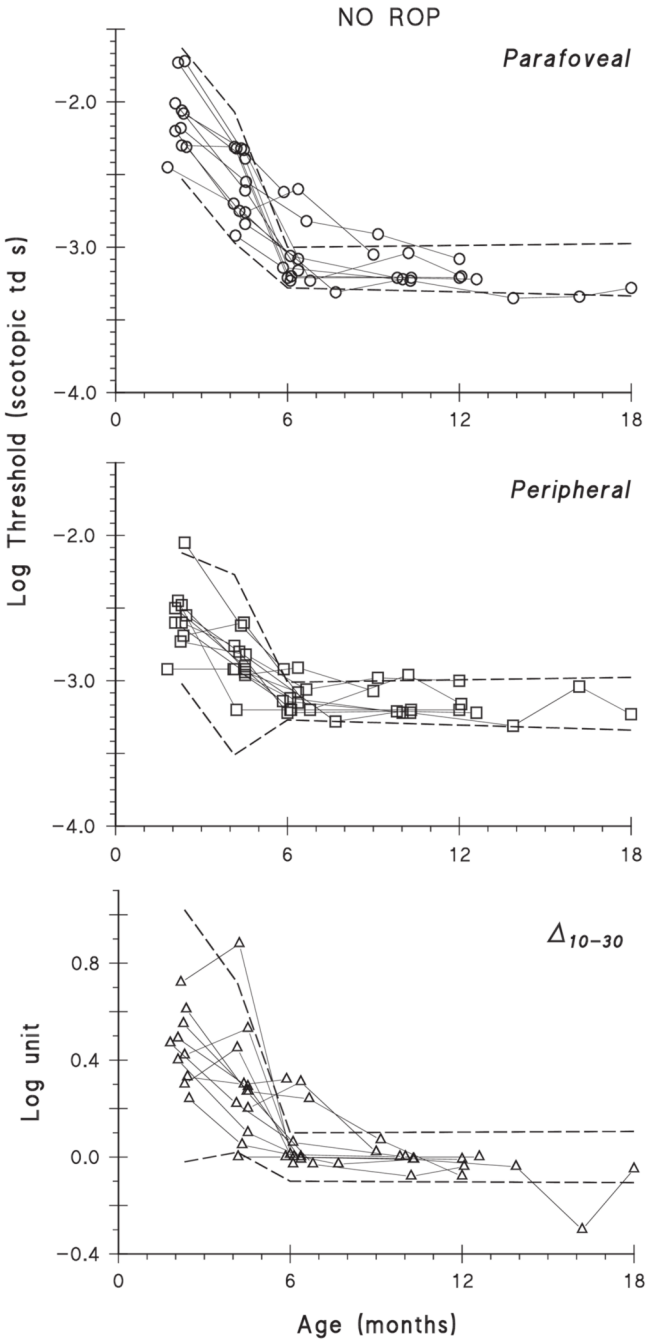

Figure 3.
Parafoveal thresholds, peripheral thresholds, and $\Delta_{10–30}$ of subjects without ROP (n = 12) plotted as a function of corrected age. *Dashed lines*: the 99% PI for normal, replotted from Figure 1C.

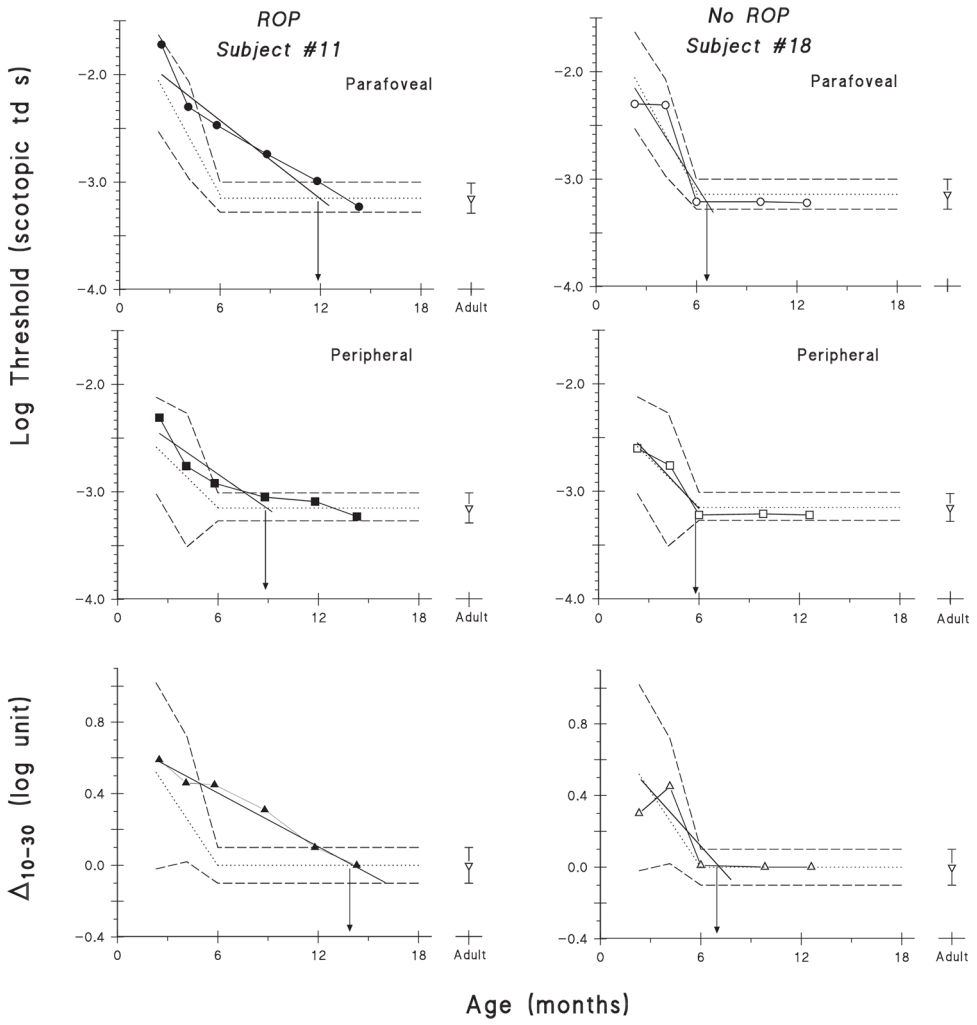

Figure 4.

Data for subject 11 with ROP and subject 18 without ROP. Parafoveal thresholds, peripheral thresholds, and $\Delta_{10–30}$ values are plotted as a function of corrected age. The points plot each subject's thresholds; the regression line, extended past the adult mean, is also shown. *Arrows* in all panels: the age at which the regression line reached the mean adult threshold (Table 2). Other features of these graphs are as in Figure 1C.

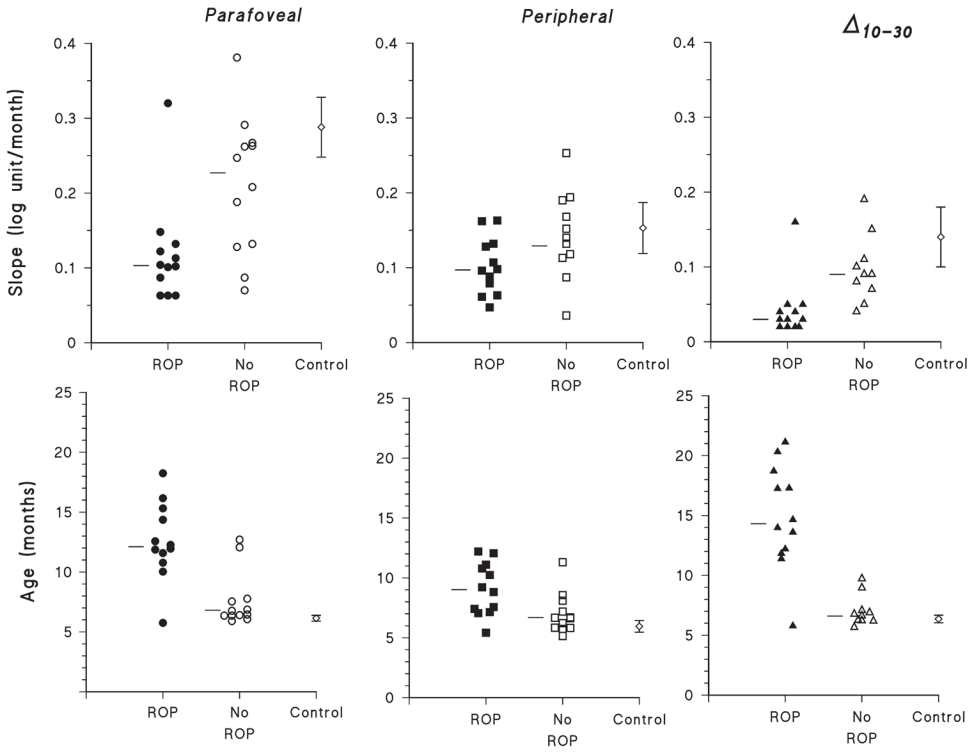

Figure 5.

Results of the regression analysis for development of parafoveal threshold, peripheral thresholds, and $\Delta_{10–30}$ *Top*: the slope of the regression line for each subject; *bottom*: the age at which each subject's regression reached the adult mean threshold. *Horizontal lines*: the medians for the ROP and no-ROP groups. The average slope and age to reach the adult mean threshold (±1 SD) for term-born control infants[7] are plotted in each panel.

Table 1

Maximum Severity of ROP

	ROP OD			ROP OS		
Subject Number	**Stage**	**Zone**	**Hours**	**Stage**	**Zone**	**Hours**
1	2	II	12	2	II	10
2	2	II	8	2	II	8
3	3	II	8	3	II	4
4	3	II	5	2	II	12
5	2	II	2	2	II	3
6	2	II	1	2	II	1
7	1	II	9	1	II	10
8	1	III	4	1	III	2
9	1	II	12	1	II	12
10	3	III	1	1	III	5
11	1	II	5	4A	III	3
12	3	III	1	3	III	2

Table 2

Summary of Regression Parameters

	Parafoveal (10°)		Peripheral (30°)		Δ_{10-30}	
	Slope (log unit/mo)	**Age at Adult Mean (mo)**	**Slope (log unit/mo)**	**Age at Adult Mean (mo)**	**Slope (log unit/mo)**	**Age at Adult Mean (mo)**
ROP	0.10 (0.06–0.32)	12.11 (5.75–18.24)	0.10 (0.05–0.16)	9.01 (5.42–12.20)	0.03 (0.01–0.16)	14.31 (5.78–36.76)
No ROP	0.23 (0.07–0.38)	6.81 (6.06–12.06)	0.13 (0.03–0.25)	6.68 (5.15–12.60)	0.09 (0.04–0.19)	6.67 (4.18–34.23)
Control*	0.28 (0.23–0.35)	6.25 (5.79–6.41)	0.15 (0.10–0.21)	6.01 (5.18–6.59)	0.14 (0.08–0.19)	6.31 (5.91–6.89)

Data are the median (range).

*Data previously reported.[7]