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The Neural Retina in Retinopathy of Prematurity

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Abstract

Retinopathy of prematurity (ROP) is a neurovascular disease that affects prematurely born infants and is known to have significant long term effects on vision. We conducted the studies described herein not only to learn more about vision but also about the pathogenesis of ROP. The coincidence of ROP onset and rapid developmental elongation of the rod photoreceptor outer segments motivated us to consider the role of the rods in this disease. We used noninvasive electroretinographic (ERG), psychophysical, and retinal imaging procedures to study the function and structure of the neurosensory retina. Rod photoreceptor and post-receptor responses are significantly altered years after the preterm days during which ROP is an active disease. The alterations include persistent rod dysfunction, and evidence of compensatory remodeling of the post-receptor retina is found in ERG responses to full-field stimuli and in psychophysical thresholds that probe small retinal regions. In the central retina, both Mild and Severe ROP delay maturation of parafoveal scotopic thresholds and are associated with attenuation of cone mediated multifocal ERG responses, significant thickening of post-receptor retinal laminae, and dysmorphic cone photoreceptors. These results have implications for vision and control of eye growth and refractive development and suggest future research directions. These results also lead to a proposal for noninvasive management using light that may add to the currently invasive therapeutic armamentarium against ROP.

Keywords

Retinopathy of prematurity; Electroretinogram; Infant visual psychophysics; Retinal development

1. Introduction

1.1. Preterm birth and retinopathy of prematurity (ROP)

Retinopathy of prematurity (ROP), which afflicts infants born before term, is characterized by abnormal retinal vasculature at preterm ages. ROP onset occurs when the neurosensory retina is quite immature. The photoreceptors are the last cells to complete maturation. Term is at 40 weeks, approximately 9 months, gestation. No matter the gestational age at birth,

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and no matter the ultimate severity of the retinopathy, the onset of ROP is at approximately 32 weeks gestation; that is, 32 weeks after the mother's last menstruation. At this age, the developmental increase in the rhodopsin content of the retina escalates, as shown in Fig. 1. The developmental increase in rhodopsin (Fulton et al., 1999a), consequent to the increasing elongation of the rhodopsin bearing rod outer segments, lags the normal vascular coverage of the peripheral retina. The course of active ROP is quite brief; ROP typically resolves in the early post term weeks (Repka et al., 2000).

The coincidence of ROP onset and rod outer segment development motivated us to consider the rods as a major player in the pathogenesis of ROP. What if the developing rod outer segments' burgeoning energy demands to support the circulating current (Ames et al., 1992), turnover of outer segments (Tamai and Chader, 1979), and phototransduction drove the retinal hypoxia that stimulated the abnormal ROP vasculature? This question led us to design and perform experiments in rat models of ROP and in preterm born infants and children that would test the relationships among the neurosensory retina, its vascular supply, and even the development of the eye as a whole.

This paper is about our studies of human ROP subjects. First we briefly summarize results from rat models of ROP that are pertinent to the interpretation of data from human subjects. Our use of noninvasive techniques facilitates translation between species.

In a rat model, retinopathy is induced by exposure of newborn pups with immature retina to alternating high and low levels of ambient oxygen. In the ROP rat, we found that deficits in the rod photoresponse calculated from the a-wave of the electroretinogram (ERG) antedated the appearance of abnormal retinal vasculature (Reynaud et al., 1995). Specifically, the kinetics of activation of rod phototransduction were slower and indicative of lower sensitivity, and the amplitude of the saturated response was smaller than in controls. While delayed development of the ROP rods could explain low sensitivity and small amplitude, the total amount of rhodopsin extracted from control and ROP rat retina did not differ significantly; this is not consistent with a mere delay in development of the rods but rather suggests dysfunction of the rods (Dodge et al., 1996; Fulton et al., 1995). By microspectrophotometry (MSP), the transverse density of the rhodopsin in the ROP rod outer segments was significantly more variable than in controls. The total rhodopsin content of the retina, calculated from the MSP data, was in good agreement with the rhodopsin content obtained by quantitative extraction of the whole retina (Dodge et al., 1996). Furthermore, by electron microscopy, the outer and inner segments of the ROP rods were disorganized and dysmorphic (Fulton et al., 1999b). Thus, the ROP rats had functional and structural evidence of hypoxic and hyperoxic injury induced by ambient conditions (Barnett et al., 2010; Dodge et al., 1996; Liu et al., 2006a; Madan and Penn, 2003; Penn et al., 1994; Reynaud et al., 1995; Roberto et al., 1996; Shao et al., 2011). It has since been confirmed that both hypoxia and hyperoxia are injurious to the immature rods (Wellard et al., 2005).

The choroidal vasculature, which is the main supplier of oxygen to the rods, may play a role in photoreceptor injury. The choroid is thin in ROP rats (Shao et al., 2011). Due to the choroid's characteristic inability to adjust to ambient conditions (auto-regulate), a thin choroid may be incapable of furnishing an adequate supply of oxygen to the ROP rods.

The sensitivity of the ROP rat rod, which was calculated from the ERG a-wave (Reynaud et al., 1995), depends on the molecular mobilities of the transduction cascade proteins in the disc membranes of the photoreceptor outer segments. Biophysical and biochemical data in ROP rat rods (Dodge et al., 1996; Fulton et al., 1995) indicate that the disease renders phototransduction inefficient. The inefficiency may occur from photon capture to movement of proteins in the disc membrane to closure of the channels in the rod outer segment. The ERG b-wave, which represents post-receptor neural activity, shows predictable consequences of the altered photoreceptor input. Thinning of the outer plexiform layer (OPL) has been observed in the ROP rat retina (Akula et al., 2010b; Dembinska et al., 2001; Lachapelle et al., 1999). Another study (Dorfman et al., 2011) found changes in synapses of the ROP rat retina that suggested limited communication between the photoreceptors and post-receptor retina. They identified cell death and synaptic retraction as possible causes of OPL thinning.

Our further study of ROP rats showed that the early status of the rods' phototransduction capabilities predicts the later hallmark vascular outcome (Akula et al., 2007a; Akula et al., 2007b; Liu et al., 2006a; Liu et al., 2006b). The converse is not, however, true; early vascular abnormality does not predict subsequent rod deficits. Thus, temporal priority supports a role for the rod photoreceptors in the pathogenesis of ROP. We found additional support for the rods' role in ROP pathogenesis. A pharmacological intervention (a visual cycle modulator) designed to reduce the rods' energy demands similarly reduced the severity of the subsequent vascular abnormalities (Akula et al., 2010b). This result is not surprising given that vascular and neural development is under the cooperative control of shared patterning molecules, the expression of which is regulated by retinal oxygenation (Akula et al., 2010a; Akula et al., 2010b; Akula et al., 2008; Klagsbrun and Eichmann, 2005). It is plausible that similar neurovascular relationships pertain to human ROP.

In human ROP subjects, we use some of the same noninvasive procedures to obtain data that permit interpretation of retinal cellular activity (Hood and Birch, 1994; Hood and Greenstein, 1990; Lamb and Pugh, 1992, 2006) and specification of the effects of ROP on retinal cells. We use the full-field ERG to assess photoreceptor and post-receptor function as a mainstay of our investigations. Generally speaking, photoreceptor and post-receptor functions are considered separate but related. We perform psychophysical studies to probe the function of photoreceptor and post-receptor retina in more detail than is achieved in the rat models. We use modern retinal imaging techniques to evaluate the structure of the photoreceptors and post-receptor laminae that mediate the functional responses assessed by ERG and psychophysical procedures. Age specific normal values for structural and functional features of the retina in infants and children are critical for valid interpretation of ROP data.

Our overall aim is to obtain new knowledge about the pathogenesis of human ROP that will lead to improved management of the disease. Additionally, we aim to learn more about vision in infants and children with a history of preterm birth and ROP. Herein we review our electroretinographic, psychophysical, and retinal imaging data and consider future directions for studies of ROP, including implications for management and treatment.

1.2. Clinical issues

The clinician's prime task is to detect ROP. Diagnosis of severe ROP is of utmost importance. Programs for examining premature infants who, by virtue of young gestational age at birth, low birth weight, and other risk factors, have been organized (for example, Gilbert, 2008; Holmstrom et al., 2015; Jalali et al., 2003; Jalali et al., 2014; Skalet et al., 2008). The details of these programs vary somewhat depending on the regional epidemiology of ROP in particular countries (Wilson et al., 2013). In the neonatal intensive care unit (NICU), the ophthalmologist inspects the infant's fundi using indirect ophthalmoscopy; the purpose is to identify abnormal retinal vasculature (ICROP, 2005). Serial examinations are performed until maturation of the vessels is complete and no retinopathy has occurred, or mild ROP develops and resolves without intervention and the retinal vasculature extends to the ora serrata, or ROP progresses to such severity that treatment is indicated. Untreated severe ROP leads to conspicuous visual impairment. Fortunately, the incidence of mild ROP exceeds the incidence of severe ROP. The severity of ROP is categorized based on vascular appearance according to the ICROP scheme (ICROP, 2005).

The criteria for treatment are based on the characteristics of the vasculature including location, spatial extent, and severity of the vascular abnormalities. Treatment is most often by laser ablation of the peripheral avascular retina (ETROP, 2003), as was the case with the ROP subjects studied by us. A good response to this therapy is resolution of the abnormal vasculature with peripheral retinal scarring at the treatment sites. Fortunately, the scarring has little impact on the peripheral visual fields in the children (Cryotherapy for Retinopathy of Prematurity Cooperative Group, 2001; Fielder et al., 2015; Harvey et al., 1997; Holm et al., 2015; Larsson et al., 2004; Quinn et al., 2011). Treatment by injection of an antibody against vascular endothelial growth factor (VEGF), which can also cause the abnormal vasculature to resolve, is coming into use; this treatment does not produce peripheral scars (Arambulo et al., 2015; Cayabyab and Ramanathan, 2016; Jefferies, 2016; Karkhaneh et al., 2016; Mintz-Hittner et al., 2016; Quinn and Darlow, 2016). Interestingly, the occurrence of significant ametropia appears to be lower in anti-VEGF treated eyes (Chen et al., 2014; Geloneck et al., 2014).

1.3. ROP subjects

In our studies, we test subjects who were born prematurely, some of whom never developed retinopathy and some of whom did develop ROP. As noted, ROP is an active disease at preterm ages (Palmer et al., 1991) and resolves during the early post term weeks (Repka et al., 2000). We use a shorthand categorization of our subjects as *No ROP*, *Mild ROP*, or *Severe ROP* according to the maximum severity of the acute phase ROP (Table 1) (Fulton et al., 2009).

According to ICROP (2005), location of the abnormal vasculature is specified by zone (I to III), severity of the vascular changes by stage (1 to 5; the higher the number, the greater the severity), and extent by clock hours (1 to 12). Zone I, the most posterior, is centered on the optic nerve and includes the macula. Zone II is an annulus concentric with Zone I that extends nasally to the ora serrata. Zone III is the remaining temporal crescent. The ICROP

zones and clock hours are shown in Fig. 2. A severe form of the disease, plus disease, strikes Zone I. Plus disease is characterized by dilation and tortuosity of the blood vessels. Throughout this paper, we designate subjects with a history of preterm birth as “ROP subjects” and, as mentioned, specify them as *Severe ROP*, *Mild ROP*, or *No ROP* (or *None*).

All prematurely born subjects in our studies underwent serial fundus examinations in the NICU using indirect ophthalmoscopy. The purpose was to identify and characterize abnormal vasculature, on which clinical diagnosis of ROP, appropriate management, and treatment were based. The schedule of examinations was similar to that in the multicenter ROP treatment trials (Hardy et al., 2004, 2005). In our *Severe ROP* group, the maximum severity was Stage 3 and the disease reached criteria for treatment according to the recommendations of the ETROP study (Hardy et al., 2004), which was laser ablation of the peripheral avascular retina. In our *Mild* group, the maximum severity was Stage 1 or 2 in Zone II or III, and by clinical criteria, the ROP resolved completely without treatment; no retinal residua were detectable by clinical examination. In our *No ROP* group, ROP was never detected in the serial examinations. (See Table 1.) We excluded subjects with retinal detachment and those who had retinal surgery other than laser treatment.

In our ROP subjects (*Severe, Mild, None*), birth weight ranged from 450 to 2275 grams and gestational age from 21 to 32 weeks. Throughout this paper, we report age as corrected weeks post term; term is 40 weeks. Corrected age is calculated as follows: Corrected Age = Gestational Age + Postnatal Age – Term. For example, the corrected age of an infant who was born at gestational age 27 weeks and tested at postnatal age 25 weeks is 12 weeks: 27 + 25 – 40 = 12 weeks.

All studies conformed to the tenets of the Declaration of Helsinki and were approved by the Boston Children’s Hospital Committee on Clinical Investigation. Written informed consent was obtained from the adult subjects and from the parents of infants and children; assent was obtained from children who were capable of providing it.

2. Stimulus specification

The structure and optical properties of an infant’s eye differ significantly from the mature eye in ways that affect specification of visual stimuli at the retina. Therefore, quantitative understanding of retinal function throughout development relies on accurate specification of stimuli in the immature eye.

2.1. Scotopic stimuli

In the adult eye, the stimulus is frequently specified in trolands, a conventional unit of retinal illuminance. The troland value of a stimulus is calculated as the product of pupil area (mm²) and stimulus intensity (cd/m²) (McCulloch and Hamilton, 2010). The infant’s eye size (Lim et al., 2015; Mactier et al., 2008; Munro et al., 2015) and pupil diameter are smaller than in an adult eye (Hansen and Fulton, 1993). However, the ocular media are less dense (Hansen and Fulton, 1989; Werner, 1982) than in the adult eye. To specify correctly the retinal stimulus in the infant’s eye, these differences must be taken into account. The retinal illuminance (E) produced by a stimulus (L) varies directly with pupil area (A) and media

density (τ_λ) and inversely with the posterior nodal distance (d) squared (Pugh, 1988; Wyszecki and Stiles, 1982). In this formulation,

$$E = L \cdot A \cdot \tau_\lambda / d^2 \quad (1)$$

we use vitreous chamber depth to estimate posterior nodal distance (Lotmar, 1976; Mactier et al., 2008; Ramamirtham et al., 2016). The wavelength of the stimulus is λ . If the average values (Table 2) of pupil area (Hansen and Fulton, 1993), posterior nodal distance (Brown et al., 1987; Isenberg et al., 1995; Mactier et al., 2008), and media density (Hansen and Fulton, 1989; Werner, 1982) for 10 week old infants are substituted for the adult values (Breton et al., 1994; Schnapf et al., 1990; Wyszecki and Stiles, 1982) in Eq. (1), equally intense stimuli at the cornea produce approximately equal retinal illuminance in young infants and adults (Brown et al., 1987; Hansen and Fulton, 1993; Malcolm et al., 2003); the infant/adult ratio is 1.07. If the infant's pupil diameter were larger than 5.2 mm, or posterior nodal distance were shorter than 12.3 mm, as may be the case in ROP eyes, retinal illuminance will be underestimated (Mactier et al., 2008) and the differences between ROP infants and controls would be even greater than reported herein.

To estimate the number of isomerizations (ϕ) of rhodopsin produced by the stimuli, we (Hansen and Fulton, 2005b) used the formula

$$\phi = L \cdot A \cdot \tau_\lambda \cdot k_\lambda \cdot (1 - 10^{-D_\lambda}) \cdot \gamma \quad (2)$$

where k_λ is a constant that includes the posterior nodal distance, the scotopic luminance efficiency, and the end-on collecting area of a single rod; γ is the quantum efficiency of isomerization; and D_λ is the optical density of rhodopsin. We assume that the end-on collecting area of the immature and mature rod and quantum efficiency of isomerization are the same in infant and adult rods (Baylor et al., 1984; Kraft et al., 1993). We also assume that the axial density of rhodopsin in the outer segment is proportional to the length of the outer segment (Baylor et al., 1984) and the rhodopsin content of the retina (Fulton et al., 1999a). Then, according to Beers' law (Alpern et al., 1987), the ratio of infant to adult isomerizations is $(1 - 10^{-D_{\text{infant}}}) / (1 - 10^{-D_{\text{adult}}})$. From the human rhodopsin growth curve (Fulton et al., 1999a), 4 week old infants have 46% and 10 week old infants 68% of the adult rhodopsin density of 0.4 (Pugh, 1975), so that rhodopsin density is 0.18 at 4 weeks and 0.27 at 10 weeks, and the calculated ratio of infant to adult isomerizations is 0.56 at 4 weeks and 0.77 at 10 weeks. Therefore, if 1 scotopic troland second (scot td s) isomerizes 8.5 molecules of rhodopsin in adults, that stimulus isomerizes 4.8 molecules of rhodopsin in 4 week olds and 6.6 molecules in 10 week olds. The implication of this analysis is that the amplification constant of phototransduction (Lamb and Pugh, 1992) is the same in infants and adults.

2.2. Photopic stimuli

Calculation of stimulus efficiency for photopic stimuli takes into account the directional sensitivity of the cone photoreceptors (Paupoo et al., 2000). Light entering the eye near the edge of a dilated pupil is less effective in stimulating the cones than light entering through the center of the pupil because of the Stiles-Crawford effect (Stiles, 1962). The directional sensitivity of the cones is described by a Gaussian profile (Nordby and Sharpe, 1988; Stiles, 1962). Paupoo et al. (Paupoo et al., 2000) integrated this profile and determined that for a dilated pupil in an adult, retinal illuminance could be calculated using an effective pupil area of 21 mm² rather than the entire area of the dilated pupil which is 50 mm²; that is, a proportion of 0.42. In the absence of infant data, we assume that the directional sensitivity of cones in the infant retina is similar to that in adults and, therefore, use the same factor (0.42) to scale the troland value of photopic stimuli in the infant eye. Alternatively, the stimuli may be specified as cd s/m².

3. Assessment of rod and rod-driven retinal function

To assess the retina as a whole, we use the full-field ERG, a massed response of the rod photoreceptor and rod-driven post-receptor neural retinal function. The photoreceptor response to light is interpreted by application of mathematical models of phototransduction to the ERG a-wave. Photoreceptor driven post-receptor activity is derived from study of the ERG b-wave.

The main components of the dark adapted ERG are the cornea negative a-wave, generated by the rod photoreceptors, and the cornea positive b-wave, generated by post-receptor activity. To probe smaller retinal regions, we use psychophysical procedures (Section 3.2).

3.1. Scotopic full-field electroretinogram (ERG)

ERG responses to full-field stimuli are recorded using previously described methods (Fulton et al., 2009; Moskowitz et al., 2016). Before testing, the patient's pupil is dilated with cyclopentolate 1% and the patient is dark adapted for 30 minutes. Then, under dim red light, after instillation of proparacaine, a bipolar Burian Allen electrode is placed on the eye and a ground electrode is placed on the skin over the mastoid. Responses to an approximately 5 log unit range of blue ($\lambda = 470 \pm 30$ nm), brief (<3 ms) stimuli (-2 to +3 log scot td s) are recorded. A family of ERG responses to flashes ranging from approximately -2 to +3 log scot td s falling on a dark adapted retina is shown in Fig. 3.

3.1.1. Rod photoreceptor function: a-wave—The a-wave originates in the collapse of the circulating current caused by a flash of light (Brown, 1968). The leading edge of the a-wave is well described by a mathematical model of the biochemical steps involved in the activation of phototransduction from photon capture by rhodopsin to closure of the channels in the outer segment membrane (Lamb and Pugh, 1992; Pugh and Lamb, 2000). In this model (Hood and Birch, 1994; Lamb and Pugh, 1992, 2006)

$$R(I, t) = R_{\text{ROD}} \cdot (1 - \exp(-\frac{1}{2} \cdot S_{\text{ROD}} \cdot I \cdot (t - t_d)^2)) \quad \text{for } t > t_d, \quad (3)$$

In this equation, I is the stimulus intensity in scot td s, S_{ROD} (scot td⁻¹ s⁻³) is a sensitivity parameter, R_{ROD} (μV) is the saturated response amplitude, and t_d (s) is a brief delay. (See Fig. 3, lower left panel.) S_{ROD} depends on the time constants of the biochemical steps in phototransduction and is related to the amplification constant of phototransduction (Lamb and Pugh, 1992, 2006). R_{ROD} is related to the number of channels in the rod outer segment membranes that are available for closure by light. t_d includes some delays in the biochemical cascade and those introduced by the amplifiers in the ERG recording system. To minimize intrusion of post-receptor potentials, we restrict fitting of the model to the leading edge of the a-wave or 15 ms.

3.1.2. Rod-driven post-receptor function: b-wave—The b-wave depends on activity of post-receptor neural cells (Brown, 1969). In scotopic conditions, the b-wave reflects activity of the ON bipolar and other second and third order retinal cells (Aleman et al., 2001; Stockton and Slaughter, 1989; Wurzig et al., 2001). The b-wave stimulus-response function is modeled using the Naka Rushton equation (Fulton and Rushton, 1978):

$$V/V_{\text{MAX}} = I/(I + \sigma) \quad (4)$$

In this equation, V (μV) is the amplitude of the b-wave produced by flash I (scot td s) and V_{MAX} (μV) is the saturated amplitude. The stimulus that evokes a half-maximum response amplitude is σ . Thus, σ is the semi-saturation constant and $1/\sigma$ is a measure of sensitivity. The stimulus-response function is fit up to those troland values at which the amplitude of the a-wave rapidly increases (~2 log scot td sec for the normal retina), resulting in a notch in the b-wave stimulus-response function (Peachey et al., 1989). (See Fig. 3, lower right panel.)

3.1.3. Normal development of the scotopic ERG—In the dark adapted eye, there is significant postnatal development of both rod photoreceptor and post-receptor activity (Fulton and Hansen, 2000). We use a logistic growth curve of the form

$$R(x)/R_{\text{MAX}} = (x^n / (x^n + x_{1/2}^n)) \quad (5)$$

to describe developmental increases in ERG photoreceptor (S_{ROD} , R_{ROD}) and post-receptor ($\log \sigma$, V_{MAX}) parameters. In this equation, R is the response at age x , R_{MAX} is the asymptotic value that approaches the adult average, and $x_{1/2}$ is the age at which R is half of R_{MAX} . The exponent (n) describes the steepness of the growth curve. All three parameters are free to vary.

For S_{ROD} , R_{ROD} , $\log \sigma$, and V_{MAX} , the developmental courses are shown in Fig. 4. Data from healthy term born infants and mature control subjects ($N=136$) recruited for the ERG

studies contributed to these growth curves; data from 14 control subjects have been added to those previously reported (Fulton and Hansen, 2000; Fulton et al., 2009). The subjects' ages were distributed from early infancy through early adulthood. The developmental courses of all four scotopic ERG parameters are similar one to the other, reaching half the adult value at 8.2 to 12.5 weeks post term, and thus, are similar to the rhodopsin growth curve (Fig. 1). The calculated parameters of these growth curves for term born subjects are summarized in Table 3. The growth curves provide predictions of the values of the response parameters at a selected age. The actual mean and standard deviation for each scotopic ERG parameter in 4 week olds, 10 week olds and adults (median age 24 years) are shown in Table 4.

3.1.4. Scotopic ERG in ROP—We and others have recorded ERG responses to full-field stimuli from infants and children with a history of preterm birth, including those with and without ROP (Akerblom et al., 2014; Birch et al., 1992; Fulton et al., 2009; Fulton et al., 2001; Hamilton et al., 2008; Kennedy et al., 1997). We calculated rod photoreceptor sensitivity (S_{ROD}) and saturated response amplitude (R_{ROD}) (Fulton et al., 2001; Hood and Birch, 1994; Lamb and Pugh, 1992) from the a-wave using the phototransduction model (Eq. 3). Post-receptor sensitivity ($\log \sigma$) and saturated response amplitude (V_{MAX}) were calculated from the b-wave (Eq. 4). The values of S_{ROD} , R_{ROD} , $\log \sigma$, and V_{MAX} for each ROP subject were compared to normal values for age (Fig. 4). The log difference from normal for age ($\log \text{normal for age}$) was calculated.

Results from two ROP subjects, expressed as $\log \text{normal for age}$, are shown in Fig. 5. Each was tested as an infant and later as a child. In infancy, both rod photoreceptor (a-wave, S_{ROD}) sensitivity and post-receptor (b-wave, σ) sensitivity in both subjects were lower than in age similar term born infants (Fulton et al., 2009). At the older age, the *Mild* subject still had low photoreceptor sensitivity (a-wave, S_{ROD}) but post-receptor sensitivity (b-wave, σ) had become nearly normal. The *Severe* subject continued to have low b-wave sensitivity at the older age as well as low photoreceptor sensitivity. This result raised the possibility that post-receptor sensitivity recovers in *Mild* but not in *Severe ROP*.

We found a similar pattern of results in a cross-sectional sample of ROP subjects ($N = 98$). These results are summarized (Fig. 6) for subjects tested as infants (median age 10 weeks; $n = 43$) and as older children (median age 10 years; $n = 55$); 14 new subjects were added after the publication of Harris et al., 2011. Furthermore, we also found that deficits in dark adapted psychophysical threshold for detection of a test stimulus 10° diameter, 50 ms duration, 20° eccentricity were correlated with post-receptor sensitivity, $\log \sigma$ (Harris et al., 2011). Subjects in the *None* group had S_{ROD} and $\log \sigma$ that were normal at both ages. In the *Mild* group, there were deficits in S_{ROD} at both ages, but the deficit in $\log \sigma$ was less in childhood than in infancy. These data are evidence that sensitivity of the post-receptor retina improves in those with a history of *Mild* group. By contrast, in the *Severe* group, significant deficits in $\log \sigma$ as well as S_{ROD} persisted. Based on these data, we speculate that beneficial reorganization of the post-receptor neural circuitry occurs in *Mild* but not in *Severe ROP*. We comment that long term follow up of patients with *Severe ROP* is indicated as the possibility of a progressive compromise in retinal function cannot be excluded.

3.1.5. Relationship of rod activity to post-receptor sensitivity—Based on Granit's classical formulation (Granit, 1947), the ERG waveform is a summation of signals originating in the photoreceptors and signals of opposite polarity originating in the post-receptor neurons. Hood and Birch (Hood and Birch, 1992) developed a dynamic model of the massed potentials of the full-field ERG. In their model, activity in the rod photoreceptor determines the post-receptor sensitivity of the dark adapted retina in which the sum of $\log S_{\text{ROD}}$ and $\log R_{\text{ROD}}$ predicts post-receptor sensitivity, $\log \sigma$, over the rod's linear range. Does this relationship pertain in normal development? Does it pertain in ROP?

To find out, we first analyzed the data (Figure 4) for normal development. For every subject, we calculated the deficit in S_{ROD} , R_{ROD} and $\log \sigma$ from the adult median value of each of these parameters ($\log$ normal). The relationship does pertain in normal development (Figure 7). As previously reported, in 4 and 10 week old term born infants (Fulton and Hansen, 2000), S_{ROD} and R_{ROD} are lower and $\log \sigma$ higher (indicating lower sensitivity) in than control adults. In Fig. 7, data from 4 week old, 10 week old, and adult subjects fall in approximately equal numbers above and below the diagonal. Thus, during development of the normal dark adapted retina, immaturity at the rod photoreceptor predicts, at least in part, the deficits in post-receptor b-wave sensitivity.

For ROP subjects, as in normal development, the data points also scatter about the diagonal (Fig. 8). For all of the preterm subjects, the photoreceptor deficit is correlated with the post-receptor deficit ($R = 0.67$; $R^2 = 0.45$; $p < 0.001$). For **Mild ROP**, the correlation between photoreceptor deficit and post-receptor deficit is 0.71 ($R = 0.71$; $R^2 = 0.51$). In **Mild** subjects, the deficit at the rod photoreceptor ($\log S_{\text{ROD}} + \log R_{\text{ROD}}$) is significantly larger ($p = 0.036$) than the deficit in post-receptor sensitivity ($\log \sigma$). This result is consistent with the post-receptor remodeling after infancy that we detected in our cross-sectional analysis (Fig. 6). See also, Harris et al. (2011). Results from **No ROP** subjects are like those of age similar term born controls.

ERG results in **Mild ROP** indicate that deactivation of the rod photoreceptor response is slower than in **No ROP** or term born subjects (Hansen et al., 2010). Perhaps use of a model of the a-wave that incorporates both activation and recovery from activation (that is, deactivation) in the rod outer segment (Robson and Frishman, 2014; Robson et al., 2003) will improve specification of the rod to rod-driven relationship in ROP.

3.1.6. Summary and conclusion—Rod photoreceptor and post-receptor responses of the neural retina show significant deficits; the more severe the antecedent ROP, the more severe the deficit. The characteristics of the photoreceptor response are indicative of slowed kinetics of the phototransduction processes, both activation and deactivation, likely a consequence of disorganized and dysmorphic photoreceptors such as has been demonstrated in the rods of rat models of ROP. Although the rod photoreceptor response parameters and post-receptor sensitivity are correlated, the communication of the rods to the rod-driven neural retina is incompletely accounted for by this correlation, and therefore, requires further study which, fortunately, is feasible using available procedures (Robson and Frishman, 2014).

From this study of the massed potentials of the full-field ERG, we turned to the finer probes offered by psychophysical studies of scotopic function in ROP subjects to learn more about rod and rod-driven post-receptor function.

3.2. Psychophysics

In our subjects with *Mild ROP*, the full-field ERG mass potentials suggested beneficial re-organization of post-receptor retina in subjects with Mild ROP but not in those with Severe ROP. We have used a psychophysical approach to investigate further scotopic retinal function in ROP in dark and light adapted conditions. The psychophysical procedures enable study of small, selected retinal regions. These are rigorous tests of vision designed to relate the physical properties of the stimulus to the visual response.

3.2.1. Scotopic threshold measurement: psychophysical method—We use a modified two-alternative preferential looking method to measure scotopic thresholds (Fulton et al., 1991; Hansen et al., 2008; Hansen and Fulton, 1989; Hansen et al., 1986). Before testing, the child, accompanied by a parent, dark adapts for 30 minutes. Then a small, flickering red fixation target attracts the child's gaze to the center of a screen. Then test stimuli are presented at a selected peripheral location to the right or left of the fixation target.

Subjects view the stimuli binocularly. On each trial, the subject looks toward the stimulus, or points to it, or verbally reports the location of the test spot. For infants and young children, an adult observer, unaware of the right/left position of the stimulus, reports the subject's looking or pointing behavior. The subject and observer receive feedback from the tester on every trial. Threshold is determined using a transformed up-down staircase that estimates the 70.7% correct point of the psychometric function (Wetherill and Levitt, 1965). At least five alternations of response type (correct, incorrect) are obtained. Control experiments show good agreement between thresholds estimated using the staircase and those estimated using the method of constant stimuli (Fulton et al., 1991; Hansen et al., 1986). The size, duration, wavelength, and eccentricity of the stimuli are selected as required in the different studies. Calibrated neutral density filters control the intensity of the stimuli.

3.2.2. Scotopic threshold development in term born subjects—Dark adapted thresholds of young term born human infants are significantly higher (sensitivity lower) than those of adults. At 10 weeks, for example, the median threshold is approximately 1 log unit higher than that of adults (Hansen et al., 1986). Thresholds for detection of a 10° diameter spot in the peripheral retina (20° eccentric) are described by the scotopic luminous efficiency function (Wyszecki and Stiles, 1982) providing evidence that these thresholds are rod mediated and not contaminated by cone mediated activity. Additional spectral sensitivity studies in 4 and 10 week old infants have confirmed that the thresholds in dark adapted infants are rod mediated (Clavadetscher et al., 1988; Hansen and Fulton, 1993; Powers et al., 1981). After correction for light losses in the ocular media, we compared the psychophysical spectral sensitivity functions in infants to the absorption spectrum of rhodopsin. The infants' functions were narrower than those of adults (Hansen and Fulton, 1993). This result is

consistent with lower axial density of rhodopsin in the immature rod with short outer segments and lower total rhodopsin content in the immature retina (Fulton et al., 1999a)

3.2.3. Spatial summation—Photoreceptor inputs are pooled by the post-receptor neural circuitry to form receptive fields. Psychophysical study of spatial summation provides a noninvasive method for assessment of retinal receptive field. For small stimuli, there is a reciprocal relationship between detection threshold and stimulus area up to the critical area for complete summation, beyond which further increases in area have little effect on threshold (Hood and Finkelstein, 1986). The critical area for complete scotopic spatial summation in dark and light adapted eyes is larger in term born 10 week old infants than in adults (Hamer and Schneck, 1984; Hansen et al., 1992; Schneck et al., 1984) suggesting that refinement of receptive field is incomplete. We measured dark adapted thresholds for detection of stimuli (0.4° to 10° diameter) that span the range of critical areas reported for both infants and adults (Hallett, 1963; Hamer and Schneck, 1984; Hansen et al., 1992; Schneck et al., 1984; Scholtes and Bouman, 1977; Zuidema et al., 1981) in 40 subjects with a history of preterm birth and in seven term born control subjects. We estimated the critical diameter for complete spatial summation from the resulting spatial summation function for each subject (Hansen et al., 2014).

We found (Hansen et al., 2014) that the critical area for complete spatial summation varied significantly with group (Fig. 9, middle panel). The mean critical area (Table 5) in *Severe* subjects was significantly larger than that in *Mild* subjects, which was, in turn, larger than in *None* and term born subjects. Subjects with *No ROP* did not differ from term subjects. The critical diameters, D_{CRIT} , for individual subjects are shown in Figure 9, lower panel. The results provide evidence that the *Mild* and *Severe* retina pool information over larger areas than the retina in *No ROP* and term born subjects. We hypothesize that pooling over larger regions is a mechanism by which the ROP retina can achieve normal dark adapted visual thresholds even though rod photoreceptor sensitivity is low (Fulton et al., 2001).

3.2.4. Temporal summation—Scotopic threshold is related to the number of quanta captured by the rod outer segment and thus on the duration of the stimulus. For brief stimuli, threshold depends upon the total energy in the stimulus integrated over time. For stimulus durations exceeding a critical duration, there is little change in threshold with further increase in duration (Barlow, 1958; Baumgardt and Hillmann, 1961; Graham and Margaria, 1935; Hood and Finkelstein, 1986; Sharpe et al., 1993; Sperling and Jolliffe, 1965). In dark adapted, healthy adults, critical duration, T_{CRIT} , is approximately 100 ms (Barlow, 1958; Baumgardt and Hillmann, 1961; Graham and Margaria, 1935; Hood and Finkelstein, 1986; Sharpe et al., 1993; Sperling and Jolliffe, 1965).

In young term born infants, no critical duration is identifiable. We found no indication of an inflection in the log threshold vs stimulus duration function. Log threshold plotted as a function of log stimulus duration, from 10 ms through 1,000 ms, is summarized by a linear relationship, with slope of approximately -0.5 (Fulton et al., 1991).

The rod photoreceptors themselves show temporal summation (Alpern and Faris, 1956; Hood and Grover, 1974; Rosenblum, 1971). These and other results imply that the temporal

properties of photoreceptor activity may be determinants of the psychophysical results (Daly and Normann, 1985; Hansen et al., 2015). In adults, the log threshold vs log duration function is characterized by a line with slope of -1 in the range of 10 through 100 ms with little change in threshold with further increase in stimulus duration. As mentioned herein, rod sensitivity in the a -wave model (S_{ROD} , Eq. 3) is related to the amplification constant of phototransduction which, in turn, is based on a series of time dependent processes in the rod outer segment (Breton et al., 1994; Lamb and Pugh, 1992). Thus, low S_{ROD} in ROP (Fig. 6) is evidence of slow transduction kinetics in the rod outer segment which is reminiscent of low S_{ROD} in the disorganized outer segments in ROP rat rods (Fulton et al., 1999b). This led us to hypothesize that T_{CRIT} would be prolonged in subjects with a history of ROP.

To determine T_{CRIT} in *Severe*, *Mild*, and *None* subjects and in term born children (ages 10 to 18 years), we measured dark adapted thresholds for detection of a 10° diameter stimulus presented 20° to the left or right of a central fixation target. Seven stimulus durations were presented, ranging from 20 to 640 ms (Hansen et al., 2015).

We found that T_{CRIT} (Table 5) was significantly longer in *Severe* and *Mild* subjects than in *No ROP* and term born subjects (Fig. 10). T_{CRIT} did not differ significantly between the *Severe* and *Mild* groups nor did it differ between the *No ROP* and term born groups. Interestingly, T_{CRIT} did not vary with severity of the ROP, whereas ERG S_{ROD} does differ significantly with ROP severity.

In addition to the published study of temporal summation (Hansen et al, 2015), we determined the temporal summation function in 1 year old ($n = 12$) and 4 year old ($n = 12$) ROP subjects. We found that, by age 1 year, the temporal summation function is the same as in older children and adults (Hansen et al., 2015). The slope of the linear portion of the function (-0.97 at 1 year and -0.87 at 4 years) is not significantly different from the slope of unity found in adults. Thus, the temporal integration function must mature between the ages of 10 weeks (when the slope = -0.5) and 1 year (when the slope approximates unity). Mean T_{CRIT} for the 1 to 4 year old subjects was 109 ms in *No ROP* and 141 ms in *Mild ROP*, similar to the values reported for older ROP subjects (Hansen et al., 2015).

3.2.5. Background adaptation—Retinal neurons respond to changes in ambient illumination by adjusting the gain or time course of their responses. It is as though the retina's goal is to keep the response nearly constant (Shapley and Enroth-Cugell, 1984). The system is designed to prevent response compression (Hood and Finkelstein, 1986). Adaptation to changing levels of illumination requires adjustment of retinal signals in photoreceptors and post-receptor neural cells (Dunn et al., 2006; Frishman et al., 1996; Shapley and Enroth-Cugell, 1984) and thus offers an approach to investigate both photoreceptor and post-receptor activity.

We measured threshold for detection of a 5° diameter, 50 ms stimulus first in the dark and then in the presence of each of six steady background lights (-2.8 to $+2$ log scot td) to obtain increment threshold functions in ROP subjects and term born controls (Hansen et al., 2016). Dim backgrounds have little effect on threshold; as background strength is increased, thresholds are elevated according to Weber's law (Hood and Finkelstein, 1986; Shapley and

Enroth-Cugell, 1984; Sharpe, 1990). We evaluated the resulting increment threshold functions for the effects of ROP on receptor and post-receptor function in ROP subjects (Hood, 1988; Hood and Greenstein, 1990).

We fit a numeric description (Hood, 1988; Hood and Greenstein, 1990) of the increment threshold function (Fig. 11) to each subject's thresholds (from Hansen et al., 2016) to calculate the values of dark adapted threshold (T_{DA}) and *Eigengrau* (A_0) that minimized the sum of squared deviations from:

$$\log T = \log T_{DA} + \log(1 + I/A_0) \quad (6)$$

where T is the threshold at background intensity I and A_0 is the background that raises the threshold by a factor of 2, that is 0.3 log unit, above the dark adapted threshold. We found that for all groups (*No ROP*, *Mild ROP*, *Severe ROP*, term born), this model provided good fits to the threshold data. The RMS error did not vary significantly between groups (Hansen et al., 2016).

According to classical psychophysical theory (Brown, 1986; Hood, 1988; Hood and Greenstein, 1990), a disease that affects the rod photoreceptor distal to the site of adaptation (presumably the rod outer segment) reduces quantum catch equally for both the test and background stimuli resulting in equal elevation of both T_{DA} and A_0 . The increment threshold function is shifted diagonally (Fig. 11, upper panel). A disease that affects the more proximal retinal pathways, at or after the site of adaptation, elevates T_{DA} ; A_0 does not change. The increment threshold function would be shifted vertically but not horizontally.

The increment threshold functions of subjects in the *Severe ROP* group were shifted diagonally relative to the increment threshold function in the *No ROP* and term born control groups. The two latter groups did not differ significantly. This result suggests that in *Severe ROP*, the pre-adaptation site, probably the rod outer segment, is affected. In these test conditions, the increment threshold functions in *Mild ROP* subjects were characterized by normal dark adapted thresholds (T_{DA} in the model), showing less marked departures from controls than found in *Severe ROP* subjects, but abnormally high *Eigengrau* (A_0).

A_0 and T_{DA} from individuals are summarized in Fig. 11, lower panel (data from Hansen et al., 2016). A_0 , the *Eigengrau*, is thought to represent a measure of intrinsic retinal noise arising in the photoreceptors and post-receptor retinal circuitry. A_0 approaches the estimated values of intrinsic retinal noise (Barlow, 1957; Baylor et al., 1984; Dunn et al., 2006; Dunn and Rieke, 2006; Frishman et al., 1996). There are relatively greater deficits in A_0 than in T_{DA} in *Mild ROP*. In the ROP subjects, whether *Mild* or *Severe*, the elevation of the *Eigengrau* is, we suspect, a consequence of increased photoreceptor and post-receptor retinal noise. In rat models of ROP, S_{ROD} is low even when rhodopsin content is normal; dysmorphic and dysfunctional rod photoreceptors are found (Fulton et al., 1999a). In both the rat models and human subjects, evidence of post-receptor remodeling is found (Akula et al., 2007a; Harris et al., 2011; Liu et al., 2006a; Liu et al., 2006b).

3.2.6. Development of parafoveal (10° eccentric) and peripheral (30° eccentric) rod mediated threshold in dark adapted subjects—We have studied the maturation of these thresholds in both healthy term born subjects and ROP subjects (Barnaby et al., 2007; Hansen and Fulton, 1999).

3.2.6.1. Parafoveal and peripheral thresholds in dark adapted term born

subjects: During development, anatomic studies of the retina have shown that elongation of rod outer segments in the parafoveal retina is delayed relative to that in more peripheral retina (Drucker and Henrickson, 1989; Hendrickson, 1993). In a study of 10 week old infants, we measured thresholds for detection of 50 msec, 2° diameter spots at 10° (parafoveal) and 30° (peripheral) eccentricities (Hansen and Fulton, 1995). Thresholds at these eccentricities in healthy adults are equal. To reduce the effects of inter subject variability, we also calculated for each subject the difference in log threshold between the two eccentricities, $_{10-30}$ (Reisner et al., 1997).

In the healthy, term born, dark adapted 10 week old infants, thresholds at both sites were higher (sensitivity lower) than those in adults. Additionally, the infants' parafoveal thresholds were 0.5 log unit higher than those in peripheral retina, whereas in adults, $_{10-30}$ = zero. After age 10 weeks, scotopic thresholds developed rapidly in term born infants, becoming adult like by age 6 months (Hansen and Fulton, 1999). Increases in quantum catch accompanying developmental elongation of the rod outer segment account for this maturation of rod mediated thresholds (Hansen and Fulton, 1999).

3.2.6.2. Parafoveal and peripheral thresholds in dark adapted ROP subjects: We tested the hypothesis that in *Mild ROP*, the rods in the late maturing parafoveal retina are more vulnerable to the effects of ROP than earlier maturing rods in the peripheral retina (Barnaby et al., 2007). The parafoveal site (10° eccentric) is within ROP zone I (Fig, 2) and the peripheral site (30° eccentric) is within zone II, as defined by ICROP (2005). Active ROP in zone I is associated with high risk of poor outcome (Early Treatment for Retinopathy of Prematurity Cooperative, 2003). We predicted that parafoveal thresholds would be more elevated than the peripheral thresholds in ROP subjects. We previously reported that the development of the rod mediated, dark adapted visual threshold in *Mild ROP* was delayed compared to that in term born infants. Parafoveal threshold development is also delayed in *Severe ROP*. The threshold values in the two groups overlap and, therefore, are combined in the cross-sectional analysis shown in Fig. 12; data from 26 new ROP subjects have been added to previously published control and ROP data (Barnaby et al., 2007; Hansen and Fulton, 1995, 1999; Reisner et al., 1997).

There was a significant delay in development of the parafoveal threshold in ROP subjects, both *Mild* and *Severe* (Fig. 12, left panel). Their parafoveal thresholds remained elevated (that is, sensitivity lower) relative to thresholds in *No ROP* subjects until at least 12 months. Peripheral threshold development was minimally delayed (Fig. 12, right panel). Parafoveal and peripheral threshold development in the term born and *No ROP* subjects was nearly identical. Analysis of data in individual subjects using a linear model indicated that the course of development of the parafoveal threshold in *Mild ROP* was significantly slower

than in *No ROP*. The course in *No ROP* was the same as that in term born controls (Barnaby et al., 2007).

The prolonged course of scotopic threshold development is evidence that even mild ROP alters development of the neural retina. The slower course at the parafoveal site suggests the late maturing parafoveal rods are particularly vulnerable to the ROP disease process, and the peripheral rods are less so. There are a number of possible explanations for the slow course of threshold development in ROP subjects. In ROP infants, rod outer segments may elongate more slowly than in term born infants, or ROP may alter the packing density (rods per unit area) of parafoveal rods with age. Redistribution of rod and cone photoreceptors in the parafovea occurs during simian development (Packer et al., 1990). Ordinarily, as the fovea develops, foveal cones pack together. Development of the fovea is delayed in infants with ROP (Isenberg, 1986). Perhaps the packing of nearby parafoveal rods and cones is also delayed or disordered (Hammer et al., 2008). A third possibility is that disorganized rod outer segments, as we found in an infant rat model of ROP (Fulton et al., 1999b), decrease the efficiency of photon capture and decrease the efficiency of the phototransduction cascade. If there were rod outer segment abnormalities in the *Mild ROP* subjects, they must have resolved sufficiently for the detection threshold to have become normal by approximately 12 months corrected age, or possibly compensatory post-receptor mechanisms, such as demonstrated in the spatial summation study (Hansen et al., 2014), come into play.

Among older children (N = 42) with a history of ROP, there is a significant association of elevated parafoveal threshold with high myopia (5D or more). Among 17 subjects with high myopia, 13 had elevated parafoveal thresholds and four had normal thresholds. Among the 25 with refractive error within normal limits for age (Mayer et al., 2001; Zadnik et al., 2003), only five had elevated thresholds and 20 had normal thresholds. Control subjects (N = 10) with myopia had normal thresholds at both sites (Reisner et al., 1997). These results show that altered rod mediated retinal function is associated with high myopia in ROP subjects.

3.2.7. Summary and conclusion—Using established psychophysical paradigms (spatial summation; temporal summation; adaptation to steady background lights; dark adapted threshold), we probed rod mediated vision in smaller patches of retina than possible using any electroretinographic procedures. The results of the scotopic spatial summation study show that the spatial organization of the ROP neural retina is coarser than normal; larger receptive fields may give the ROP retina an advantage for detection of light. The longer critical duration found in the temporal summation study is consistent with the prolonged kinetics of rod phototransduction found in the ROP retina. Deficits in function of both rod photoreceptor and post-receptor neural retina account for the ROP retina's altered adaptation to background lights. The development of the dark adapted threshold mediated by the late maturing parafoveal rods is delayed compared that mediated by the peripheral rods.

4. Central retina and cone and cone-driven responses

The central retina includes a region with specialized structures, namely the macula and fovea. Only cones are present in the fovea. Nonetheless, the majority of the retina's cones are peripheral to the fovea. Deficits in visual acuity are well described in ROP; the deficits range from subtle to severe and vary with ROP severity. (Reviewed in Fulton et al., 2009.)

4.1. Photopic full-field ERG

First, we provide an overview of cone and cone-driven function in the retina as a whole. Results obtained in term born infants and in mature subjects are briefly summarized. Then we address the cones and cone-driven function in ROP.

4.1.1. Normal development of photopic full-field ERG—We studied cone and cone-driven ERG responses to full-field stimuli in term born 4 and 10 week old infants. We found that the cone mediated responses are relatively more mature than the rod mediated responses in the same subjects. Cone sensitivity (S_{CONE}) and saturated amplitude (R_{CONE}) are 60% to 70% of that in adults' compared to rod photoresponse parameters which are only 40% to 50% of adults' (Hansen and Fulton, 2005a). In these healthy young infants, the b-wave stimulus-response function is monotonic rather than showing the adult's "photopic hill" with roll-off of response amplitude at high intensities (Lachapelle et al., 2001; Peachey et al., 1992; Rufiange et al., 2003; Rufiange et al., 2002; Ueno et al., 2004; Wali and Leguire, 1992). We reasoned that the OFF cone bipolar pathway was immature as the roll-off has been attributed to the OFF pathway (Hansen and Fulton, 2005a). We have conducted two new experiments to evaluate ON and OFF contributions to the cone ERG response in 10 week old term born infants.

We (Altschwager et al., 2015) recently recorded ERG responses to a 150 ms stimulus presented on a steady, rod saturating background that elicits both an ON response (b-wave) and an OFF response (d-wave) (Sieving, 1993). Representative responses from a term born infant and adult are shown in Fig. 13, upper panel. The implicit time of the d-wave was significantly longer in the 10 week old infants than in adults (Fig. 13, lower panel). There was no difference in d-wave amplitude between the groups (Altschwager et al., 2015). This is additional evidence of an OFF pathway immaturity in healthy 10 week old infants.

In the second experiment, we used a model of the photopic b-wave stimulus response relationship (Fig. 14) that combines the sum of a Gaussian function that assesses the OFF component and a logistic function that assesses the ON component to model the photopic b-wave (Hamilton et al., 2007). We recorded photopic stimulus response functions in healthy term born 10 week olds ($n = 6$) and adult controls ($n = 12$) to evaluate the relative contribution of ON and OFF activity. The amplitude at the peak of the Gaussian differed significantly between infants [$51.31 \pm 14.5 \mu\text{V}$ (SEM)] and adults [$108.92 \pm 8.10 \mu\text{V}$ (SEM)], consistent with an OFF pathway immaturity (Altschwager et al., 2015). These data provide additional evidence that the cone-driven OFF response in infants is relatively more immature than the ON response. The amplitude of the peak of the Gaussian was the only parameter of the Hamilton model that differed significantly between infants and adults.

4.1.2. Cone and cone-driven full-field ERG in ROP—We have found that ROP has relatively less effect on cone than on rod mediated ERG responses. Significant deficits in cone mediated responses are limited to subjects with severe ROP (Fulton et al., 2008). The maturation of peripheral cones is largely complete before onset of ROP, and it is the peripheral cones (rather than the foveal cones) that are the major contributors to the photopic ERG responses to full-field stimuli. Compared to rods, the cones, which have twice as many mitochondria and greater aerobic ATP production, may be protected against hypoxia (Perkins et al., 2003). Additionally, the cones' capacity to utilize endogenous glycogen may protect against the adverse effects of hypoxia and attendant hypoglycemia (Nihira et al., 1995).

We found that the cone photoresponse parameter S_{CONE} was normal in the *No ROP* subjects, minimally reduced in the *Mild ROP* group, and below the normal mean in *Severe ROP* subjects (Fulton et al., 2008). The shape of the ROP cone b-wave stimulus-response functions were the same as in age similar term born controls. Thus, the neurovascular disease ROP appears not to discriminate ON from OFF circuitry of the cone-driven pathways. The average amplitude of the b-wave responses to full-field stimuli is mildly attenuated in the ROP subjects. The amplitude (or response density) of the multifocal ERG (mfERG), which samples cone-driven activity in the central retina, is also reduced in ROP subjects (Fulton et al., 2005).

4.1.3. Summary and conclusion—Cone photoreceptor and cone-driven post-receptor neural responses to full-field stimuli are relatively less affected by ROP than are the rod and rod mediated responses. The cone photoreceptors, with the exception of those in the central retina, are already quite mature at the ages during which ROP is an active disease.

4.2. Multifocal electroretinogram (mfERG)

The topography of responses from a large number of small, discrete regions in the central retina is assessed by multifocal electroretinography (mfERG). This contrasts massed ERG response to full-field stimulation that is dominated by the peripheral retina (Hood, 2000; Sutter and Tran, 1992). The main contributor to the mfERG response is cone initiated activity in the bipolar cells (Hood et al., 2002).

4.2.1. Normal development of mfERG—The structure of the fovea and central retina does not reach maturity until well into childhood (Hendrickson and Yuodelis, 1984; Lee et al., 2015; Yuodelis and Hendrickson, 1986). To study central retinal function, we recorded mfERG responses evoked by a pattern of 61 hexagons on a 43° diameter region centered on the fovea in healthy, term born 10 week olds (Hansen et al., 2009). During testing, an observer continuously monitored the infant's fixation. Responses were recorded only when the observer reported that the infant was alert and looking at the center of the stimulus display; if the infant looked away, the segment was discarded and rerecorded. Control experiments showed that an observer could reliably report when adult subjects looked outside the central 2.8° hexagon and that changes of fixation within the central hexagon produced by an adult subject scanning along the border of that hexagon throughout the trial did not appreciably change the amplitude or implicit time of any component. Menz et al.

(Menz et al., 2004) also reported that small changes of fixation have no significant effect on the overall topography of the mfERG response.

We found that the waveform of the first order kernel of the mfERG was similar in term born infants and adults. In adults, response density is high at the center and decreases markedly from the center to the periphery. In infants, the topography of the responses differs dramatically; the response amplitude varies little with eccentricity. The density of cones and cone bipolar cells in the infant retina is flat whereas in adults, there is a marked gradient in cell density with eccentricity (Candy et al., 1998). These mfERG results demonstrate significant immaturity of the central retina beyond the well-known foveal immaturity (Hansen et al., 2009). Immaturity of the central retina as well as immaturities of the brain constrain infants' visual function (Candy et al., 1998; Curcio and Hendrickson, 1991; Leone et al., 2014; Mayer et al., 1995).

4.2.2. mfERG in ROP—In a study of mfERG responses from *Mild ROP* subjects tested in childhood and adolescence (Fulton et al., 2005), we found that the amplitude of the first order kernel was significantly smaller and latency significantly longer than in healthy, term born controls. The difference between ROP and control subjects was greatest at the center and least in the periphery. These results were confirmed in a recent study by Michalczuk et al. (Michalczuk et al., 2016). They found significant differences in P1 amplitude from subjects with mild (N=8) and severe, treated (N=7) ROP compared to those in term born controls (N=17). We hypothesized that ROP alters the developmental re-distribution of cells in the central retina and that bipolar cell distribution would be different in ROP subjects. OCT results (Hammer et al., 2008) from the same ROP subjects who had mfERG recording (Fulton et al., 2005) were consistent with this hypothesis, showing that the post-receptor laminae are thicker in ROP subjects than in controls.

Does prematurity alone alter central retinal function? Altschwager and colleagues (Altschwager et al., 2016) recorded mfERG responses from children and adolescent ROP subjects using 103 hexagons. The mean amplitudes in the *Mild ROP* and *No ROP* groups were similar and were smaller than in term born controls. Thus, preterm birth alone may be associated with mild but statistically significant deficits in central retinal function. This result complements the reported thickening of post-receptor retinal laminae in the central retina in *Mild ROP* and *No ROP* (Akerblom et al., 2012; Ecsedy et al., 2007; Lee et al., 2015; Yanni et al., 2013).

In an ongoing study, preliminary data from infants show that *No ROP* subjects have mfERG responses similar to those in term born 10 week olds. However, in ROP infants, mfERG responses are smaller than in *No ROP* and term born subjects.

4.2.3. Summary and conclusion—Responses recorded from small, discrete retinal regions are smaller in preterm subjects than in term born subjects, with the largest difference occurring at the center and decreasing toward the periphery. This functional abnormality is associated with structural abnormality of the central retina as demonstrated by OCT.

4.3. Retinal structure

The structure of the central retina has traditionally been studied using anatomic methods. More recently, noninvasive retinal imaging using optical coherence tomography (OCT) has opened access to a broader sample of subjects. Furthermore, importantly, the noninvasive OCT has enabled longitudinal studies of development (Lee et al., 2015).

More than 100 years ago, development of the fovea and central retina from preterm ages onward was illustrated in the Bach and Seefelder atlas of ocular anatomy (Bach and Seefelder, 1914). These drawings (Fig. 15) represent micrographs of cross sections of the macula at preterm, term, and post term ages. The laminar structure of the retina is evident even at preterm ages. The ganglion cells are found in the innermost retinal layer near the vitreous and the photoreceptors in the outer layer. As development goes forward, the cells in the inner retinal layers move away from the center (Yuodelis and Hendrickson, 1986). Invisible in these drawings of the photoreceptor layer is a rod free zone; only cone photoreceptors are present (Hendrickson et al., 2012). The average diameter of the rod free zone decreases from about 1600 μm at 22 weeks gestation to about 700–750 μm in adults and the average number of cones per 100 μm in the rod free zone increases from 14 to 42 during this period (Yuodelis and Hendrickson, 1986). At approximately 22 weeks gestation, the immature cones are short and fat. The length of foveal cone outer segments increase from about 3 μm in the newborn to as long as 40 to 50 μm in the adult (Yuodelis and Hendrickson, 1986). With increasing age, the cones mature, develop specialized inner and outer segment structures, become long and slender, and pack closely one to the other, which favors resolution of fine visual targets. The area of the rod free zone at 22 weeks gestation is 4 to 5 times that in the adult macula. Quite early, a vascular ring is laid down concentric with the center of the rod free zone, which is the site of the fovea. How the fovea is formed remains under study. Growth of the eye ball continues preterm to term to adult; the posterior retina, including the macula, keeps its same overall dimensions while the peripheral retinal area grows and expands enormously. At term, the diameter of the eye is approximately that of a U.S. dime (~16 mm), and in an adult, nearly that of a quarter (~25 mm) (Munro et al., 2015). Some believe that this growing force contributes to the formation of the fovea, perhaps pulling the retina over the vascular ring (Provis et al., 2013; Provis et al., 2000; Springer and Hendrickson, 2004a; Springer and Hendrickson, 2004b, 2005).

4.3.1. Retinal imaging: optical coherence tomography (OCT)—More recently, the capability to image the retina in the living eye with the same fidelity as afforded by light microscopy has provided new perspectives on the retina even in infants and in ROP subjects. Spectral domain OCT (SD-OCT) has been applied to the study of retinal development and to the study of effects of ROP on retinal structure (Dubis et al., 2012; Lee et al., 2015; Vajzovic et al., 2015). Retinal layers of OCT scans have been compared to those seen in anatomic studies (Spaide and Curcio, 2011; Vajzovic et al., 2012). Several studies have found that the fovea is shallower and the total retinal thickness in the fovea and parafoveal retina is greater in ROP subjects than in term born controls (Akerblom et al., 2012; Akerblom et al., 2011; Ecsedy et al., 2007; Maldonado et al., 2011; Recchia and Recchia, 2007; Swanson et al., 2014; Tariq et al., 2011; Wang et al., 2012). Fig. 16 shows representative OCT images of the

central retina from a term born subject and from subjects with *Mild* and *Severe ROP*, illustrating the shallower fovea in ROP.

4.3.2. Retinal imaging: scanning light ophthalmoscopy (SLO)—Adaptive optics scanning light ophthalmoscopy (AO-SLO) allows visualization of the cone photoreceptors. We studied the density and packing geometry of the extrafoveal cones using AO-SLO in *Severe ROP* (n = 5), *Mild ROP* (n = 5) and term born control (n = 8) subjects (ages 14–26 years) at temporal eccentricities 4.5°, 9°, 13.5°, and 18° (Ramamirtham et al., 2016). We used a multimodal adaptive optics retinal imager (Hammer et al., 2011; Hammer et al., 2012) to capture AO-OCT retinal images simultaneously to the SLOs. The SLO visualized individual cone photoreceptors *en face* while the OCT visualized retinal cross-sections in which the cone nuclei were visible in the photoreceptor layers; post-receptor laminae were also displayed. It has been shown that standard, confocal SLO imaging poorly visualizes photoreceptors if their outer segments are abnormal. Because our anatomic studies in a rat model of ROP found marked outer segment disorganization, we also used an offset aperture method (Chui et al., 2012b).

The offset aperture technique is believed to visualize the cone mosaic, regardless of outer segment morphology or alignment, by collecting the light scattered by the cone inner segments. The OCT, too, visualizes cones independent of their outer segment status. Effects of group (*Severe ROP*, *Mild ROP*, control), eccentricity, and aperture were evaluated. Confocal aperture (upper panel) and offset aperture (lower panel) images for a representative subject in each group are shown in Fig. 17 (Ramamirtham et al., 2016).

Before evaluating cone density and geometry, we were careful to account for potential differences in image magnification between our subjects. Because ROP eyes are characterized by a wider than normal distribution of refractive errors (see Section 5.1), we measured corneal curvature, anterior chamber depth, lens thickness and axial length and calculated the ‘angular subtense’ of 1° of retina for each individual subject by

$$\text{angular subtense} = \tan(1^\circ) \cdot (\text{axial length} - N'F') \quad (7)$$

where $N'F'$ is the position of the secondary nodal point of the eye. To calculate $N'F'$ we adopted Bennett’s step along formulae and supplied each subject’s measured values of axial length, anterior corneal curvature, anterior chamber depth and lens thickness. Dividing initial cone density (cells degree⁻²) by the square of angular subtense (mm²/degree²) specified density in cells mm⁻². Despite *Severe ROP* eyes being significantly more myopic than the *Mild* and control eyes, the angular subtense did not differ significantly between groups.

As predicted, we more easily discriminated cones in offset aperture (Fig. 17, lower panel) than in confocal images (upper panel) in eyes with *Severe ROP*. However, even in the offset images, there was evidence of cone loss and the packing pattern was less regular in *Severe ROP* than in *Mild ROP* and controls. To determine whether low cone density in *Severe ROP*

SLO images resulted from lower image quality or loss of cones, we also counted cones in the OCT. We did not find evidence of cone loss in these images. We evaluated the quality of the AO corrections in every eye and found that it was equivalent among groups. We suspect that the optical properties of the inner ROP retina or of the cones themselves are altered in a way that negatively affects photoreceptor imaging.

4.3.3. Summary and conclusion—In the ROP eye, the foveal pit is shallow, likely due to failure of the normal centrifugal migration of post-receptor structures. In the extrafoveal retina, evidence of dysmorphic cone photoreceptors and altered cone packing is obtained by adaptive optics imaging of the cells.

5. Eye growth and refractive development

It is well known that the retina is an important controller of eye growth and refractive development (Troilo, 1992; Troilo and Wallman, 1991). Furthermore, there is a vast body of literature supporting the role for local factors in the eye for the control of eye growth and refractive development (Smith, 2011; Smith et al., 2013; Wallman et al., 1987; Wildsoet and Schmid, 2000). Therefore, it is reasonable to expect that the functional deficits in the ROP retina would have significant biological association with ocular growth and refractive development. The mechanisms have yet to be identified.

5.1. Refractive error in ROP

The high incidence of ametropia, particularly myopia, in eyes born preterm demonstrate perturbations in ocular growth (Fielder and Quinn, 1997; Fledelius, 1996a, b; Larsson et al., 2003; Lue et al., 1995; O'Connor et al., 2002; O'Connor et al., 2006; Quinn et al., 2008; Quinn et al., 2013). While the molecular mechanisms underlying these abnormalities have yet to be fully specified, it is unlikely that they are the same as those in experimental myopia (Troilo, 1992; Troilo and Wallman, 1991).

Consistent with the results of others (Chen et al., 2010; Fledelius et al., 2015; Hellgren et al., 2016; Holmstrom and Larsson, 2005; Larsson et al., 2015; Quinn et al., 2008; Quinn et al., 2013), refractions performed on 284 ROP subjects (Fig. 18) who have been participants in our studies of retinal function and structure indicate that their frequency of ametropia increases with the severity of their antecedent ROP. Myopia outside the prediction limits for normal refractive development (Mayer et al., 2001; Zadnik et al., 2003) occurred more frequently in **Mild ROP** and **Severe ROP** than in **No ROP** subjects. The percent of subjects in each ROP group with ametropia (both myopia and hyperopia) is shown in Fig. 19. Myopia seldom occurred in the **No ROP** subjects. In fact, hyperopia was more common than myopia in the **No ROP** subjects, whereas we observed only a single case of hyperopia outside normal limits in **Severe ROP**.

5.2. Model of eye growth in ROP

We developed a model of eye growth and applied it to extant magnetic resonance images obtained from term and preterm born subjects (Munro et al., 2015). To account for the different ages at which our subjects were imaged, we summarized the growth of the

intraocular structures by fit of logistic growth curves (Eq. 5) to observations in term eyes and preterm eyes with and without ROP. The ages at half-maximum adult value ($x_{1/2}$) for nearly all intraocular structures indicated delayed growth in ROP eyes but not in **No ROP** eyes, suggesting that preterm birth alone does not markedly affect eye growth. The ROP eyes were characterized by steeper corneas, thicker lenses with both steeper anterior and posterior surface curvatures, and relatively short anterior segments. We expect that these anatomic changes increase the dioptric power of the anterior segment of the eye and shorten the posterior nodal distance, resulting in the commonly cited increase in incidence of myopia in ROP eyes, in spite of their shorter than expected axial length. It is worth noting that, despite the fact that the cornea is a less powerful convergent surface than the lens, the former contributes approximately two thirds of the total refracting power to the eye (~43/60 D) because the aqueous humor provides a weaker index of refraction than air (Freeman and Fincham, 1990). Thus, even if the scale of the ROP-induced changes to the lens is larger than to the cornea, they may have a lesser impact on spherical equivalent; our modeling suggests that this is the case. And a steep cornea may be a natural correlate of a smaller eye.

Studies in animals in which extra-ocular lenses were used to induce retinal hyperopia or myopia show that eye growth is respectively accelerated, or retarded, in order to minimize retinal defocus (Schmid and Wildsoet, 1997; Smith et al., 2014; Smith et al., 2003), an outcome that persists even if the optic nerve is transected or the accommodation system inactivated (Troilo, 1992; Wallman, 1993). Furthermore, regional defocus affects only that ocular region. Thus, the control of eye growth is almost entirely a local phenomenon (Smith, 2011; Smith et al., 2013; Wallman et al., 1987; Wildsoet and Schmid, 2000). Our studies of refractive development in a rat model of ROP elegantly recapitulate our human findings of delayed growth, including of the anterior segment (Chui et al., 2012a; Zhang et al., 2013). If the neural retina controls eye growth, the abnormally avascular peripheral ROP retina may, therefore, underpin some of the abnormalities in the ROP eye, especially of the posterior segment. The anterior segment abnormalities may be a consequence of alterations in posterior segment growth (e.g., perhaps the eye is simply “squeezed”), or their growth may be independently delayed. More work is needed to disentangle these explanations which are not mutually exclusive. In any event, the short-eyed myopia found in the ROP rat offer insights about ocular development that cannot be obtained using traditional models of induced ametropia. For example, we have found that dopamine levels are low in ROP eyes, despite their being short (Zhang et al., 2013) and note the long-recognized role of dopamine as a “stop-signal” for eye growth (Iuvone et al., 1991).

5.3. Summary and conclusion

Refractive errors are frequent in the eyes of former preterms; myopia is common in those with a history of **Severe ROP**. Although widely acknowledged that central and peripheral retina control eye growth and refractive development, the models that pertain to experimental ametropias do not explain ROP myopia. New testable hypotheses are needed to explain ROP ametropia.

6. Summary and future directions

There is an enduring deficit in the rod photoreceptor response which is detectable in early infancy and also a decade after the active ROP disease has resolved. In **Mild ROP**, rod-driven post-receptor deficits are significant in infancy but less at older ages. The psychophysical thresholds register the persistent effect of rod and rod-driven post-receptor dysfunction on vision (Barnaby et al., 2007; Hansen et al., 2016; Hansen et al., 2015; Hansen et al., 2014; Reisner et al., 1997) and characterize the effects of remodeling of the post-receptor ROP neural retina (Fulton and Hansen, 2000; Hansen et al., 2016; Hansen et al., 2015). For instance, the increased receptive field size, which is greater the more severe the ROP, is taken as evidence of compensation for the deficient receptor inputs to the post-receptor retinal neurons.

The rod dysfunction at early ages in both infants and rat models of ROP points to an important role for the rods in the pathogenesis of ROP. Rods have the highest demands for oxygen and energy of any cells in the body (Lau and Linsenmeier, 2012; Steinberg, 1987), outnumber the cones 20 to 1, and mature later than the cones (Hendrickson, 1993). The rods show an up-surge in developmental elongation of their outer segments and escalating oxygen demands to support the circulating current, turn-over of outer segment material, and phototransduction processes that are coincident with the onset of ROP (Fig. 1).

Normally the rods' oxygen is provided almost entirely by the choroidal circulation which normally matures in advance of the retinal circulation (Provis et al., 1997). In subjects with ROP, both at preterm ages (Erol et al., 2016) and in adolescence (Anderson et al., 2014), the choroid is too thin. These human data do not give temporal priority to the choroidal abnormality over the onset of ROP. However, in a rat model (Shao et al., 2011), the thin choroid is established by age 7 days, just when the rat rod outer segments are beginning to elongate along with concomitant rapid increase in rhodopsin content of the retina, and thus well in advance of the age at which the retinal vascular abnormalities of ROP are seen. Possibly the thin choroid in the ROP rat is among the factors that contribute to dysfunction and dysmorphia of the rods, abnormalities that are found despite having normal rhodopsin content (Dodge et al., 1996; Fulton et al., 1999a).

As rod outer segment development goes forward, the energy and oxygen needed to power the circulating current, phototransduction processes (Fulton and Hansen, 2000; Fulton et al., 1995), and turn-over of outer segment material (Tamai and Chader, 1979) may be unmet by an abnormal, thinned choroid. Oxygen levels in the choroid register the ambient oxygen conditions (Barnett et al., 2010; Shao et al., 2011) used to induce the rat retinopathy; and in the preterm infants, oxygen levels are perturbed by the infants' cardio-pulmonary condition and its management. Both hypoxia and hyperoxia are injurious to immature rods (Wellard et al., 2005). It appears plausible that the thin choroid, which does not auto-regulate to counteract the hypoxia or hyperoxia, deprives the rod of its customary oxygen, and so injures the rod. The demand for oxygen is shifted to non-choroidal sources, namely the inner retina (Cringle and Yu, 2010; Cringle et al., 2006). Thus, the stage is set for the hypoxic retina to instigate the retinal vascular response which is the clinical hallmark of ROP.

6.1. Implications for eye growth and refractive development

ROP eyes are notorious for developing high myopia in infancy and early childhood (Quinn et al., 2008; Quinn et al., 2013; Quinn et al., 1992). The myopia both in the children and rat model (Chui et al., 2012a; Zhang et al., 2013) have led to the term “small eye myopia”. The ROP posterior segment and sclera grows much less than expected for the degree of myopia (Chui et al., 2012a; O’Connor et al., 2006; Zhang et al., 2013). As reviewed above, the choroid in the rat model of ROP and also in human ROP is too thin. On average, the choroid is thinned by only 50 to 60 microns in ROP adolescents (Anderson et al., 2014), whereas the dioptric change in axial length (despite the “small eye myopia”) is measured in millimeters (Cook et al., 2003, 2008; O’Connor et al., 2002; O’Connor et al., 2006). Thus, if the choroid is involved in the pathogenesis of ROP myopia, it must be through molecular mechanisms rather than directly controlling optical length of the eye. In experimentally induced ametropia, molecular mechanisms are involved in the control of scleral growth as well as contributing to the dioptric shift of the photoreceptor lamina at the posterior pole (Nickla and Wallman, 2010). But how would limited growth of the sclera and axial length contribute to the other features of the myopic ROP eye, namely the thick lens and the steep cornea? The answer to this question is unknown.

Besides retarded scleral growth, the role of the peripheral retina in the control of ROP eye growth and refractive development warrants consideration. The CRYO-ROP and ETROP studies (Quinn et al., 2008; Quinn et al., 2013; Quinn et al., 1992) have shown that high myopia (>5 diopters) is common in eyes treated by ablation of the peripheral retina (ETROP, 2003). Approximately half of eyes treated by laser developed high myopia (>5 diopters); only ~25% of eyes treated by intravitreal injection of an anti-VEGF agent developed high myopia (Geloneck et al., 2014). The mechanisms by which the peripheral retina is involved in control of overall eye growth and refractive development have been investigated in chick, tree shrew, marmoset, and rhesus macaque (Zhu et al., 2013). We note that in experimental ametropia, peripheral defocus or deprivation has significant effect on eye shape and refractive error, whereas foveal vision is not essential for refractive development (Huang et al., 2011; Smith, 2011; Smith et al., 2014). Therefore, the abnormal foveal structure in severe ROP (Fig. 16) may not be a driving force for the development of myopia in these eyes. This is a testable hypothesis.

6.2. Implications for management and treatment of ROP

Noninvasive therapy may be possible by controlling light exposure. The aim is to decrease the energy demands by the developing rods. Rods use less energy in the light because light suppresses the dark current, that is, the circulating current, the maintenance of which requires considerable energy (Ames et al., 1992; Winkler et al., 2000). Thus, at ages during which ROP is an active disease, a low level of light is predicted to have a beneficial effect on the rods, and in turn, on ROP. Indeed, putative reduction of the rods’ energy demands by pharmacologic intervention reduced the severity of disease in a rat model of ROP (Akula et al., 2010b). The previous LIGHT-ROP trial (Reynolds et al., 2002; Reynolds et al., 1998), conceived and run in the era when photic injury to the retina by military and medical equipment exposures was of great concern, was based on the premise that light was injurious to the retina. Limiting light exposure to the eyes of premature infants had no effect on the

incidence and severity of ROP (Jorge et al., 2013; Phelps and Watts, 2000, 2001). However, a low, non-injurious level of light, rather than dark, is known to decrease the circulating current. Noninvasive therapy may be possible by controlling light exposure.

In the preterm infant, during the ages at which there is a mismatch between the energy demands of the rods and the incompletely vascularized preterm retina (Fig. 1), the strategy would be to exploit the power of light to regulate the circulating current. Light could be used to offset the deleterious effects of the ambient oxygen environment, either hyperoxia or hypoxia, both of which are injurious to photoreceptors (Wellard et al., 2005). The fetus is normally hypoxic relative to the extra-uterine environment. If born preterm, high oxygen administered to counter the immaturity of the infant's lungs leads to periods of hyperoxia. Typically, the developing retinal vasculature has reached the ora serrata by term (Fig. 1), but this hyperoxia dampens the expression of pro-angiogenesis growth factors, such as VEGF, and inhibits normal vascularization of the retina. Later, when the infant's pulmonary status has stabilized, a return to room air is mandated. This, in turn, causes hypoxia in the unsupplied inner retina, evidenced by high levels of retinal VEGF (Hartnett, 2010). Thus, the ROP retina is assailed by periods of both hyperoxia and hypoxia—but both of these states can be specifically, and noninvasively, targeted by controlling the ambient light.

During the hyperoxic stage, maintenance of the infant in total darkness would maximize the energy demands of the rod photoreceptors by permitting the circulating current to continue unabated. This might serve to absorb injurious oxygen and encourage normal vascularization of the peripheral retina. During the hypoxic stage, which is characterized by pathological angiogenesis, continuous light, even at relatively low levels, would damp the circulating current, diminishing the angiogenic signal and protecting the retina from both hypoxic damage and neovascularization. Turnover of outer segment material, another function of the energy greedy rods, may also be beneficially manipulated by the schedule of light exposure (Besharse and Hollyfield, 1979; Besharse et al., 1977; Grace et al., 1999; Green and Besharse, 2004; LaVail, 1976). In short, selection of timely lighting conditions may first promote normal angiogenesis and then decrease pathologic angiogenesis, all the while protecting the immature rods. This offers a new, noninvasive, nondestructive approach to ROP management. Shrewd manipulation of light may also be exploited to benefit patients with other neurovascular retinal diseases (Miller et al., 2013). The results of the CLEOPATRA study (Sivaprasad et al., 2014), in which nighttime light masks are used to treat diabetic retinopathy, are awaited.

6.3. Conclusion

We have presented evidence demonstrating that the photoreceptors and post-receptor retinal neurons play a role in the ROP disease processes. We also introduce a new perspective on the control of ROP eye growth and refractive development. Our investigations of ROP show slow rod activation, noise in the rods, vulnerability of later-maturing parafoveal rods, and compensatory post-receptor remodeling of spatial vision,. This body of knowledge leads us to propose a straightforward, noninvasive, non-destructive treatment of ROP using light.

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Article Highlights

- Retinopathy of prematurity (ROP) involves the neurosensory retina.
- The status of the immature rods may be a driver of ROP pathogenesis.
- Evidence of photoreceptor injury persists years after ROP is an active disease.
- Post-receptor retina reorganizes to compensate for deficient photoreceptor inputs.
- The late maturing central retinal is especially vulnerable to the effects of ROP.

Figure 1.

Rhodopsin content and large vessel coverage of the temporal retina. The purple curve shows the developmental increase in retinal rhodopsin content in the human eye, normalized to the median adult rhodopsin content, 7.19 nmol/retina (Fulton et al., 1999a). At age 5-weeks post-term, rhodopsin content reached 50% of the adult value (95% confidence interval: 0–10 weeks). Data from Fulton et al. (Fulton et al., 1999a) copyright Association for Research in Vision and Ophthalmology. The red arrow indicates the onset of prethreshold ROP at 32 weeks gestation (Palmer et al., 1991) which coincides with the period of rapid developmental increase in rhodopsin content. The points show percent vessel coverage, estimated from Figure 6 in Provis, 2001 (Provis, 2001); a logistic growth curve (brown line) is fit to the points.

Figure 2.

Rod ring superimposed on diagram used to describe location (zones) and extent (clock hours) of retinopathy (ICROP, 2005). The “rod ring” (Hendrickson, 1994), indicated by the purple oval band, is an annular region with a high density of rods that is concentric with the fovea and extends horizontally to the approximate eccentricity of the optic nerve head. N indicates nasal; T indicates temporal.

Figure 3.

Sample rod mediated full-field ERG records and model fits of the a-wave and b-wave from a 1 year old subject with *Severe ROP*. Upper panel: Dark adapted ERG responses to a series of blue flashes increasing in strength from top to bottom, left to right. The troland values are indicated to the left of each trace. Calibration bars pertain to all waves. Lower left panel: The solid lines show the first 40 ms of the response to the five brightest flashes; the red dashed lines show fits of Equation 3 to the a-waves. The parameters rod photoreceptor sensitivity (S_{ROD}), amplitude of the saturated rod response (R_{ROD}), and a brief time delay (t_d) are indicated. Lower right panel: The points indicate b-wave amplitude plotted as a function of stimulus intensity; the curve shows the fit of Equation 4 to the b-waves. The parameters post-receptor sensitivity ($\log \sigma$) and saturated amplitude (V_{MAX}) are indicated.

Figure 4.

Growth curves for ERG parameters and rhodopsin. The photoreceptor parameters (S_{ROD} and R_{ROD}), and the post-receptor parameters (σ and V_{MAX}) are plotted as a function of log age. Parameters of these curves are shown in Table 3. Data from all but 14 of these term born subjects have been reported previously (Fulton & Hansen, 2000; Fulton et al., 2009). The rhodopsin growth curve (Fulton et al., 1999a), normalized to the median adult value, is also shown.

Figure 5.

Photoreceptor sensitivity (S_{ROD}) and post-receptor sensitivity ($\log \sigma$) for two subjects tested in infancy and later in childhood. One subject had a history of *Mild ROP* and the other a history of *Severe ROP*.

Figure 6.

Photoreceptor sensitivity (S_{OD}) and post-receptor sensitivity (σ) for ROP subjects and term born controls. For S_{OD} (left panel) and for σ (right panel), the mean (± 1 SEM) for each group is plotted as the log difference from normal for age in infancy (median age 10 weeks) and in childhood (median age 10 years). Data from 85 of the ROP subjects were reported in Harris et al. (2011); 13 new ROP subjects were included in the current analysis.

Figure 7.

Deficits in post-receptor sensitivity ($\log \sigma$) as a function of the sum of deficits in photoreceptor sensitivity (S_{ROD}) and saturated amplitude (R_{ROD}) in term born subjects. Data are shown for 4 and 10 week old infants and for adults. Each point represents data from an individual subject. The range of deficits in adult post-receptor sensitivity is indicated by the horizontal red dashed lines, the range of adult photoreceptor sensitivity by the vertical red dashed lines; the median adult value is at (0,0). The dotted line has a slope of 1.0. Data from all but 14 of these subjects were reported in Fulton et al., 2009; data from 14 new term born subjects were added.

Figure 8.

Deficits in post-receptor sensitivity ($\log \sigma$) as a function of the sum of deficits in photoreceptor sensitivity (S_{ROD}) and saturated amplitude (R_{ROD}) in the three groups of ROP subjects [median age 7.5 (range 0.1 to 23.3) years]. Each point represents data from an individual subject. All other features of the graph are the same as in Figure 7. Data from 70 of the subjects were reported in Harris et al. (2011); data from 13 new ROP subjects were added. Subjects tested using skin electrodes in the Harris study were excluded from the analysis because of the uncertainty in specifying saturated rod amplitude (R_{ROD}) from skin electrode recordings.

Figure 9.

Rod-mediated spatial summation. Upper panel: Spatial summation functions are shown for a representative subject from each group. Middle panel: Log threshold is plotted as a function of log stimulus area. Average D_{CRIT} values are used to construct a summary function for each group. For small spots, threshold depends on the total energy of the stimulus (slope = -1 on log-log coordinates) up to a critical diameter (D_{CRIT}). For stimuli larger than (D_{CRIT}), threshold changes little (slope ≈ 0). The two lines intersect at D_{CRIT} . Lower panel: Values of D_{CRIT} are plotted for individual subjects in the three ROP groups and for each term born control. The mean D_{CRIT} value for each group is indicated by the color-coded dotted line. Data from Hansen et al., 2014; copyright Association for Research in Vision and Ophthalmology.

Figure 10.

Rod mediated temporal summation. Upper panel: Temporal summation functions are shown for a representative subject from each group. Middle panel: Log threshold is plotted as a function of log stimulus duration. Thresholds were recorded for seven stimulus durations (10 to 640 ms); the x-axis has been truncated to emphasize the range of durations that show complete summation. For brief stimulus durations, threshold depends on the total energy of the stimulus (slope = -1 on log-log coordinates) up to a critical duration (T_{CRIT}). For stimuli longer than T_{CRIT} , threshold changes little (slope ≈ 0). The two lines intersect at T_{CRIT} . Lower panel: Values of t_{CRIT} are plotted for each subject in the three ROP groups and for each term born control. The mean T_{CRIT} value for each group is indicated by the color-coded dotted line. Data from Hansen et al., 2015; copyright Association for Research in Vision and Ophthalmology.

Figure 11.

Rod increment threshold functions and deficits in dark adapted threshold (T_{DA}) and the Eigengrau (A_0). Upper panel: Log threshold in *No ROP*, *Mild ROP*, and *Severe ROP* as a function of log background intensity; the function for term born controls (not shown) does not differ significantly from that in the *No ROP* subjects. The stimulus was a 50 ms, 5° diameter flash presented 20° eccentric. The curves plot Equation 6 using median T_{DA} and A_0 from each group. Dotted lines: For the *No ROP* curve, the horizontal asymptote is at T_{DA} ; the oblique line (slope = 1) intersects T_{DA} at A_0 , the background level that elevates threshold by a factor of 2 (0.3 log units). Lower panel: Deficit in T_{DA} plotted as a function of deficit in A_0 . Each point represents an individual subject. The range of T_{DA} values in term born controls is indicated by the horizontal red dashed lines, the range of control A_0 values by the vertical red dashed lines; the median control value is at (0,0). The prediction for a preadaptation site effect is shown by the dotted diagonal line with slope = 1.0. Data from Hansen et al., 2016; copyright Association for Research in Vision and Ophthalmology.

Figure 12.

Rod mediated, dark adapted thresholds. Mean ($\pm$ SEM) threshold in term born, **No ROP**, and **ROP** subjects (both **Mild** and **Severe**) is plotted as function of age in the parafovea (10° eccentricity; left panel) and in the periphery (30° eccentricity; right panel). The analysis includes 29 term born control subjects and 127 preterm subjects, many of whom were tested at more than one age; data obtained at all sessions were included in the analysis. Twenty-six new ROP subjects have been added; 101 of the 127 ROP subjects were reported by Reisner et al., 1997 and Barnaby et al., 2007; all 29 control subjects were reported by Hansen & Fulton, 1995 and Hansen & Fulton, 1999.

Figure 13.

ERG ON and OFF responses to a long flash. Upper panel: ERG responses to a 150 msec full-field flash presented on a steady background recorded from a term born 10 week old infant and from an adult control subject. The ON and OFF responses are indicated. The time course of the stimulus is represented by the horizontal line above the x-axis. Lower panel: Implicit time of the OFF response (d-wave) for individual 10-week old infants and adults. The horizontal dotted lines indicate the median for each group. Data from Altschwager et al, 2015 ARVO presentation; copyright Association for Research in Vision and Ophthalmology.

Figure 14.

Photopic b-wave stimulus-response relationship. Upper panel: The model of the photopic b-wave stimulus-response relationship combines the sum of a Gaussian function that assesses the OFF component (solid green curve) and a logistic function that assesses the ON component (solid blue curve) to model the photopic b-wave (dashed red curve) (Hamilton et al., 2007). Lower panels: The amplitude of the b-wave is plotted as a function of flash intensity in a 10 week old term born infant (left) and an adult control subject (right). The red dashed curve in each of the lower panels shows a fit of the model to the data. Data from Altschwager et al, 2015 ARVO presentation; copyright Association for Research in Vision and Ophthalmology.

Figure 15.

Drawings of macular cross sections. These drawings represent micrographs of cross sections of the macula at ages ranging from preterm to post term. From Bach and Seefelder, 1914; digital image from <https://archive.org/stream/b21288008#page/n3/mode/2up>

Figure 16.

Optical coherence tomography (OCT) images. OCT images from a term born control subject and subjects with *Severe* and *Mild ROP*; the central $\sim 15^\circ$ ($\pm 7.5^\circ$ from the center of the pit) are shown. All three subjects were adolescents (age 13–18).

Figure 17.

Adaptive optics scanning light ophthalmoscopy (AO-SLO) images. Representative registered and averaged images ($0.25^\circ \times 0.25^\circ$) obtained from a term born subject, a **Mild ROP** subject, and a **Severe ROP** subject at four temporal eccentricities (4.5° , 9° , 13.5° , and 18°) using confocal aperture (upper panel) and offset aperture (lower panel) are shown. Adapted from Ramamirtham et al., 2016; copyright Association for Research in Vision and Ophthalmology.

Figure 18.

Spherical equivalent refraction in ROP subjects as a function of age. Data are shown for 1,087 refractions of one eye in 284 ROP subjects. For subjects who had ERG recording and/or retinal image, data from the tested eye was used; for subjects who participated in the binocularly performed psychophysical experiments, data from the left eye was used. One to 22 (median = 2) refractions were performed on an individual; all refractions are shown. Upper panel: 309 refractions from 44 **Severe ROP** subjects; middle panel: 581 refractions from 151 **Mild ROP** subjects; lower panel 197 refractions from 89 **No ROP** subjects. Data from 279 of the subjects and 1,027 of the refractions were reported by Moskowitz et al., 2016; data from five new subjects and 50 new refractions have been added. The black lines indicate the 95% prediction limits for normal refractive error, plotted using values from Mayer et al. (2001) for 1 to 48 month olds and from Zadnick et al. (2003) for school aged children.

Figure 19.

Percent of individuals with ametropia in each ROP group. Each of the 284 subjects whose data are shown in Figure 18 was counted only once. *Severe ROP*, n = 44; *Mild ROP*, n = 151; *No ROP*, n = 89.

Table 1

Categories of ROP subjects (Fulton et al., 2009).

ROP Category	Clinical Features
Severe	Stage 3 [*] ; treated
Mild	Stage 1 or 2, Zone II or III [*] ; resolved spontaneously
None	No ROP ever

^{*}
(ICROP, 2005)

Table 2

Average values for term born 10 week old infants and adults used for calculation of retinal illuminance.

	10 week old infant	Adult
Pupil diameter (mm)	5.2	8.0
Posterior chamber depth (mm)	12.3	16.2
Transmissivity of the ocular media	0.63	0.43
Retinal illuminance produced by 1 cd s/m ²	0.0884	0.0824

Table 3

Growth curve parameters of scotopic ERG derived from healthy term born subjects (N=136).

Parameter	R_{MAX} (Adult median)	$X^{1/2}$ (weeks)	n
S_{ROD} (log scot td ⁻¹ s ⁻³)	1.95	12.5	0.65
R_{ROD} (μVolts)	385	12.3	0.64
Log σ (scot td s)	-0.80	13	0.80
V_{MAX} (μVolts)	408	8.2	0.93

Table 4

Full-field scotopic ERG parameters in healthy term born subjects (mean, SD).

Parameter	4 week olds 22–39 days (N = 39)	10 week olds 63–78 days (N = 23)	Adults 8–60 (median 24) years (N = 74)
S_{ROD} (log scot td ⁻¹ s ⁻³)	1.34 (0.06)	1.63 (0.12)	1.95 (0.08)
R_{ROD} (μVolts)	152 (58)	167 (53)	374 (88)
Log σ (scot td s)	0.27 (0.58)	−0.30 (0.24)	−0.78 (0.13)
V_{MAX} (μVolts)	174 (83)	204 (60)	410 (82)

Table 5

Critical values for spatial and temporal summation.

Spatial Summation - D_{CRIT}			
Group	N	Mean	SD
Severe ROP	7	2.37	0.46
Mild ROP	17	1.79	0.36
No ROP	16	1.23	0.17
Term	7	1.30	0.16

Temporal Summation - T_{CRIT}			
Group	N	Mean	SD
Severe ROP	7	147.6	18.88
Mild ROP	23	127.5	19.89
No ROP	15	101.1	16.46
Term	5	101.0	19.47