# Effect of Retinopathy of Prematurity on Scotopic Spatial Summation

Ronald M. Hansen, Jena L. Tavormina, Anne Moskowitz, and Anne B. Fulton

Department of Ophthalmology, Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts, United States

Correspondence: Ronald M. Hansen, Department of Ophthalmology, Boston Children's Hospital and Harvard Medical School, 300 Longwood Avenue, Boston, MA 02115, USA; ronald.hansen@childrens.harvard.edu.

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**Purpose.** To evaluate scotopic retinal organization in retinopathy of prematurity (ROP) through a study of spatial summation.

**Methods.** Thresholds for a range of stimulus diameters (0.4°–10°) were measured using a two alternative, spatial, forced choice psychophysical procedure. The critical diameter ($D_{CRIT}$) for complete summation was estimated in subjects with a history of severe ROP ($N = 7$) and mild ROP ($N = 17$). Subjects who were born preterm and never had ROP ($N = 16$) and term-born subjects ($N = 7$) were also tested. The subjects ranged in age from 9 to 17 (median 13.5) years.

**Results.** Critical diameter for complete spatial summation was significantly larger in ROP subjects than in subjects who never had ROP and in term-born control subjects. Critical diameter varied significantly with severity of ROP.

**Conclusions.** The larger $D_{CRIT}$ values in ROP are consistent with altered organization of the post receptor retina. This may offer the ROP retina a strategy for achieving noise reduction and good dark-adapted visual sensitivity.

Keywords: retinopathy of prematurity, psychophysics, scotopic sensitivity, spatial summation

The development of the rod-mediated, dark-adapted visual threshold in infants with a history of retinopathy of prematurity (ROP) is delayed compared with that in term-born infants.[1] The dark-adapted threshold in term-born infants reaches the adult value by age 6 months[2]; threshold in infants who had mild ROP does not reach the adult value, on average, until age 12 months.[1] Why there is a significant delay in the development of visual sensitivity in ROP is not completely understood.

In infancy, ERG results indicate that both rod photoreceptor (a-wave) sensitivity and post receptor (b-wave) sensitivity in ROP subjects are lower than in term-born infants.[3] At older ages (median 10 years), in those who had mild ROP, photoreceptor sensitivity is low but post receptor sensitivity is normal, whereas in those who had severe ROP, both photoreceptor and post receptor sensitivity remain low.[4] Thus, it appears that post receptor b-wave sensitivity recovers in mild but not in severe ROP. These results led us to hypothesize that retinal circuitry reorganizes in mild ROP.[4]

Photoreceptor inputs are pooled in the post receptor retina, which is organized into receptive fields.[5] Psychophysical study of spatial summation provides a noninvasive assessment of retinal receptive field organization. For small stimuli, there is a reciprocal relation between threshold and stimulus area up to a critical area for complete summation, beyond which further increases in area have little effect on threshold.[6] In addition to neural circuitry in the retina, neurons located in higher visual centers may also contribute to setting the size of the critical area for complete spatial summation.[5]

To investigate post receptor retinal organization, we measured threshold for a range of stimulus sizes in children and adolescents with a history of preterm birth. From the resulting spatial summation functions, we estimated the critical area for complete summation and compared critical area in subjects who had ROP with that in subjects who never had ROP and with that in term-born control subjects.

## Methods

### Subjects

Thresholds were measured in 40 subjects with a history of preterm birth (Table). The subjects ranged in age from 9 to 17 (median 13.5) years. All had serial fundus examinations in the newborn intensive care nursery similar to those used in the multicenter ROP treatment trials.[7] According to the International Classification of Retinopathy of Prematurity (ICROP),[8] the stage of ROP indicates the severity of abnormal blood vessel growth, with Stage 1 being the least severe. Location of the abnormal blood vessels is specified by zone. There are three concentric zones centered on the optic nerve head; Zone I is the most posterior.

Based on these examinations, each subject was categorized according to maximum acute-phase ROP as severe ROP ($n = 7$), mild ROP ($n = 17$), or no ROP ($n = 16$). Those in the severe category were treated by laser ablation of avascular peripheral retina; the maximum severity was Stage 3.[8] Those in the mild category had ROP that did not require treatment; by clinical criteria, their ROP resolved completely. Their maximum severity of ROP was Stage 1 or 2 in Zone II or III.[8] In these ROP subjects, the disease was symmetric in the two eyes. Subjects in the no ROP category had serial examinations and ROP was never detected. No subject had a history of retinal detachment or retinal surgery other than laser treatment. Gestational age at birth ranged from 23.5 to 32 (median 27) weeks and birth weight from 460 to 2095 (median 894) g.

**Table.** Subject Characteristics, Median (Range)

| Group | N | Gestational Age, wk | Birth Weight, g | Age at Test, y | LogMAR VA OU | Spherical Equivalent, D | |
|---|---|---|---|---|---|---|---|
| | | | | | | OD | OS |
| No ROP | 16 | 29.5 (26.0 to 32.0) | 1100 (460 to 2095) | 13.0 (10.2 to 15.3) | −0.05 (0.32 to −0.16) | +0.06 (−3.88 to +1.31) | +0.37 (−4.19 to +1.38) |
| Mild ROP | 17 | 26.0 (23.5 to 29.0) | 787 (500 to 1270) | 13.6 (10.1 to 16.9) | −0.08 (0.08 to −0.20) | +0.16 (−5.06 to +3.87) | +0.19 (−6.50 to +3.94) |
| Severe ROP | 7 | 27.0 (25.0 to 29.0) | 700 (575 to 940) | 14.4 (10.7 to 17.8) | 0.10 (0.54 to 0.00) | −3.94 (−12.13 to −1.13) | −3.50 (−12.13 to +0.31) |

Although, on average, those with severe ROP were born earlier and had lower birth weight, there was considerable overlap among the preterm groups. Seven healthy, term-born subjects age 9 to 17 (median 12.7) years served as controls.

The study conformed to the tenets of the Declaration of Helsinki and was approved by the Children's Hospital Committee on Clinical Investigation (Boston, MA, USA). Written informed consent was obtained from the parents and assent from the children before each session.

## Procedure

Rod-mediated threshold for detection of 50 ms, blue (Wratten 47B, $\lambda < 440$ nm) spots was estimated using a two alternative, spatial, forced-choice procedure.[9] Stimuli were presented 20° to the left or right of a dim, red, flickering central fixation target on a dark rear projection screen. Eight stimuli ranging from 0.4° to 10° in diameter were used; this spans the range of critical diameters reported for infants and adults.[10–15] Calibrated neutral density filters controlled the intensity of the stimuli. Calculation of retinal illuminance was based on luminance measured using a calibrated photodiode (IL 1700; International Light, Newburyport, MA, USA) placed in the position of the subject's eye. The scotopic troland values of the stimuli were calculated taking each subject's measured pupil diameter into account.

After 30 minutes of dark adaptation, the subject, positioned 50 cm in front of the rear projection screen, was asked to look at the central fixation target using both eyes. Then, the fixation target was extinguished and a stimulus was presented. The subject reported stimulus position (right or left) on every trial and received feedback. Threshold was determined with a transformed up-down staircase (step size 0.3 log unit) that estimates the 70.7% correct point of the psychometric function.[16] The staircase started with a stimulus 2 to 3 log units above the anticipated threshold.[9] Three to five alternations were obtained to determine the threshold. In healthy adult subjects, the mean threshold for the 10° diameter stimulus is −3.9 (SD = 0.12) log scotopic troland seconds.[17]

## Analyses

Log threshold (scotopic troland seconds) was plotted as a function of log stimulus area (degrees$^2$). The critical area for complete spatial summation was defined as the intersection of a line with slope −1.0 fit to thresholds for the smallest stimuli and a horizontal line drawn through the average of the thresholds for the three largest stimuli. For each subject, we report the diameter ($D_{CRIT}$) of the area for complete summation.

Analysis of variance was used to determine differences among the groups (severe ROP, mild ROP, no ROP, and term born). The outcome measures were $D_{CRIT}$ and the threshold for the 10° stimulus. The Scheffé test was used to make post hoc comparisons between groups. For all tests, the criterion level of significance was $P$ less than or equal to 0.01.

## Results

Representative spatial summation functions from preterm subjects and a term-born control are shown in Figure 1; all subjects had $D_{CRIT}$ near the median for their group. Critical diameter values for the three groups of subjects with a history preterm birth (severe ROP, mild ROP, no ROP) and term-born controls are shown in Figure 2. Critical diameter varied significantly with group ($F = 22.9$; $df$: 3, 43; $P < 0.001$). Results of the Scheffé test indicated that $D_{CRIT}$ in those with severe ROP was significantly larger than in all other groups (term, mild ROP, and no ROP; $P < 0.001$). In subjects with mild ROP, $D_{CRIT}$ values overlapped with those in the no ROP ($P = 0.002$) and term-born groups ($P = 0.01$), but the average $D_{CRIT}$ was significantly larger. Critical diameter in the preterms who never had ROP did not differ from that in the term born controls.

For the preterm subjects, threshold for the 0.4° diameter varied significantly with group ($F = 8.02$; $df$: 2, 36; $P = 0.001$). Relative to the no ROP group, the average threshold for the 0.4° stimulus was elevated 0.65 log unit in the severe ROP group and 0.32 log unit in the mild ROP group. For the largest stimulus (10° diameter), mean thresholds in the mild and severe ROP groups were within 0.1 log unit of the mean

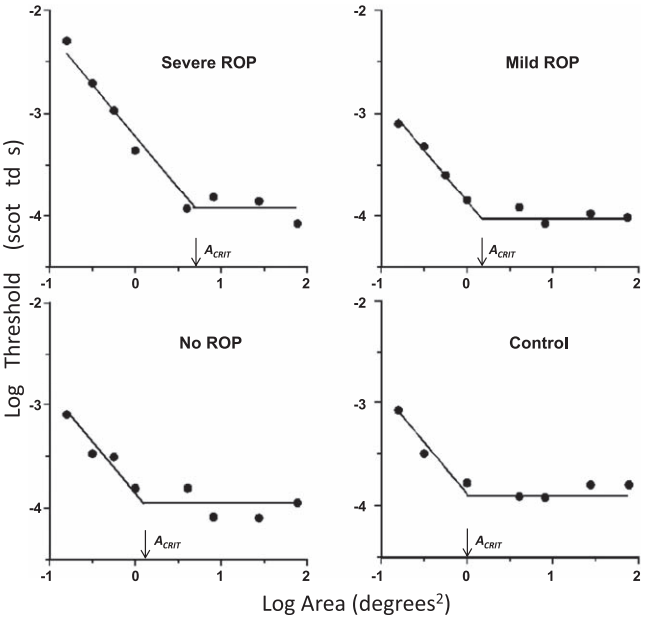


**Figure 1.** Representative spatial summation functions. Log threshold is plotted as a function of log stimulus area for subjects from the three groups of former preterm subjects: severe ROP, mild ROP, and no ROP. For comparison, results from a term-born subject are also plotted. The intersection of a line with slope = −1.0 fit to the three the smallest stimuli and a line with slope = 0 through the average threshold for the three largest stimuli is the critical area (indicated by the *arrow*). Note that the two thresholds near the critical area were not included in the curve fits.

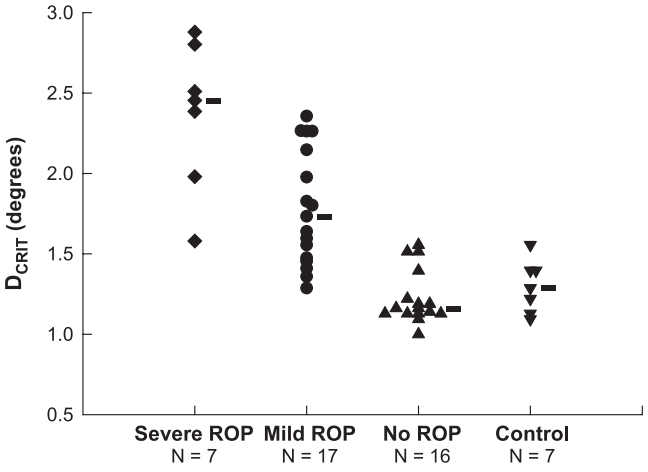


**Figure 2.** Critical diameter values in severe ROP, mild ROP, no ROP, and term-born control groups. Each subject is represented by a point. The number of subjects in each group is indicated. The median $D_{CRIT}$ value for each group is indicated by the *horizontal bar*.

threshold in the no ROP group. Thus, integrating visual signals over a larger area compensated for the threshold elevation for small stimuli. Thresholds for the 10°-diameter stimulus did not vary significantly with group ($F = 0.53$; *df*: 3, 43; ns).

## Discussion

The critical diameter for complete spatial summation ($D_{CRIT}$) is significantly larger in subjects with a history of ROP than in former preterms who never had ROP and in term-born controls. These results show that $D_{CRIT}$ varies significantly with the severity of ROP. The enlarged $D_{CRIT}$ values are found years after the ROP resolved in early infancy.

Critical diameter is considered a subjective correlate of the receptive field center lying within its inhibitory surround.[18] Psychophysical studies have shown that $D_{CRIT}$ varies with retinal adaptation level, retinal eccentricity, stimulus duration, and wavelength.[6,11,13,14,19,20] Furthermore, changes in $D_{CRIT}$ during development[10–12] and aging[20,21] are interpreted as indicative of alterations of neural retinal organization.[10–12,20,21] Electrophysiology has demonstrated the receptive field characteristics of retinal ganglion cells and of receptive fields in the central visual system.[22–24] We suspect that changes in $D_{CRIT}$ in our ROP subjects are due to altered organization of the post receptor neural retina.

Spatial summation improves stimulus detection in the presence of noise. Increasing the pooling of photoreceptor inputs to post receptor units theoretically increases the probability that a dim stimulus will be detected by the subject. The ROP retina may employ this strategy to achieve normal dark-adapted visual sensitivity for large stimuli even though rod photoreceptor sensitivity is unambiguously low.[4]

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