Retinal and Perceptual Responses to Peripheral Blur

A thesis presented to the graduate faculty of
the New England College of Optometry in partial fulfillment
of the requirements for the degree of Master of Science

Emily Bomee Jeong

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This manuscript has been read and accepted by the Thesis Examination committee in satisfaction of the thesis requirement for the Degree of Master of Science.

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Abstract

Retinal and Perceptual Responses to Peripheral Blur

Background:

Previous studies indicate that normal blur sensitivity and peripheral retinal image quality are necessary for normal ocular development and accurate regulation of eye growth. Two important remaining questions are the objective of the present studies: which area(s) of the retina and what as aspects of blur are important in the process of emmetropization? Our work will increase the understanding of retinal and perceptual responses to blur in peripheral vision.

Methods:

We conducted two cross sectional studies in a group of healthy young adults with emmetropia (n=12; Mean SE: -0.16 ± 0.35D) or myopia (n=15; Mean SE: -3.26 ± 2.25D). The first study investigated retinal ERG responses to different types of simulated optical blur: Defocus (DEF), Spherical Aberration (SA), Oblique Astigmatism (J45), and a combination of Defocus and Astigmatism (J45+DEF). Blur was applied to naturalistic images ("dead leaves") at three different eccentricities: across the entire image (0-Deg), in the periphery keeping the central 6 degrees clear (6-Deg), and in the periphery keeping the central 12 degrees clear (12-Deg). For the second study, we used psychophysical procedures to evaluate perception of blur – Intrinsic Blur and Perceptual Criterion thresholds - for the same images and conditions. For this task, the simulated optical blur was applied to one of four quadrants and subjects were asked to indicate which quadrant was perceived to be the blurriest. Lastly, results from both studies were used to assess correlations between retinal and perceptual responses to peripheral blur.

Results:

An effect of eccentricity was found in the retinal responses for DEF and SA (not for the other two types of blur): decreased pERG responses were observed as blur was presented at eccentricities closer to the fovea. Reponses were lower for the 6-Deg images compared to 12-Deg images ($t=2.488$, $p=0.048$), but no differences were found between the 0-Deg and 6-Deg images, or the original non-blurred and the 12-Deg images. There was no refractive error effect in the retinal pERG responses. There was, however, an effect of refractive error for Intrinsic Blur, with myopes showing higher Intrinsic Blur levels for all types of blur except DEF compared to emmetropes ($F=0.679$, $p=0.449$, $\eta^2=0.023$). There was also an effect of eccentricity in the perception of blur, with higher levels of Intrinsic Blur and Perceptual Criteria when blur was presented more peripherally. Differences were noted between the 0-Deg and 6-Deg images, but no differences between the 6-deg and 12-Deg images. The effect of eccentricity in Intrinsic Blur was higher in myopes compared to emmetropes ($p<0.001$, $\eta^2=0.092$). Significant positive correlations were found for emmetropes between retinal and perceptual responses for DEF (0.1μm; $r=0.720$, $p<0.029$, 0.3μm; $r=0.686$, $p<0.041$) and SA (0.1μm: $r=0.820$; $p<0.007$, 0.3μm: $r=0.770$, $p<0.015$, and 0.5μm: $r=0.887$; $p<0.001$) blur, and for myopes only for SA blur ($r=0.61$, $p<0.033$).

Conclusions:

Retinal and perceptual responses to simulated optical blur show most detrimental effects when blur is presented between 6 and 12 degrees eccentricity, suggesting this are may be the location of blur decoding signals for adults with emmetropia or myopia. No differences were noted in retinal

responses between these two refractive groups, indicating that if there is an effect of retinal responses in myopia development, this is compensated for later in life. On the other hand, an effect was found in Intrinsic Blur thresholds between emmetropes and myopes, with noisier visual systems in myopes. No differences were noted for Perceptual Criteria, it appears that once blur is detectable, the ability to differentiate blur of myopes is comparable to that of emmetropes. When comparing these results with our previous data on perception of Gaussian blur, we conclude that the higher Intrinsic Blur levels in myopia is likely due to optical factors. Our results of different perception and retinal responses to DEF than SA suggest that there may be aspects of image quality other than defocus blur driving blur encoding and emmetropization, further studies in children are needed to prove this hypothesis.

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1. General Introduction

1.1 Myopia: a Failure of Emmetropization

Myopia has become a major public health concern with rapidly increasing prevalence over the last few decades[1]. Myopia is an epidemic in certain parts of the world[2], and poses an increased risk of visual impairment and blindness[3], decreased quality of life, and a heavy global economic burden[4]. Correcting myopia through optical means or refractive surgery does not decrease these risks. There is an urgent need to further understand the mechanisms of myopia development and progression, to ultimately create successful prevention and treatment therapies.

In order for an eye to successfully emmetropize and not develop myopia, it needs to accurately grow axially so that the optical power matches the length of the eye and images of far objects fall at the retina. Myopia occurs when this process of emmetropization fails and the eye continues to grow longer[5].

The specific mechanism whereby emmetropization fails in some children is yet to be determined. It is known, however, that regular exposure to adequate visual stimuli during early childhood is important to accurately regulate eye growth, and that retinal blur causes excessive elongation of the eye, resulting in myopia[6]. Two important remaining questions are: (1) which area(s) of the retina are important in the process of emmetropization? and (2) what type of blur causes a failure of emmetropization?

1.2 Retinal Image Quality and Blur in Myopia

Blur is a visual signal used for everyday vision, for example to accommodate and accurately focus images located at different distances in space on the retina, but also plays an important role as a feedback signal for emmetropization. Any disruption of the process to accurately detect blur visual signals may prevent the growing eye from the feedback needed to stop elongating and therefore result in the development or progression of myopia. It has been shown in animal models that placing negative lenses (causing hyperopic defocus blur) causes myopia; and even more interestingly, that inducing a myopic blur may result in recovery from myopia[7–10]. These findings have yet to be directly translated into humans. The leading hypothesis from these studies is that

hyperopic defocus blur can cause myopia and myopic defocus blur may reverse it[11]. It is important to note that placing optical lenses in front of the eye has other consequences on the retinal image quality than merely defocus, for example, modification of the retinal image size and the accommodation response (which in turn affects spherical aberration - SA)[12]. Although it is generally acknowledged that retinal image quality plays a crucial role in emmetropization and the development of myopia, the specific aspects of retinal image quality that are important for signaling eye growth are yet to be determined. To bring light to this question, we investigate in this thesis how the retina responds to different types of simulated blur and how these are subjectively perceived in myopes compared to emmetropes.

In addition, differences in blur sensitivity and perception between emmetropes and myopes have been noted in previous studies. Rosenfield & Abraham-Cohen[13] found that there were significant differences between myopes and emmetropes mean blur threshold meaning that myopes have decreased sensitivity to blur. They suggest that these findings could mean that myopes may have more difficulty detecting retinal defocus, which could be resulting in axial elongation and ultimately, myopia[13].

1.3 Peripheral Vision and Peripheral Blur in Myopia

Previous studies on animal models have shown evidence of the role of peripheral blur on the development of myopia[14]. For example, rhesus monkeys are able to emmetropize normally even when their central retinas are ablated. However, when there is interference with the peripheral retina, their eyes progress towards myopia[14]. These studies have further shown that visual signals directly at the fovea may not be required for normal emmetropization and that peripheral retinal signals play a bigger role in eye growth[15].

Findings from animal models and humans studies further emphasize the role of peripheral blur in myopia and current models of emmetropization generally agree on the importance of peripheral retinal control[14] as it has been shown that peripheral blur with or without clear central vision may induce myopia[16]. Ciuffreda et al.[17] proposed in 2007 that myopia development is a result of the interactions between foveal and peripheral retina visual input. They found that mean blur detection and blur discrimination thresholds increased with eccentricity and that objective blur thresholds were larger in myopes compared to emmetropes in the visual periphery periphery[17]. Our group has

recently shown that monocular sensitivity to blur across the periphery in myopes is decreased compared to emmetropes, but the effect dissipates when images are observed under binocular conditions[12]. These findings agree with those by Ciuffreda et al.[17] In a related study, Labhishetty et al.[18] investigated the effect of non-foveal retina stimulation and its effect on accommodative responses when the fovea was simultaneously stimulated or not. The rationale for their paradigm is that in everyday life, it is uncommon for just either the peripheral retina or the fovea to be stimulated individually or separately. Their study found that stimuli presented in the periphery (8 degrees) exhibited a significant effect on accommodation, overriding the effect of foveal blur. Their results indicate that peripheral stimuli affect the accommodation response to a central target. Their findings carry the implication that peripheral retinal image quality is important in emmetropization. In addition, a number of studies have found a significant effect of near peripheral blur (all at around 8 degrees centricity) in the accommodation response even if the target at the fovea is clear[19,20]. These findings provide a basis for our hypothesis that the near peripheral retina, within 6 to 12 degrees, may exhibit higher sensitivity to blur and thus, may play a larger role in emmetropization than that of the fovea.

The idea that peripheral blur is important in myopia development has also been applied to clinical trials of myopia control treatments. With evidence of decreased blur sensitivity and discrimination at the retinal periphery in myopes compared to emmetropes, methods for myopia control have targeted this area in aims to reduce myopia progression. For example, multifocal contact lenses that correct peripheral hyperopic blur in addition to central myopic refractive error have been shown to slow down axial length growth in several studies[15] and are now approved by the FDA for the clinical use of myopia control in the US[21]. In a recent randomized trial (BLINK study), Walline et al.[22] found that high add power multifocal lenses (but not median add power lenses) resulted in less myopia progression compared to single vision contact lenses[22]. Orthokeratology lenses are another treatment for myopia control that may work via manipulation of peripheral blur[23]. Orthokeratology lenses correct myopia by flattening the central cornea while redistributing corneal epithelial cells to the mid periphery. Peripheral optics, lower and higher levels aberrations, are also altered following these changes in corneal shape[24]. The incremental flattening towards the center of the results in light being correctly refracted onto the entire retina[23]. Similarly to the use of multifocal soft contact lenses, the manipulation of peripheral image quality with orthokeratology lenses has been hypothesized to be the mechanism for their effect in

controlling myopia progression[24]. Several studies have indeed proven slower progression of axial length growth in children wearing orthokeratology lenses compared to control groups wearing glasses or other types of contact lenses[23,24].

We have recently evaluated peripheral blur perception measuring sensitivity to blur. This study will be further explained in chapter 4.

In this recent study[12] , we found decreased sensitivity to Gaussian blur with more peripheral eccentricities under both monocular and binocular conditions in adults with emmetropia or myopia. Interestingly, myopes showed significantly reduced sensitivity to blur under monocular conditions, but their sensitivity improved under binocular conditions. Gaussian blur is not as relevant to emmetropization as optical blur, as shown in previous animal models. We now therefore aim to evaluate the effect of different types of peripheral optical blur in the detection and discrimination of blur by adults with emmetropia or myopia.

1.4 Electroretinogram (ERG) Responses in Myopia

The ERG test is used to measure the electrical activity generated by retinal cells in response to a specific stimulus. The recorded electrical response is elicited by a change in the retinal potential caused by changes in the flux of transretinal ions. The quality of the retinal image is highly dependent on the optics of the eye, and it has been shown that pattern ERG (pERG) responses change depending on the amount of defocus blur[25], with higher responses when there is no blur (i.e., emmetropia)[25]. Recently, Chin et al. used multifocal ERG's to measure retinal responses to stimuli with simulated defocus presented at different eccentricities[26]. They found larger responses to blur in the peripheral regions with stronger responses in the area corresponding to 8-12 degrees of eccentricity. From this finding and the perceptual studies described in the previous section, it appears that the human retina may have a decoding system for optical blur located in the near retinal periphery.

Electrophysiological studies have further shown that there are differences between emmetropes and myopes in multifocal ERG responses. Specifically, it has been found that myopes exhibit reduced amplitudes of responses and that these types of responses are more pronounced in the periphery[27]. Ismael et al.[28] showed similar results, where higher myopes had decreased multifocal ERG responses that worsen towards the retinal periphery. In addition, they found that these higher myopes had a thinner retinal nerve fiber layer that correlated with the reduced ERG

responses[28]. Correlations between retinal thickness and ERG responses were also found to be stronger at the retinal periphery of 10-15 degrees eccentricity[29]. In these cases, the amplitude of ERG responses were significantly decreased with increasing myopic refractive error and greater in the periphery[29]. In addition to the correlation between decreased ERG amplitudes and retinal thickness at the near retinal periphery, it has also been shown that moderate to high myopes exhibit decreased spatial resolution acuity compared to emmetropes at the near peripheral retina[30]. Previous ERG studies on humans have shown a decreased amplitude and delayed latency in myopes, particularly at the peripheral retina[2]. These attenuated ERG responses in myopes appear to be related more to their increased axial length rather than the refractive error of the eye[31].

Differences in flash ERG responses have been found between lens-induced and deprivation myopia in animal models[32], suggesting two different mechanisms are involved in causing myopia. Flicker ERG studies in chicks also indicate that retinal responses to hyperopic and myopic defocus may be different[2]. A small study (n=8) in humans found no significant effect of refractive blur (with plus and minus lenses) correction on multifocal ERGs[33].

There are also differences in the ERG responses to hyperopic defocus compared to myopic defocus, which further suggests an effect of refractive group in retinal responses. ERG's have also been used in studying the effect of Atropine for myopia control, with the Atropine group exhibiting lower ERG responses compared to a control group of children. This study showed an increase in dopamine neurotransmitter release and a reduced b- and d-waves on the ERG response led to attenuated RPE potentials and a reversed c-wave on the ERG[34]. The dopamine release was quantified and measured by high performance liquid chromatography combined with electro-chemical detection [34].

Our study aims to measure retinal responses to different types and magnitudes of simulated optical blur across the retina using pERGs in a group of young adults with emmetropia or myopia. The results from this study will be compared to the perceptual responses to blur to the same images.

Our study aims to measure retinal responses to different types and magnitudes of simulated optical blur across the retina using pERGs in a group of young adults with emmetropia or myopia. The results from this study will be compared to the perceptual responses to blur to the same images.
In order to better understand the processing of blur in the visual system, it is important to compare the retinal responses with the perceptual responses. This is because retinal processing of blur may not directly translate to the perceptual processing of blur. This could be because there are higher

level mechanisms involved in blur perception that are not involved in the retinal processing of blur. Additionally, there may be differences beyond the retinal level of blur processing that could be observed in psychophysical studies.

1.5 Study Aims and Hypothesis

The objective of this study is to increase our understanding of retinal and perceptual responses to near-peripheral blur. The specific aims are:

Specific Aim-1: To evaluate retinal pERG responses to various types of simulated optical blur across the near-peripheral retina in young adults with myopia or emmetropia.

For this purpose, we obtained pERG measures from the subject's dominant eye to simulated optical blur presented at different retinal eccentricities across the central 12 degrees. Four different types of simulated optical blur that may be relevant to emmetropization were used: (1) Defocus, (2) Spherical Aberration, (3) Oblique Astigmatism, and (4) a combination of Defocus and Oblique Astigmatism. Optically blur was applied at three different peripheral eccentricities and three levels of blur were presented for each condition.

We hypothesized that:

- *An effect of eccentricity will be found in retinal responses (pERG amplitude) for varied amounts of optical blur.*
- *Adults with myopia will exhibit impaired retinal responses (decrease pERG amplitude) to optically blurred stimuli in the near-peripheral retina compared to emmetropes.*

Specific Aim-2: To evaluate blur perception of the same types of simulated optical blur presented across the near-peripheral field in young adults with myopia and emmetropia.

For this purpose, we obtained psychophysical responses of perception of blur from the subject's sensory dominant eye while viewing optically blurred stimuli presented at different retinal eccentricities across the near periphery. The same four types of simulated optical blur used in the ERG studies were used in the psychophysics studies: (1) Defocus, (2) Spherical Aberration,

(3) Oblique Astigmatism, and (4) a combination of Defocus and Oblique Astigmatism. Again, simulated optical blur was applied at three different peripheral eccentricities. The simulated blur was presented in one of four quadrants and subjects were asked to indicate which quadrant appeared blurriest.

We hypothesized that:

- *Myopes will exhibit increased Intrinsic Blur and decreased Blur Criteria compared to emmetropes.*
- *This effect will be more pronounced as the blur is presented further in the periphery.*

Specific Aim-3: To relate retinal responses from the pERG studies to peripheral blur perceptual responses from the psychophysics studies for each type and amount of peripheral blur.

We hypothesized that:

- *Retinal responses to peripheral blur will be correlated with peripheral Intrinsic Blur thresholds, but not with peripheral Perceptual Criteria, in both emmetropes and myopes.*

2. General Methodology

This thesis comprises two cross-sectional studies performed over two visits, each visit lasting no more than two hours. Both studies were conducted in the same group of healthy young adults recruited within the New England College of Optometry (NECO) student and staff population. We enrolled a total of n = 30 subjects who met the following inclusion criteria:

1) 18-28 years of age, to avoid presbyopia and other aging effects.
2) BCVA = 0.0 LogMAR or better in each eye.
3) Refractive error within +0.50D and -6.00D in each eye, with no more than 1.25D of cylinder in either eye.
4) No history of amblyopia, binocular vision abnormalities, ocular surgery, or ocular diseases that may compromise central or near peripheral vision.

Subjects were classified as: "Myope", if they had a best-correction spherical equivalent (SE) between -0.50D to -6.00D in each eye; or "Emmetrope", if they had a SE between +0.75D to -0.25D in each eye.

Both studies were approved by the NECO Institutional Review Board and complied with all requirements regarding the testing of human subjects.

2.1. Screening of Subjects

Following explanation of the studies procedures and the subject signing the informed consent form after all questions were answered, a vision screening was conducted to confirm inclusion criteria, as listed above. Once the Informed Consent Form was signed, a de-identifier form was completed and subjects were assigned a study number, no identifiable information was used from this point on.

The vision screening included measurement of visual acuity at distance and near and, if required, completed objective and subjective refraction to determine the subject's best optical correction. Refraction was only performed if the subject was not able to see 0.00 LogMAR (20/20 Snellen) in either eye with their habitual correction. The vision screening also included determination of the subject's dominant eye, using the sensory dominance method. While looking at a distant target, a plus lens was introduced in front of each eye separately. The eye that viewed the distant target to be more blurry was noted to be their dominant eye. Subjects who passed the

vision screening and met all inclusion criteria participated in the experimental studies. The order of the experimental studies was randomized. Subjects underwent a second vision screening at the beginning of the second visit to ensure that there no changes to their vision or ocular health from the first visit.

For the study described in Chapter 3 (Retinal Responses to Blur – pERG), we tested 27 healthy young adults (mean age 24.9 ± 1.4 years, mean BCVA: 20/20, mean SE: -1.67± 2.03), with a refraction (SE in dominant eye) range of +0.50 to -8.00D. Myopes (n=15; Mean SE: -3.26 ± 2.25D), Emmetropes (n=12; Mean SE: -0.16 ± 0.35D).

For the study described Chapter 4 (Perceptual Responses to Blur - Psychophysics), we tested 30 (24.9 ± 1.4 years) healthy young adults with myopia (n=16, SE: -3.20±2.85D) or emmetropia (n=14, SE: +0.07±0.20D).

We retained 70% (n=21 and a total of 30 subjects) of the ERG subjects to participate in both studies. This means that a total of 21 subjects participated in both the ERG and blur perception study. Of those 21 subjects, 12 were myopes and 9 were emmetropes.

2.2. Experimental Procedures

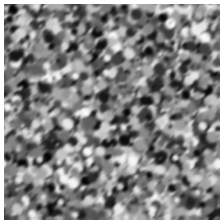
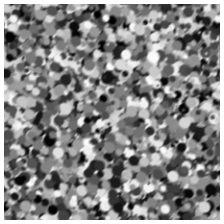
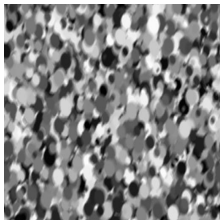
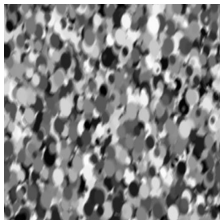
In brief, for the Retinal Responses to Blur study, we evaluated pERG responses to different types of simulated optical blur presented at various eccentricities, as described in Chapter 3. With the non-dominant eye patched, subjects were instructed to fixate at the center of a screen with their dominant eye while observing briefly presented images.

For the Perceptual Responses to Blur study, the same eye was used to psychophysically evaluate the perception of the same types of simulated optical blur presented at the same eccentricities. As described in Chapter 4, the only difference of the stimuli used in this study is that each quadrant of the image was blurred by a different amount, as the task for the subject was to determine which quadrant was perceived to be the blurriest using the four arrow keys on a keyboard.

For both studies, four different types of simulated optical blur were applied to 'dead leaves' naturalistic images: Defocus (DEF), Spherical Aberration (SA), Oblique Astigmatism (J45), and a combination of Astigmatism and Defocus (J45+DEF). These specific types of blur were chosen because they are found in all individuals when viewing natural scenes found every day and are thought to be important in the development of refractive errors[35]. Dead leaves images were chosen

as stimuli as they contain a wide range of spatial frequencies and the individual object contrast can be varied[12].

The images (Figure 2.1.) were convolved with each type of blur at one of three different eccentricities: 0-Deg (the entire image is blurred), 6-Deg (the entire image except the central 6 degrees are blurred), and 12-Deg (the entire image except the central 12 degrees are blurred). These eccentricities were chosen based on previous research, as described in Chapter 1. The images were blurred with one of three different amounts of blur: 0.5, 0.3, and 0.1μm. Pilot studies were conducted to determine the amounts of blur to be investigated[36]. A fourth type of image, the original image, with no blur (CLEAR), was also used.

Defocus (DEF)	**Spherical Aberration (SA)**	**Astigmatism (J45)**	**Combination of J45 and DEF**
			
Magnitude of Blur Used:			
0.5, 0.3, 0.1 μm	**0.5, 0.3, 0.1 μm**	**0.5, 0.3, 0.1 μm**	**0.354, 0.213, 0.071 μm**

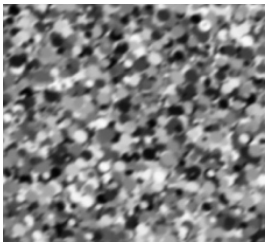
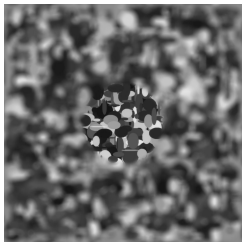
0-Deg	**6-Deg**	**12-Deg**
		
The entire image is blurred, no clear central area.	The entire image was blurred, except for a central disc of 6 degrees radius.	The entire image was blurred except for a central disc of 12 degrees radius.

Figure 2.1. Simulated optical blur conditions used in the pERG study and at varying eccentricities. Eccentricity refers to the central area of the image that is not blurred. (e.g., 6-Deg indicates all image but the central 6 degrees are blurred).

The dead leaves stimuli were computed using 2000 ovals in random orientation. The luminance, blur, and disparity of each ellipse used were controlled for in each trial. The size of these ovals was drawn at random from a uniform distribution with a minimum of 0.1 degrees and a maximum of 3 degrees. The greyscale of the ellipses was also drawn randomly from a uniform distribution, giving rise to local variation in image contrast. The images were computationally blurred using MATLAB R2015b (MathWorks Inc., USA). Images were then convolved in the Fourier domain[37]. The final aberrated images were obtained by going back to the spatial domain doing an inverse Fourier Transform. The amount of aberration was then quantified by the root mean square wavefront error (RMS) and the square of the coefficient of each Zernike polynomial function[38]. The resultant mean RMS levels ranged from 0.1μm to 0.5μm. Aberrations were applied to the images' point spread function (PSF) for a 5mm pupil. Pupil sizes were not measured between each subjects. Considering the similar age across all of our subjects, we did not expect there to be a specific effect of aberrations due to differences in pupil sizes. After blurring of the stimuli images, the luminance histogram of the images was rescaled to the fix the global RMS contrast of all images of 0.25, and pixel values falling outside the range of 0-255 were fixed. The stimuli were displayed on a CRT monitor (GDM-520 SONY Trinitron) controlled by MATLAB and Psychtoolbox which subtended 30deg x 30deg of visual angle at a viewing distance of 40cm. The stimuli were then contrast reversed at 2Hx and had a mean luminance of 52.5 cd/m^2.

3. Retinal Responses to Blur - pERG

3.1 Introduction

The retinal response to a specific stimulus can be measured using ERG. As discussed in the General Introduction chapter, increasing evidence indicates that the quality of the retinal image, and in particular the peripheral retina, plays an important role in the emmetropization process[5,11,13,39–47]. A retinal image that is blurred only at certain retinal eccentricities might be the culprit for abnormal eye growth.

The pERG technique uses a pattern reversal stimulus and primarily measures retinal ganglion cells activity. Using a pERG is a non-invasive and quantitative way to assess central retinal function. In addition to measuring retinal ganglion cell activity, pERG can be used clinically in diagnosing/managing optic nerve and retinal diseases[48]. The use of more naturalistic images to elicit retinal responses is desired over the use of checkerboards stimuli that are traditionally used for pERGs. Therefore, we used dead leave images with varying spatial frequencies and contrast as the stimulus for our measures of retinal responses[49]. As noted in Chapter 2, dead leaves images have advantages over traditional checkerboard stimuli because they can be manipulated in contrast and spatial frequencies to simulate a more natural viewing stimulus[49].

In this study, we measured retinal pERG responses while different types of simulated optical blur (DEF, SA, J45 and a combination of J45+DEF) were presented at different retinal eccentricities (0-Deg, 6-Deg and 12-Deg), as described in Chapter 2 (Figure 2.1. and Table 3.1.)[36]. The pERG responses were also measured to non-blurred (CLEAR) images. Our aim was to identify the type of optical blur and eccentricity for which the retina is most sensitive to. We hypothesized that the retinal area between 6 and 12 degrees may be most sensitive, and that SA may impair retinal responses more than DEF. Our results may have applications in future studies on understanding how retinal blur affects abnormal eye growth.

3.2 Methods

Following the vision screening as described in Chapter 2, the subject was tested with the pERG system using the following protocol:

1. After the skin of contact was wiped with an alcohol wipe, scrubbed, and cleaned, three electrodes (Figure 3.1.), a ground and a reference electrode (both 9mm gold-cup), and a DTL active electrode were placed according to the International Society for Clinical Electrophysiology of Vision (ISCEV) guidelines[48].

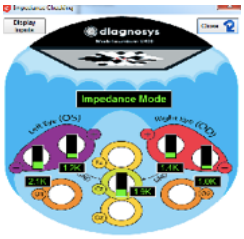
Ground Electrode	Reference Electrode	DTL Active Electrode	Epsion Diagnosys
			
Ground electrode, placed in the forehead.	Reference electrode, placed in the earlobe, same side as the dominant eye.	DTL active electrode lies along the lower lid and is secured by electrode stickers at the inner and outer canthus of the eye.	Once Electrodes are connected, the ERG software will show us the impedance ensuring good connectivity to obtain recordings.

Figure 3.1. Steps to set up the ERG electrodes.

2. The subject was wearing their best refractive correction. Pupils were not dilated to maintain the habitual quality of the retinal image.

3. The subject was set up on a chin and forehead rest at 50 cm from the cathode ray tube monitor that will display the stimuli to remain stabilized for the duration of the testing.

4. The subject was exposed to a total of 46 variations of stimuli (Table 3.1.), as described in Chapter 2.

5. The subject was instructed to fixated at a crosshair located at the center of the screen at all times. The electrophysiological responses of the dominant eye were recorded simultaneously using the Epsion Diagnosys program that was triggered externally by MATLAB. 256 sweeps of 250ms epoch were averaged for each stimulus.

6. Subjects were allowed to take as many breaks as needed in between stimuli presentations. Each image was presented in random order for each subject.

7. The average P1 and N2 (Figure 3.2.) amplitude obtained from the pERG were used in comparison analyses. The N2 amplitude was measured across all types, amounts of blur, and eccentricities.

Table 3.1. Characteristics of the stimuli used for pERG testing. The eccentricity refers to the extend the blur is presented up to, from the periphery to the center, e.g., a 0-Deg image was blurred entirely, 6-Deg image was blurred up to 6 degrees eccentricity.

Type of simulated optical blur	**Eccentricity**	**Magnitude of blur (μm)**		
No Blur (CLEAR)	0-Deg	0.0		
Defocus (DEF)	0-Deg	0.5	0.3	0.1
	6-Deg	0.5	0.3	0.1
	12-Deg	0.5	0.3	0.1
Spherical Aberration (SA)	0-Deg	0.5	0.3	0.1
	6-Deg	0.5	0.3	0.1
	12-Deg	0.5	0.3	0.1
Oblique Astigmatism (J45)	0-Deg	0.5	0.3	0.1
	6-Deg	0.5	0.3	0.1
	12-Deg	0.5	0.3	0.1
Combination J45 + DEF	0-Deg	0.354	0.213	0.071
	6-Deg	0.354	0.213	0.071
	12-Deg	0.354	0.213	0.071

3.3 Data Analysis

The signals that we are interested in is the **P1** and **N2** waveform (Figure 3.2.). We were interested in these signals because they both reflect physiological activity from the retina. The P1 signal represents the bipolar and ganglion cell activity whereas the N2 signal represents mainly ganglion cell activity. The P1 and N2 amplitude for each subject was used in a mixed model ANOVA. Specifically, a univariate analysis of variance was computed to analyze the effects that refractive error, blur type, blur amplitude and eccentricity had on the N2 and P1 amplitudes.

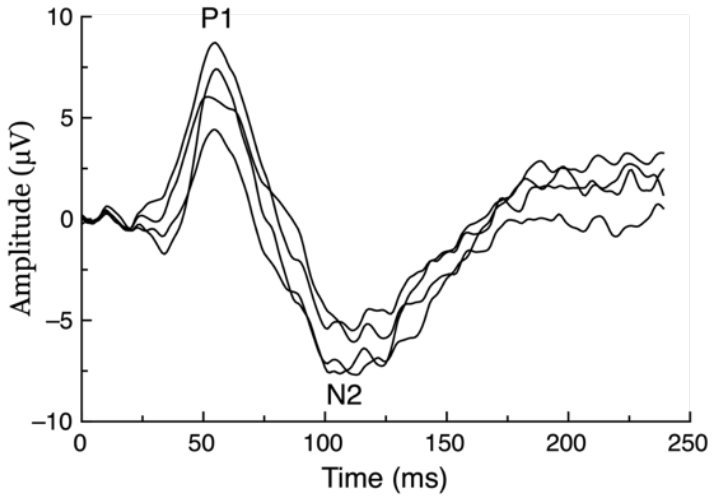


Figure 3.2. ERG Waveform. The P1 wave reflects the initial positive signal originating from the bipolar and retinal ganglion cells. It originates from the outer retina[48]. The N2 wave is the negative signal that follows the P1 wave. It originates from the inner retina and reflects ganglion cell activity. The N2 waveform can be used clinically to assess optic neuropathies (i.e., differentiating between demyelinating and ischemic optic neuropathies)[48].

3.4 Results

An overall effect of blur **amount** (N2: $F=29.465$, $p<0.001$; P1: $F=13.025$, $p<0.001$), blur **eccentricity** (N2: $F=11.614$, $p<0.001$; P1: $F=4.117$, $p=0.017$), and **type of blur** (N2: $F=19.248$, $p<0.001$; P1: $F=7.939$, $p=<0.001$) was found for both **N2** (Figure 3.3.) and **P1** responses (Figure 3.4.). No overall effect of refractive group was found with either the N2 or P1 signals. Significant **interactions** between **eccentricity** and the **amount of blur** were found for **N2** for DEF ($F=3.672$, $p=0.014$), SA ($F=4.836$, $p=0.030$), and J45 ($F=3.375$, $p=0.020$); no interactions were found for J45+DEF ($F=0.399$, $p=0.808$).

Effect of Amount of Blur:

There was an overall effect of blur amount on the pERG responses, as described above, with specifically significantly lower N2 amplitudes for larger blur amounts for DEF [responses to 0.5µm blur were significantly smaller than those to 0.3µm ($p<0.001$) and 0.1µm ($p<0.001$)], and for SA [responses to 0.5µm were significantly smaller than those to 0.3µm ($p<0.001$) and 0.1µm ($p<0.001$)]. P1 amplitudes were also significantly lower with larger blur amounts for SA [responses to 0.5µm ($p<0.003$) and 0.3µm ($p<0.006$) gave smaller values than 0.1µm]. There were no significant effect of the amount of blur for either J45 or J45+DEF.

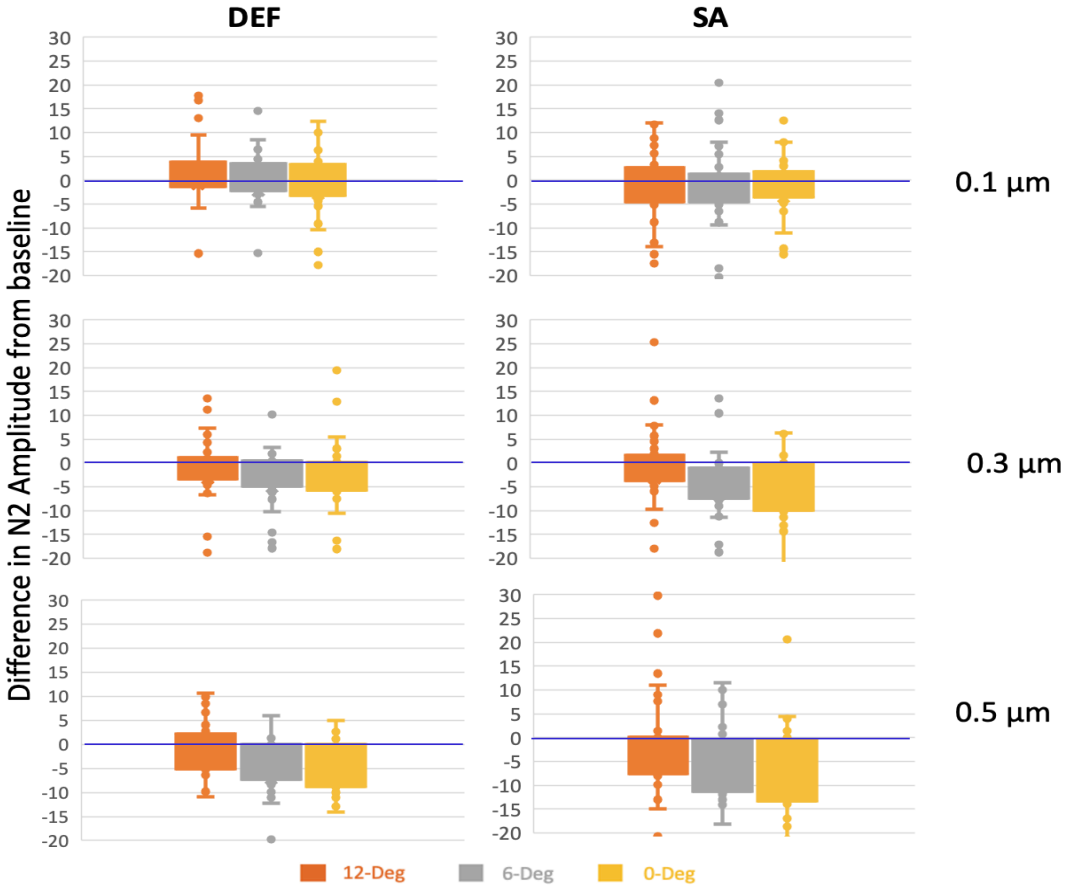


Figure 3.3. Effect of amount of blur (0.1µm, 0.3µm, 0.5µm) and blur eccentricity (0-Deg, 6-Deg, 12-Deg) on the **N2** responses for all subjects for DEF and SA. Data shown is the difference in **N2** normalized to each subject's baseline (CLEAR image). Error bars correspond to ±1SE.

Effect of Blur Eccentricity:

There were no significant differences in in the pERG response between the CLEAR (no blur) image and the image that only had blur applied outside the central 12 degrees [N2: DEF 0.5µm, p=0.233, SA 0.3µm, p=0.583 and 0.5µm, p=0.118; P1: SA 0.3µm, p=0.958 and 0.5µm, p=0.062). On the other hand, a significant effect of blurring the image up to the central 6 degrees was found, with significantly lower responses for the 6-Deg image compared to the CLEAR (no blur) image [N2: DEF 0.5µm, p<0.001, SA 0.3µm, p=0.010, and 0.5µm, p=0.001; P1: SA 0.5µm, p=0.038).

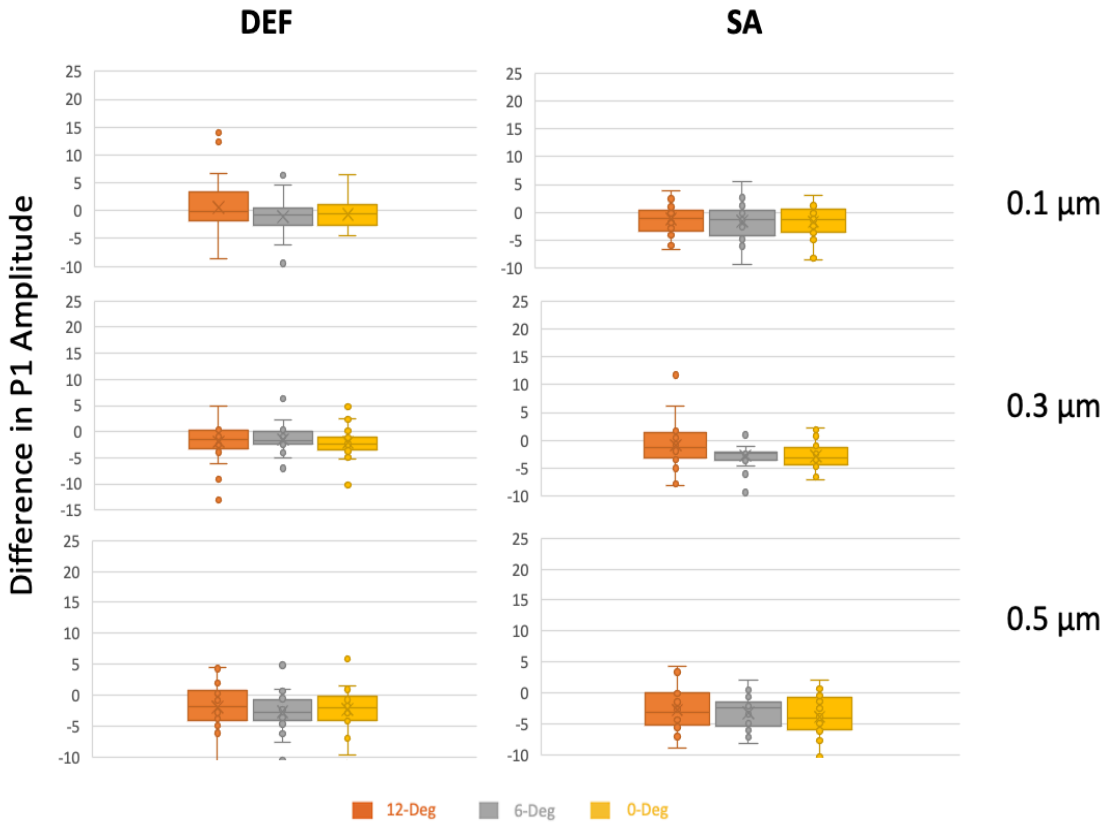


Figure 3.4. Effect of amount of blur (0.1µm, 0.3µm, 0.5µm) and blur eccentricity (0-Deg, 6-Deg, 12-Deg) on the **P1** responses for all subjects. Data shown is the difference in **N2** normalized to each subject's baseline (CLEAR image). Error bars correspond to ±1SE.

The responses to the 0-Deg image (entirely blurred) were lower than for the 12-Deg image for SA [N2: 0.3µm, p=0.003 and 0.5µm, p=0.002; P1: 0.3µm, p=0.048), but not for DEF [N2: 0.5µm, p=0.233). There were no statistically significant differences between the 6-Deg and 0-Deg images

for either the N2 responses [DEF 0.5 µm, p=0.995, SA 0.3µm, p=0.287 and 0.5µm, p=0.135) or the P1 responses [SA 0.3µm, p=0.361 and 0.5µm, p=0.722].

There were no statistically significant differences in the pERG responses between the 12-Deg and 6-Deg images [N2: DEF 0.5µm, p=0.127, SA 0.3µm, p=0.158 and 0.5µm, p=0.284; P1: SA 0.3µm, p=0.796 and 0.5µm, p= 0.961].

Effect of the Type of Blur:

Although pERG responses decreased as a function of amount of blur for both DEF and SA, there was an overall effect of blur type on the N2 responses for the 0-Deg condition, as shown in Figure 3.5. N2 responses for DEF 0.3µm were higher than for SA 0.3µm (p=0.018). Similarly, responses for DEF 0.5µm were higher than for SA 0.5µm (p=0.025). P1 responses for DEF 0.3µm were also higher than for SA 0.3µm (p=0.018) and responses for DEF 0.5µm were higher than those for SA 0.5µm (p=0.025). No differences were found on the P1 responses between the 0-Deg images of DEF and SA for 0.3µm (p=0.181) or 0.5µm (p=0.279).

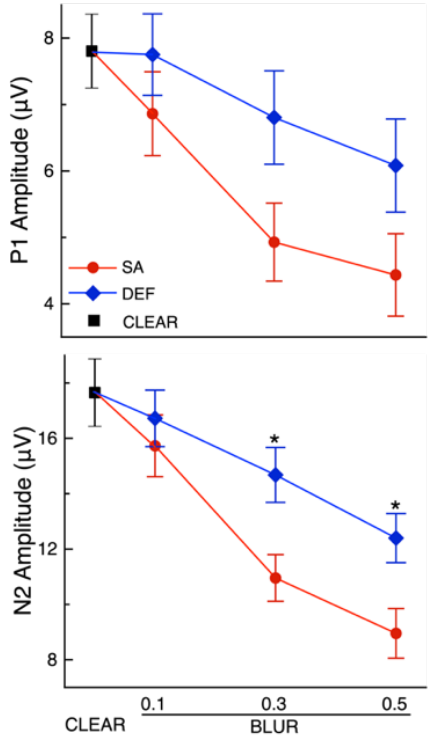


Figure 3.5. P1 (top) and N2 (bottom) amplitudes for the 0-Deg condition decreased as a function of amount of blur (0.1, 0.3 and 0.5µm) for both DEF and SA. The error bars correspond to ±1SE and asterisks indicate the statistically significant differences (p<0.05) between the SA and DEF conditions.

Effect of the Refractive Error:

Refractive error had no effect on the N2 ($F=3.125$, $p=0.078$) (Figure 3.6.A.) or P1 amplitudes ($F=2.329$, $p=0.127$) (Figure 3.6.B.). For this current study, there were not enough subjects enrolled to divide subjects into high and low myopes. However, we ran statistical analyses on the small number of high and low myopes and found that there was no trend. It is also important to note that we did not know if our myope subject had progressing myopia.

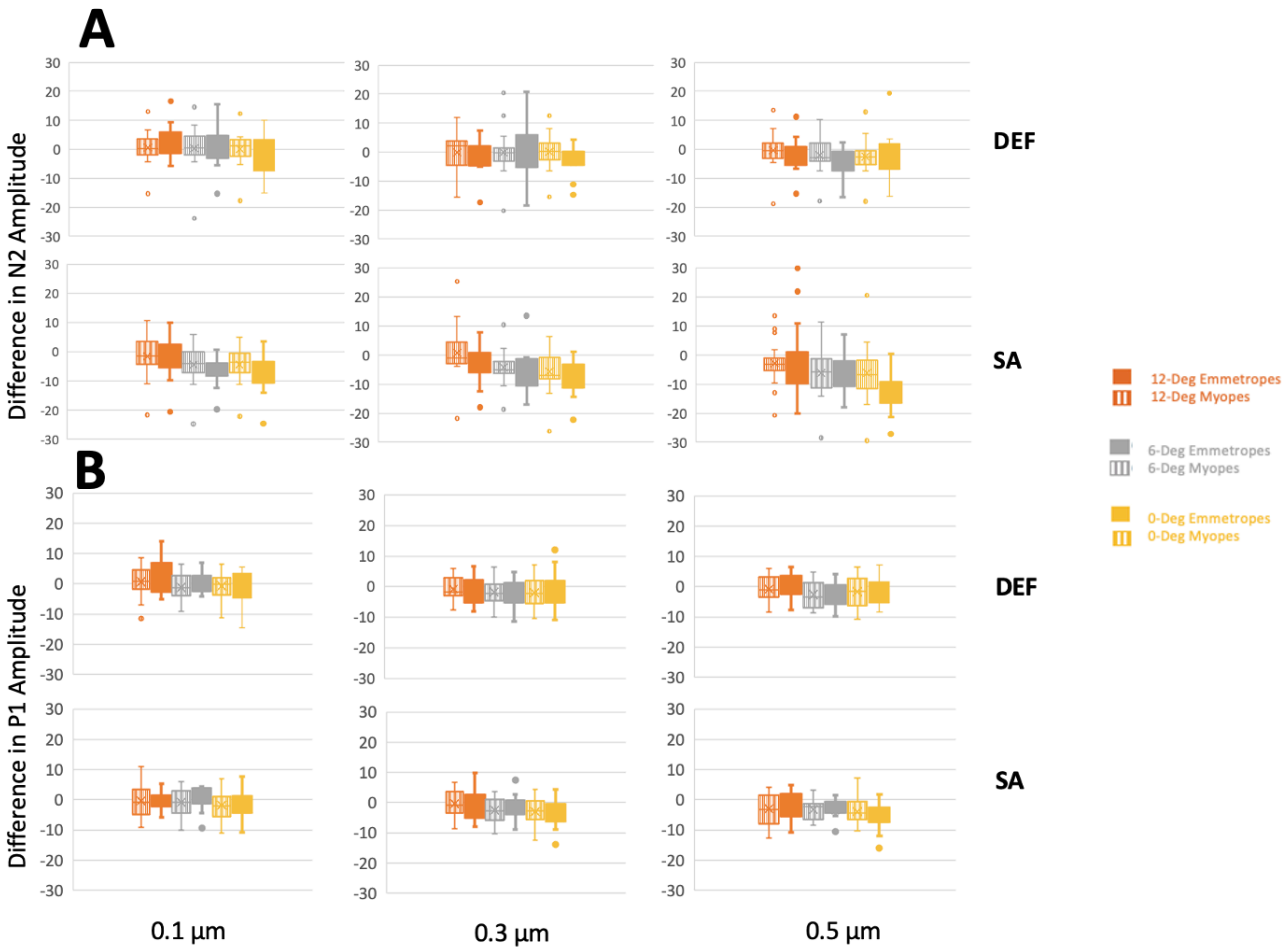


Figure 3.6. Effect of refractive group on **N2 amplitude (A)** and **P1 amplitude (B)** within blur eccentricity, blur amount, and blur type. Error bars correspond to ±1SE.

3.5 Discussion

In this study, we measured for the first time ERG responses to naturalistic stimuli digitally blurred with different types of optical blur presented at various eccentricities. Manipulating the

images computationally instead of using ophthalmic lenses allowed us to control for the location of the retinal blur and avoid inducing secondary changes typically induced by lenses such as minification or magnification or changes in accommodation (with subsequent changes in SA).

In agreement with previous studies, we found that blur applied to the entire image (0-Deg) resulted in decreased pERG responses compared to the responses to CLEAR (not blurred) images. Also as expected, the effect of blurring the image was greater (i.e., more reduced retinal responses) when larger amplitudes of blur were applied.

The most interesting result of this study is the effect of specific peripheral eccentricities in retinal responses. Retinal responses, both N1 and P2, were equally reduced when blur was presented up to 6 degrees eccentricity (6-Deg) compared to blurring the entire image (0-Deg). On the other hand, images blurred only up to the clear central twelve degrees (12-Deg) did not significantly affect retinal responses compared to the non-blurred (CLEAR) images. These findings indicate that the retinal area between 6- and 12 degrees eccentricity suffers the most detrimental effect of blur and therefore may be the location of blur decoding signals. As discussed in our introduction, our findings go in line with previous studies that propose that the near peripheral retina may play a larger role than the fovea in eye growth[15]. Numerous animal studies have emphasized the near peripheral region and blur perception in the near periphery to be an important factor in myopia development[7–12]. Previous studies have indicated that near peripheral area at around 8 degrees of eccentricity is the most important in blur perception, which is consistent with our findings.

As expected, there was a significant effect of the amount of blur for both DEF and SA. However, there were no significant differences between the CLEAR image and either the J45 and J45+DEF conditions (both with applied astigmatic blur). This could be because astigmatic blur elongates stimuli only at one meridian while leaving the orthogonal meridian with little effect. Although the energy at each spatial frequency changes with astigmatic blur, this only occurs for very high spatial frequencies within a specific range of orientations. Even though orientation sensitive retinal ganglion cells have been identified in the primate retina[50], it may be that the amount of J45 blur was just not enough to produce an observable or significant response in the pERGs.

Another factor to consider is that post-receptoral responses decrease with lower luminance contrasts and spatial frequencies[36]. Image statistics (Appendix I) on the stimuli we used in our

study shows a systemic increase in the lower spatial frequency content as the amount of blur increased, which may also account for the reduced pERG responses found with increasing amounts of blur.

In general, differences observed among the various optical types of blur used in this study may be attributed to the spatial variations that occur in the local contrast and luminance of the dead leaves' stimuli. Inducing DEF and SA blur reduces the amplitude of high spatial frequencies and when the image's global RMS is rescaled, the contrast increases the relative amplitude of lower spatial frequency components. Therefore, both contrast and spatial frequency ranges change due to the induced blur. This may explain that even though pERG amplitudes were reduced with both DEF and SA conditions, SA blur impacted the pERG amplitude more than DEF blur. There were no significant differences between the contrast ranges of DEF or SA blur as the RMS contrast was always kept at 0.25 across all different types and amounts of blur. There were also no differences in the distribution of low and intermediate spatial frequencies between the DEF and SA blur types, but there were differences at high spatial frequencies. SA blur showed a higher power spectrum at higher spatial frequencies ranges, which could have caused the differences in pERG responses found between the DEF and SA blur types (SA blur caused lower responses than DEF blur). Nevertheless, the differences observed between DEF and SA may imply that SA blur impacts the retinal responses to a greater extend and may therefore play a more important role in the emmetropization process. This may be because compared to DEF blur (where images appear just out of focus), SA blur is a type of blur that arises after light hits a spherical surface (like our corneas and lens). We believe that SA blur takes into account the optical elements of ones eyes whereas DEF blur does not.

We found no effect of refractive group on the pERG responses in the group of young adults with emmetropia and myopia who participated in this study. We had hypothesized that we would find differences between refractive groups in retinal responses as previous literature using psychophysical techniques indicated that myopes may be less sensitive to peripheral blur than emmetropes. However, it appears that these previous findings on subjective psychophysical responses do not translate directly to objectively measured retinal responses. The difference may be because subjective responses incorporate higher level cortical processes. A separate process may occur beyond the initial encoding of blur where myopes and emmetropes process blur the same way at the retinal level, but this does not translate directly into the perception of blur. With

this in mind, the goal of our final study (Chapter 5) will be to investigate whether there are correlations between pERG responses to blur measured in this study and the perceptual responses to blur measures in the study described in Chapter 4.

4. Perceptual Responses to Blur – Psychophysics

4.1 Introduction

As discussed in the General Introduction chapter, it is established that image quality and blur signals play an important role in emmetropization. The near periphery may be the retinal area that plays the most important role in encoding blur, and thus, in normal emmetropization. Previous studies have indicated the importance of the near peripheral retina in myopia development and have shown that visual signals directed at the near peripheral retina may play a larger role in controlling eye growth compared to visual signals directed at the central fovea[17]. The importance of near peripheral blur is applied clinically in myopia control treatments, as these methods target the near retinal periphery.

There are two important aspects to the perception of blur: (1) detection of blur (i.e., the smallest amount of blur – threshold – needed for the perception of the blur, and (2) discrimination of blur (i.e., the amount of blur needed to add to an already blurred image – background blur – to appreciate the difference from the background blur)[12]. We will investigate both in this study. Blur perception measures exhibit a typical 'dipper' shape function that shows best performance at a nonzero amount of reference bur[12,51]. This dipper shape exists because as the reference level of blur increases, blur discrimination is initially facilitated by additivity of variance. As reference blur becomes greater than the intrinsic blur of ones' internal system, discrimination performance will decrease which is in accordance with Weber's law. This describes how we obtain the typical dipper data and this is grounded in both signal detection theories of sensory discrimination and decision making[12]. In our previous study of blur perception, Gaussian blur was used but in this study, various types of optical blur will be used while using the same conditions as described in our pERG retinal response study[36].

In Watson and Ahmuda's[51] thorough review of blur discrimination, they describe how psychophysical studies on blur perception have consistently shown that blur discrimination follows a typical 'dipper' shape (which we obtained as well). The shape of this function indicates that blur discrimination performance is best when there's a nonzero amount of blur (the system already detects blur), compared to discrimination for zero baseline blur[12]. This is because when blur is at near-zero levels the visual system has to overcome the intrinsic blur (optical aberrations + neural noise) level in order to discriminate blur, which represents the first dip of the function.

Once blur is detected, a perceptual criterion is used to determine the level of blur, in our paradigm to indicate which quadrant is blurriest, which is the amount of blur needed between already detectable blur stimuli in order to differentiate blur. As the amount of blur beyond intrinsic blur becomes much greater, performance eventually decreases as Weber's Law which does not hold for extreme stimulations[51].

The purpose of this study was to measure the sensitivity and sources of sensitivity differences to different types and levels of simulated optical blur across the visual field[52].

4.2 Methods

The procedures for this study were as follows:

1. The subject was set up with a chin rest and forehead rest at 50cm from the screen.
2. An eye patch was used to cover the non-dominant eye so the subject was tested monocularly with the dominant eye, as in the pERG measurements.
3. A total of four trials were run, one for each of the four types of simulated optical blur stimuli (Figure 2.1. and Table 4.1.), the same used in the pERG study.
4. A Tobbii eye tracker was used to ensure the subject's dominant eye was fixating at the center of the screen for the duration of the trial. The stimulus was only presented when the eyetracker detected that the subject was indeed fixating at the center of the stimulus.

Table 4.1. Simulated optical blur conditions used in the psychophysics study. The types of blur and eccentricities were the same used in the ERG study. For this staircase psychophysical task, five pedestal blur levels were used. These blur levels determine the amount of blur that is being added to the optical blur of interest.

Optical Blur Type	**Eccentricity** (degrees)	**Pedestal Blur Levels** (μm)
Defocus (DEF)	0, 6, 12	0.01, 0.03, 0.09, 0.27, 0.81
Spherical Aberration (SA)	0, 6, 12	0.01, 0.03, 0.07, 0.18, 0.50
Astigmatism (J45)	0, 6, 12	0.01, 0.03, 0.10, 0.32, 1.00
Combination of J45 + DEF	0, 6, 12	0.01, 0.03, 0.09, 0.27, 0.81

5. The dead leaves stimulus was presented with an overlaying blur at one of five pedestal blur levels at one of the three eccentricities (Table 4.1.). The pedestal blur levels refer to the baseline level of blur that we are comparing our responses to.

6. The blurriest portion of the image appeared in either the superior, inferior, right, or left quadrant of the image (Figure 4.1.). Using the arrows on the keyboard, the subject was instructed to select which quadrant appeared blurrier to them.
7. The fixation point turned green if they answered correctly, and red if they answered incorrectly.

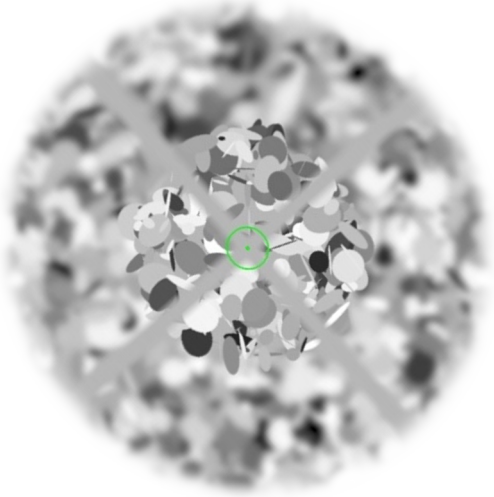


Figure 4.1. Example stimuli used in the psychophysics study.

From the raw psychophysical data, blur discrimination thresholds were fit with a two-parameter dipper function (Figure 4.2.): Intrinsic Blur and Perceptual Criterion. The blur dipper function was parameterized with the following equation:

$$\Delta b = \sqrt{\left(1 + {}^{1}\!/\!_{S}\right)\left(\sigma_i^2 + \sigma_e^2\right)} - \sigma_e$$

The blur increment threshold Δb varies as a function of the external (pedestal) blur σ_e applied to the stimulus and is modulated by two parameters: blur sensitivity S and intrinsic blur σ_i. This function takes into account the proportional increase of the blur threshold with increasing external blur[12]. The first dip we see in this function is the intrinsic blur of a subject's visual system. The intrinsic blur represents the amount of blur that needs to be added to baseline blur to reach a certain criterion. This type of blur arises from both optical imperfections (aberrations) of the eye and neural sources from the visual pathway. Perceptual criterion represents the amount of blur that is

needed in order to differentiate two blurry images that are already above threshold and detectable by the visual system[51].

We obtained a dipper shape function for each of the conditions of our study, which is consistent previous studies.

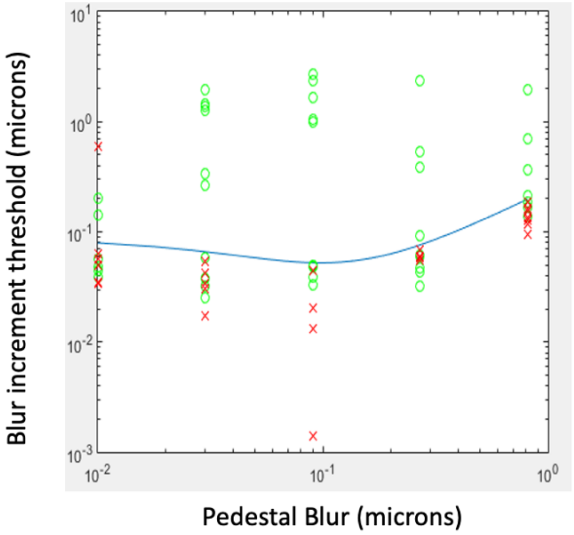


Figure 4.2. Sample blur perception raw data for one subject. Thresholds to DEF blur with increasing pedestal blur levels presented at 0-Deg (left), 6-Deg (middle), and 12-Deg (right) are shown. The green circles indicate a correct response, and the red x symbols indicate an incorrect response. Correct answers are above the threshold, and incorrect answers are below the threshold.

4.3 Data Analysis

A mixed model analysis in SPSS was used to analyze the Intrinsic Blur and Perceptual Criterion values to evaluate the effects of the different types of blur and eccentricity as well as the effect of refractive group.

4.4 Results

Intrinsic Blur results showed an overall effect of eccentricity, with higher levels of intrinsic blur at the more peripheral conditions (Figure 4.3.). This effect was overall significantly higher in myopes compared to emmetropes ($p<0.001$, $\eta^2=0.092$).

Higher levels of **Intrinsic Blur** were found for myopes compared to emmetropes for SA blur at all eccentricities (0-Deg: F=11.457, p=0.002; 6-Deg: F=7.203, p=0.012; 12-Deg: F=6.203, p=0.019), J45 blur at 6-Deg and 12-Deg eccentricity (6-Deg: F=9.343, p=0.005; 12-Deg: F=5.749, p=0.023), and combination blur (J45+DEF) at 6-Deg eccentricity (F=10.220, p=0.003). This effect was not found for DEF blur (F=0.679, p=0.449, η^2=0.023).

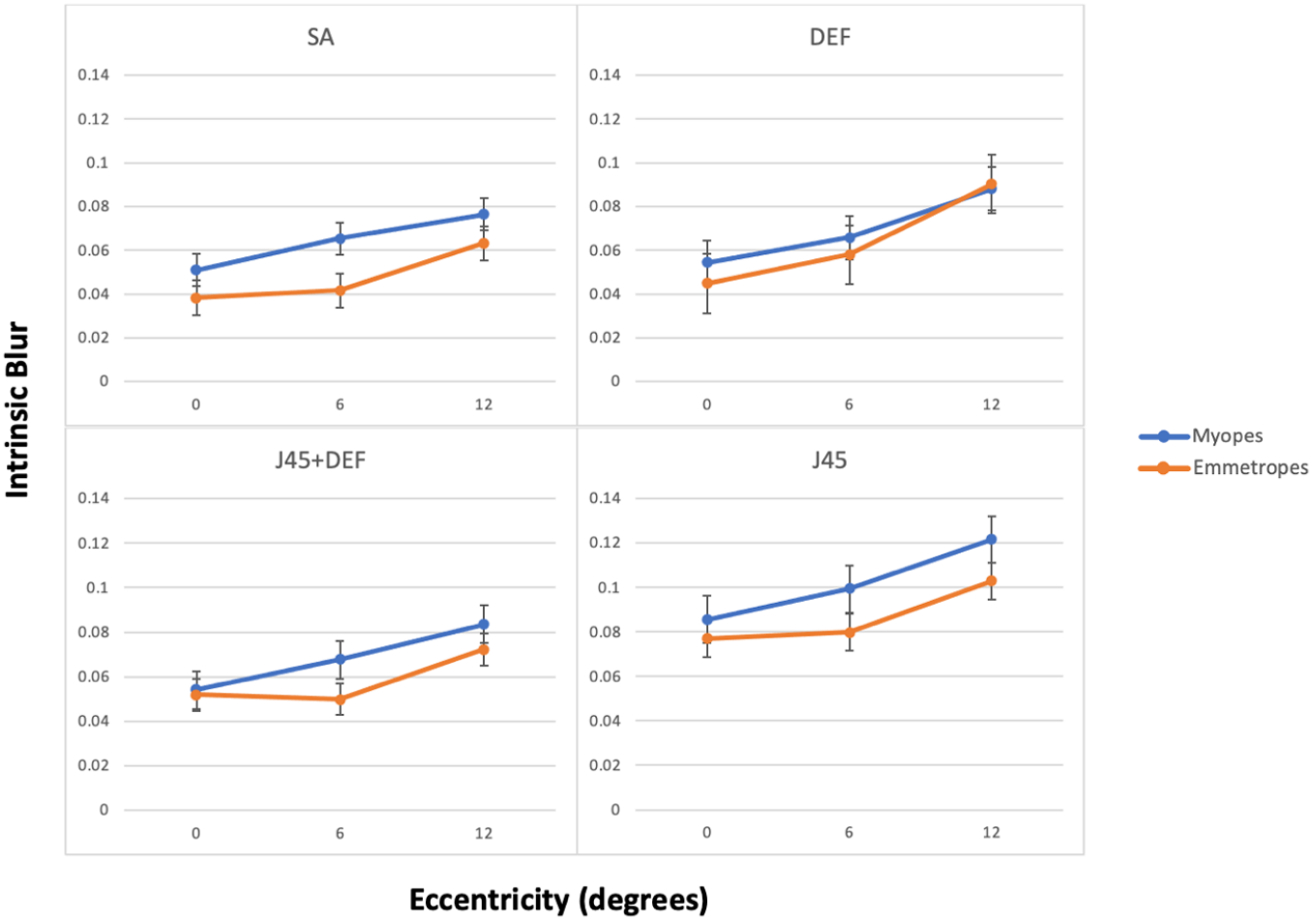


Figure 4.3. Intrinsic Blur as a function of eccentricity (0-Deg, 6-Deg and 12-Deg) for each blur type (SA, DEF, J45, J45+DEF) for myopes (blue) and emmetropes (orange). The error bars represent ±1SE.

Perceptual Criterion also showed an overall effect of eccentricity, with higher thresholds at increased eccentricities for DEF blur (F=9.310, p<0.001, η^2=0.243) and combination (J45+DEF) blur (p<0.001, η^2=0.279), but not for SA (F=2.185, p=0.122, η^2=0.070) or J45 blur (F=1.391,

p=0.257, η^2=0.046). Perceptual criterion results were no different between emmetropes and myopes (F=2.221, p=0.131, η^2=0.071) (Figure 4.4.).

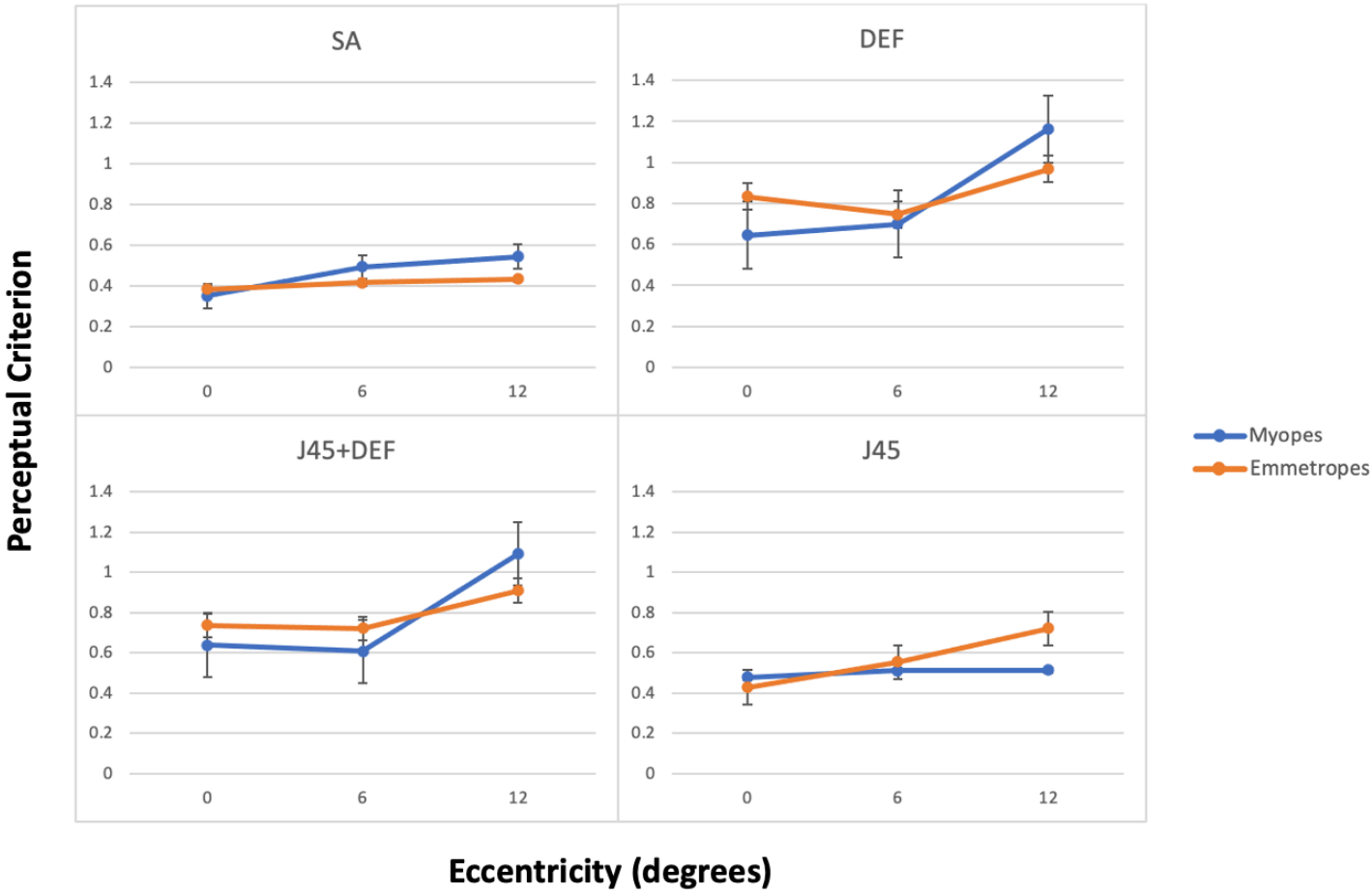


Figure 4.4. Perceptual Criterion as a function of eccentricity (0-Deg, 6-Deg and 12-Deg) for each blur type (SA, DEF, J45 and J45+DEF) for myopes (blue) and emmetropes (orange). Error bars correspond to ±1SE.

4.5 Discussion

Intrinsic blur was higher in myopes and more pronounced in the periphery for all types of simulated optical blur used in this study. This indicates that myopes exhibit more difficulty than emmetropes when discriminating these simulated optical blur types. As intrinsic blur represents the amount of blur needed to be added to a baseline level blur before it is detectable, myopes may have an overall noisier intrinsic visual system. This paradigm does not differentiate per se whether myopes have higher levels of intrinsic blur due to poorer optics or increased neural noise.

On the other hand, perceptual criterion represents the amount of blur that is needed in order to differentiate two blurry images that are already above threshold and detectable by the visual system. Our results show that perceptual criterion is eccentricity-dependent, but there were no significant differences between emmetropes and myopes. This result indicates that even though myopes have an overall blurrier visual system (as illustrated by the intrinsic blur findings), once the visual system reaches their detectable criterion, the amount of blur needed for myopes to discriminate between blurry images is no different than for emmetropes. Once their blur threshold is reached, their performance is the same despite having different thresholds to begin with. To reiterate, myopes may suffer a blurrier visual system but once their perceptual criterion is met, their performance and ability to differentiate blur is the same as that of emmetropes.

Interestingly, in our previous study using Gaussian blur[12], no difference was found in intrinsic blur values between myopes and emmetropes. However, when Gaussian blur was observed, myopes showed worse perceptual criterion monocularly that improved binocularly (no differences were found between refractive groups binocularly). The deficits in processing Gaussian blur only under monocular conditions in myopes were attributed to masking under binocular summation[12]. Gaussian blur increases image noise and smooths out details, so the stimuli typically appear out of focus. As discussed previously, this type of blur is not as relevant in the effect of ocular development and emmetropization as other types of optical blur such as defocus, astigmatism, or spherical aberration. Therefore, we used simulated optical blur in both studies of this thesis (retinal responses to blur – Chapter 3- and perception of blur – Chapter 4). It is interesting that the findings for perception of optical blur are different than those we previously reported with Gaussian blur. We now find that myopes exhibit higher intrinsic optical blur levels compared to emmetropes. This may indicate that they have an overall poorer optical system than emmetropes where myopes seem to exhibit higher levels of optical, not neural, intrinsic blur compared to emmetropes. This conclusion can be drawn from the fact that in our previous blur perception study using Gaussian blur, we found that there were refractive differences between myopes and emmetropes. However, in our current study using optical blur, there were no refractive group differences.

These differences in intrinsic blur between refractive groups were found for spherical aberration, astigmatism and the combination of astigmatism and defocus, but not for images that were blurred only with defocus blur. This may indicate that there are other aspects of blur than defocus playing a role in emmetropization and may explain why the responses to optical lenses

found in studies involving animal models do not directly translate to human studies. Ophthalmic lenses induce other changes in retinal image quality than defocus blur. For example, they induce spherical aberration as they also affect accommodation. Ophthalmic lenses also induce changes such as minification or magnification of the retinal image. Another possible explanation is that since myopes inherently have a blurrier visual system (higher intrinsic blur), they have developed a compensation mechanism that has allowed them to perform similarly to emmetropes under DEF blur conditions.

Overall our findings indicate that there were higher levels of intrinsic blur and perceptual criterion at more peripheral conditions when going from 0-Deg, 6-Deg, to 12-Deg eccentricity. Additionally, myopes exhibited even higher intrinsic blur compared to emmetropes with increasing eccentricity. Our findings from this current study may go in line with the findings that the retinal area between 6 and 12 degrees is the area important in blur detection.

In order to assess how these various types of optical blur affect image quality and whether they play a role in the emmetropization process, further studies are need to be done to assess their impact on younger subjects, children, still undergoing emmetropization. A longitudinal study measuring perception of various types of optical blur in emmetropic children who are followed over time to see if they develop myopia is necessary to test the hypothesis that specific types of optical blur may disrupt the emmetropization process and cause myopia. We are currently conducting such study at our Children's Vision Lab at NECO. The PICNIC (Preventing Myopia: Investigating Contributing factors to Nearsightedness in Children) study is investigating which aspects of image quality, perhaps others aside from defocus blur, could play an important role in blur encoding and emmetropization.

5. Correlation between ERG and Perception Measures

5.1 Introduction

The results from the two studies described in Chapter 3 and Chapter 4 were used to assess correlations between objective retinal responses to simulated peripheral optical blur and perceptual responses to the same types of simulated peripheral optical blur.

The processing of blur by the visual system comprises two steps: (1) processing at the retina level, which is dependent on the optical quality of the eye, and (2) once blur is detected by the retina, it is further interpreted at higher visual processing levels[16]. Once blur has been detected at the retinal level, there are higher level processes that are required to carry out our everyday tasks such as scanning our environment, driving, and reading[17]. Blur perception plays a crucial role in accommodation and also provides us with relative and absolute depth of objects.

Blur perception and processing is dependent on the type of blur that is being used to degrade images. Different types of blur qualitatively produce different images. For example, defocus blur presents as a simple disc and it is proportional to defocus in diopters and pupil size; as the blur disk diameter increases, so do the amount of defocus blur[53]. The types of blur that are of most interest in the development of myopia are defocus, spherical aberration and astigmatism.

We compared the responses to these types of optical blur by both the retina and higher perceptual levels to further our understanding of where within the visual pathway the effects of eccentricity and refractive error are happening. Some questions that we aimed to answer are: do the higher levels of intrinsic blur found in myopes correlate to decreased retinal responses for each type of optical blur and eccentricity? Given that we only found differences in intrinsic blur, not in perceptual criterion between emmetropes and myopes, we hypothesized that retinal responses to peripheral blur will be **correlated with intrinsic blur thresholds but not with perceptual criterion.** It is important to note, however, the ERG stimuli are suprathreshold, whereas the psychophysical task is measuring perceptual thresholds.

5.2 Methods

Correlation analyses were completed in SPSS between the pERG (N2 and P1) and blur perception (Intrinsic Blur and Perception Criterion) data. Any outliers in our data was removed

before running these analyses. As a reminder, P1 signals are the initial signal that originates from the retinal ganglion cells and the outer retinal photoreceptors whereas N2 signals are the second signal that arrives from the inner retina and reflects ganglion cell activity. Correlations were run for the 21 subjects (ages 25.19±1.40 years) that completed both studies. Of those 21 subjects, 12 were myopes (SE: -2.66±1.97D) and 9 were emmetropes (SE: +0.05±0.17D). The correlations were run with all subjects (emmetropes and myopes) together, and also within each refractive group to investigate any existing correlations in myopes and emmetropes.

5.3 Results

All subjects:

When data from all subjects were correlated between the pERG and psychophysical responses, no significant correlations were found for the DEF or the combination (J45+DEF) conditions between either N2 and P1 responses and either intrinsic blur or perceptual criterion. There were also no significant correlations for the SA and J45 between N2 or P1 and intrinsic blur. However, there were two significant correlations noted (Figure 5.1.): **Perceptual Criterion** were positively correlated with N2 pERG responses for 0.3µm blur at 6-Deg for SA (r=0.452, p=0.040), and J45 (r=0.437, p=0.048).

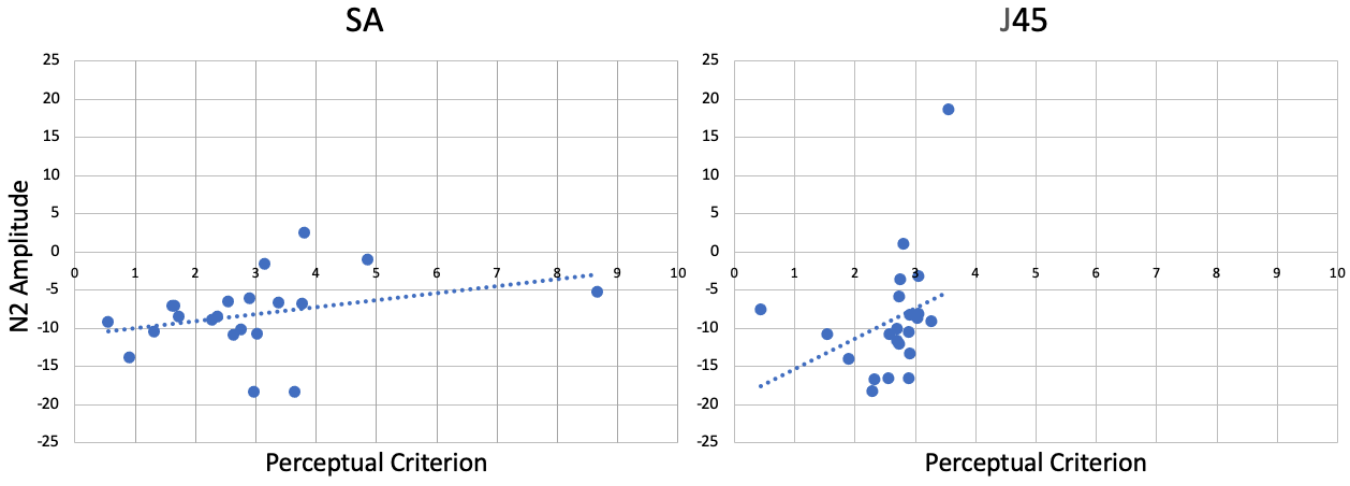


Figure 5.1. Significant positive correlations were noted at 6-Deg eccentricity for 0.3µm blur between the perception criterion and the N2 pERG amplitudes for both SA and J45 blur.

When the correlations were run separately for each refractive group (emmetropes and myopes), some notable significant correlations were found as described below.

Emmetropes:

Intrinsic Blur thresholds at **0-Deg** (entire image blurred) were positively correlated with N2 for all **SA** blur amounts (0.1µm: r=0.820; p=0.007, 0.3µm: r=0.770, p=0.015, and 0.5µm: r=0.887; p=0.001), as shown in Figure 5.2. **Intrinsic Blur** thresholds for SA at **12-Deg** (image with least amount of blur) were also positively correlated with P1 for 0.3µm blur (r=0.762, p=0.017), as shown in Figure 5.3. No correlations were found between Intrinsic Blur and N2 for 6-Deg SA.

Blur Perceptual Criterion thresholds for **SA** at **12-Deg** were negatively correlated with P1 only for the 0.1µm blur amplitude (r=-0.745, p=0.021) (Figure 5.3.). No correlations were found between Blur Perceptual Criterion and P1 for the 0-Deg and 6-Deg images, nor for N2 for any images.

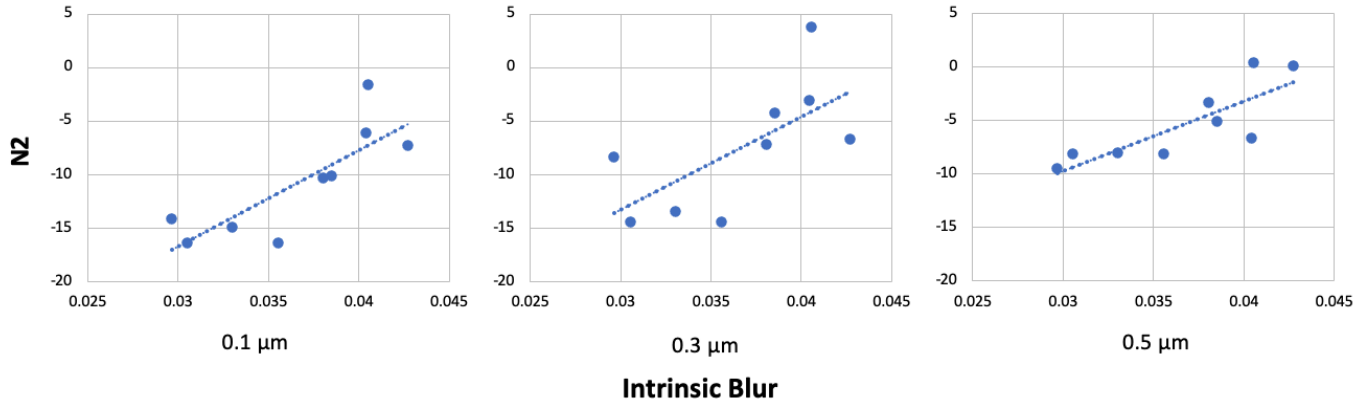


Figure 5.2. Significant positive correlations were noted for SA at 0-Deg (entire image blurred) between the intrinsic blur values and N2 responses for all levels of blur (0.1µm, 0.3µm, 0.5µm) in emmetropes.

For **J45** (oblique astigmatism), **Perceptual Criterion** thresholds at **6-Deg** were significantly positively correlated with N2 for 0.1µm (r=0.669, p=0.049) and 0.3µm (r=0.837, p=0.005) blur levels. There was a positive trend at **12-Deg** for 0.1µm (r=0.661, p=0.053) and 0.3µm (r=0.711, p=0.032) blur levels.

For combination of aberrations (**J45+DEF**), no correlations were between either Intrinsic Blur or Perceptual Blur Criterion and N2 or P1.

For **DEF** blur, **Intrinsic Blur** thresholds at **6-Deg** were positively correlated with N2 for 0.1µm (r=0.720, p=0.029) and 0.3µm (r=0.686, p=0.041) blur levels.

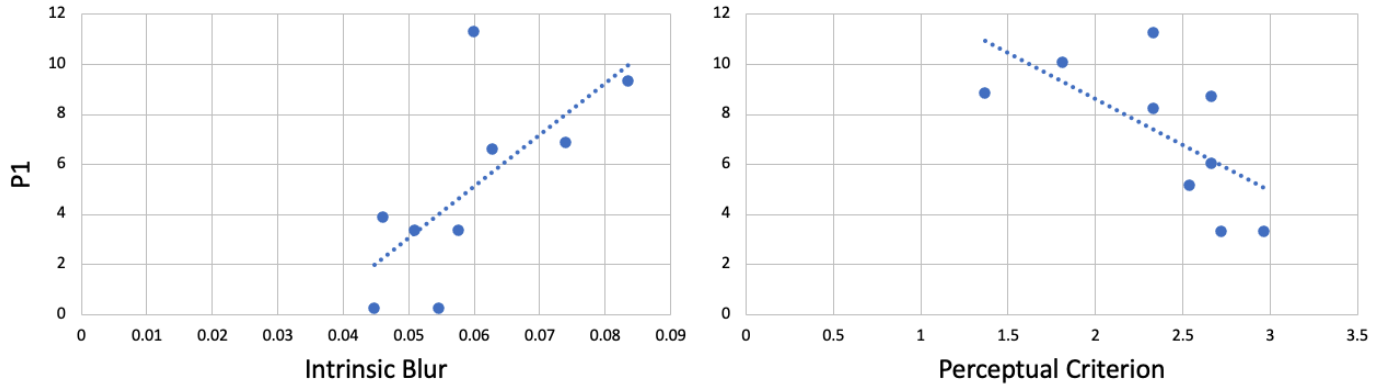


Figure 5.3. Significant positive correlations were noted for SA at 12-Deg (only the furthest periphery blurred) between the intrinsic blur values and P1 (for 0.3µm) and between the perceptual criterion and P1 (for 0.1µm) in emmetropes.

Myopes:

For **SA**, **Perceptual Criterion** thresholds at **0-Deg** (entire image blurred) were positively correlated with N2 for 0.3µm (r=0.61, p=0.033). Blur **Perceptual Criterion** thresholds at **12-Deg** were also positively correlated with P1 for blur amounts 0.3µm (r=0.636, p=0.026) and 0.5µm (r=0.615, p=0.033). There were no significant correlations between Intrinsic Blur and ERG responses for SA in myopes.

For **J45** (oblique astigmatism), **Intrinsic Blur** thresholds at **0-Deg** were negatively correlated with N2 for 0.1µm (r=-0.608, p=0.036) and with P1 for 0.5µm (r=-0.732, p=0.007). Intrinsic Blur thresholds at **6-Deg** were significantly positively correlated with P1 for 0.1µm (r=0.61, p=0.033). Blur **Perceptual Criterion** thresholds at **0-Deg** were positively correlated with P1 for 0.3µm (r=0.601, p=0.039).

For combination of aberrations (**J45+DEF**), **Intrinsic Blur** thresholds at **0-Deg** were negatively correlated with N2 for blur 0.1µm (r=-0.608, p=0.036) and with P1 for 0.5µm (r=-0.732, p=0.007). Blur **Perceptual Criterion** thresholds at **0-Deg** were positively correlated with P1 at 0.3µm (r=0.601, p=0.039) and negatively correlated for **12-Deg** with N2 at all blur levels (0.1µm: r=-0.774, p=0.003, 0.3µm: r=-0.580, p=0.048, and 0.5µm: r=-0.727, p=0.007), as shown in Figure 5.4.

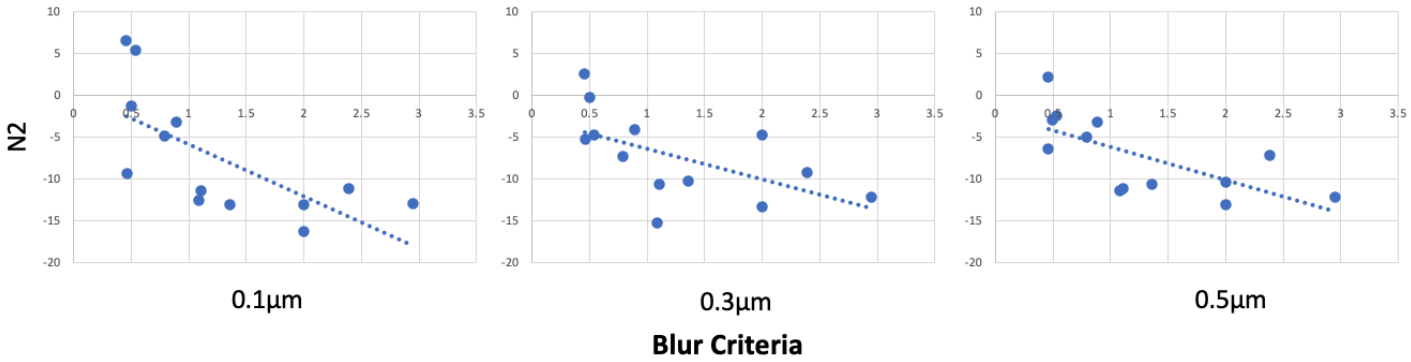


Figure 5.4. Significant negative correlations were found for all pERG N2 responses and perceptual criterion values for all amounts of blur for the J45+DEF condition.

There were no correlations for **DEF** between either Perceptual Blur Criterion or Intrinsic Blur and pERG responses (either N2 or P1) in myopes.

5.4 Discussion

When data for all subjects were analyzed, we found a general trend of stronger retinal responses to blur correlated with lower perceptual blur criterion. This correlation was statistically significant at 6-Deg eccentricity for Perceptual Criterion with SA and J45 blur types. These results may indicate that for SA and J45, our ability to distinguish between two blurred images and our corresponding retinal responses exist at around this eccentric location.

Myopes showed significant correlations between retinal responses and both the Intrinsic Blur and Perceptual Criterion conditions when using images that were entirely blurred (0-Deg). This was seen for SA, J45 and for combination of aberrations (J45+DEF), but not for DEF. This is interesting as Intrinsic Blur (not Perceptual Blur) was higher in myopes than emmetropes for all types of optical blur (at all eccentricities) except DEF. Since myopes experience DEF during uncorrected conditions, it may be likely that myopes have developed a compensatory/adaptation mechanism for this type of blur which may be the reason we did not observe a significant correlation in myopes. On the other hand, emmetropes only showed correlations between retinal responses and Intrinsic Blur for the 0-Deg images blurred with SA, not for the other types of blur and not for Perceptual Criterion. This may indicate that emmetropes are more sensitive to SA blur compared to myopes and may imply that SA is the optical blur that plays an important role in the

emmetropization process. In the pERG study, it was also found that SA blur had a greater impact on retinal responses than DEF blur.

For the 6-Deg images, myopes only exhibited a positive correlation between retinal and perceptual responses for blur for J45, whereas emmetropes exhibited a correlation for DEF blur. This finding may also be related to a compensatory mechanism myopes have developed for DEF blur described above. These correlations can be connected to the findings found in both the pERG and perceptual blur studies. In our perceptual blur study differences between refractive groups in the intrinsic blur condition were found for SA, J45, and J45+DEF blur but not for DEF blur. As discussed above, a significant correlation was not observed in myopes for DEF blur at 6-Deg.

For the 12-Deg images, myopes exhibited a positive correlation between retinal and perceptual responses for blur for SA and J45+DEF, whereas emmetropes exhibited a positive correlation with SA. This finding may be tied back to SA being an important type of blur in the emmetropization process.

In the pERG study, DEF and SA, not J45, resulted in a significant reduction in the P1 and N2 retinal responses in myopes and emmetropes. However, there was only a significant correlation finding for emmetropes.

Decreased N1 and P2 amplitudes were also observed between 6-Deg and 12-Deg and we hypothesized that this may be the retinal location used for encoding blur signals. Our significant positive correlation findings between refractive groups at 6- and 12- degrees were found for DEF and SA blur for emmetropes. These were also the only two types of optical blur that decreased P1 and N2 retinal responses in both myopes and emmetropes. These findings together further imply that between 6- and 12- degrees may be the retinal location for blur encoding and that DEF and SA optical blur may be the major types of blur important in this process.

In our perceptual blur study, higher levels of intrinsic blur were found for myopes compared to emmetropes for all optical blurs except DEF blur while perceptual criterion results were no different between emmetropes and myopes. Our subsequent correlation study show that even with decreased P1 and N2 signals to DEF and SA, this is not translated into myopes intrinsic blur threshold for DEF blur as there were no significant correlations found here. This goes in line with what was discussed earlier with how myopes may have developed a compensatory mechanism for this type of optical blur.

When taking all of these findings into account, it appears that SA may play a larger role in emmetropization than DEF blur.

6. General Conclusions

Findings from both the retina and perception studies suggest that the area between 6 to 12 degrees eccentricity may play a major role in blur encoding and thus, could be important in emmetropization.

In the pERG study, we found that the amplitude of retinal responses decreases when blur is applied to the entire image (0-Deg) compared to the CLEAR image, and this reduction is more significant with larger amounts of blur. It was also found that the pERG responses to the 6-Deg images were not different from the 0-Deg (entirely blurred) images, but were reduced compared to the 12-Deg images. This is the basis for our hypothesis that the area for blur encoding in the retina is between 6 and 12 degrees eccentricity.

In the blur perception study, it was found that although both intrinsic blur and perceptual criterion thresholds increase in the periphery overall in both refractive groups, this effect was most pronounced for intrinsic blur with spherical aberration, astigmatism, and a combination of defocus and astigmatism blur for myopes, indicating that myopes may have more difficulty discriminating these types of blur.

The difference in intrinsic blur here are likely due to optical factors and this effect was more pronounce as the blur was presented further in the periphery. Perceptual criteria were also eccentricity dependent, but there were no significant differences between refractive error groups. This finding indicates that although myopes have an overall blurrier visual system, they perform the same as emmetropes at differentiating optical blur once it can be detected. As discussed previously, this finding may be due to other aspects of image quality such as different type of optical bur. Based on the findings collectively from all three of our studies, SA optical blur may be the major factor in blur encoding and emmetropization.

When we correlated retinal responses to blur with blur perception, for emmetropes intrinsic blur thresholds for DEF at 6-Deg were positively correlated with N2. No correlations were noted for perceptual criterion or intrinsic blur with neither N2 or P1 in myopes. This could mean that although myopes can experience DEF blur as emmetropes do, they may have developed a higher level mechanism to compensate for this type of blur.

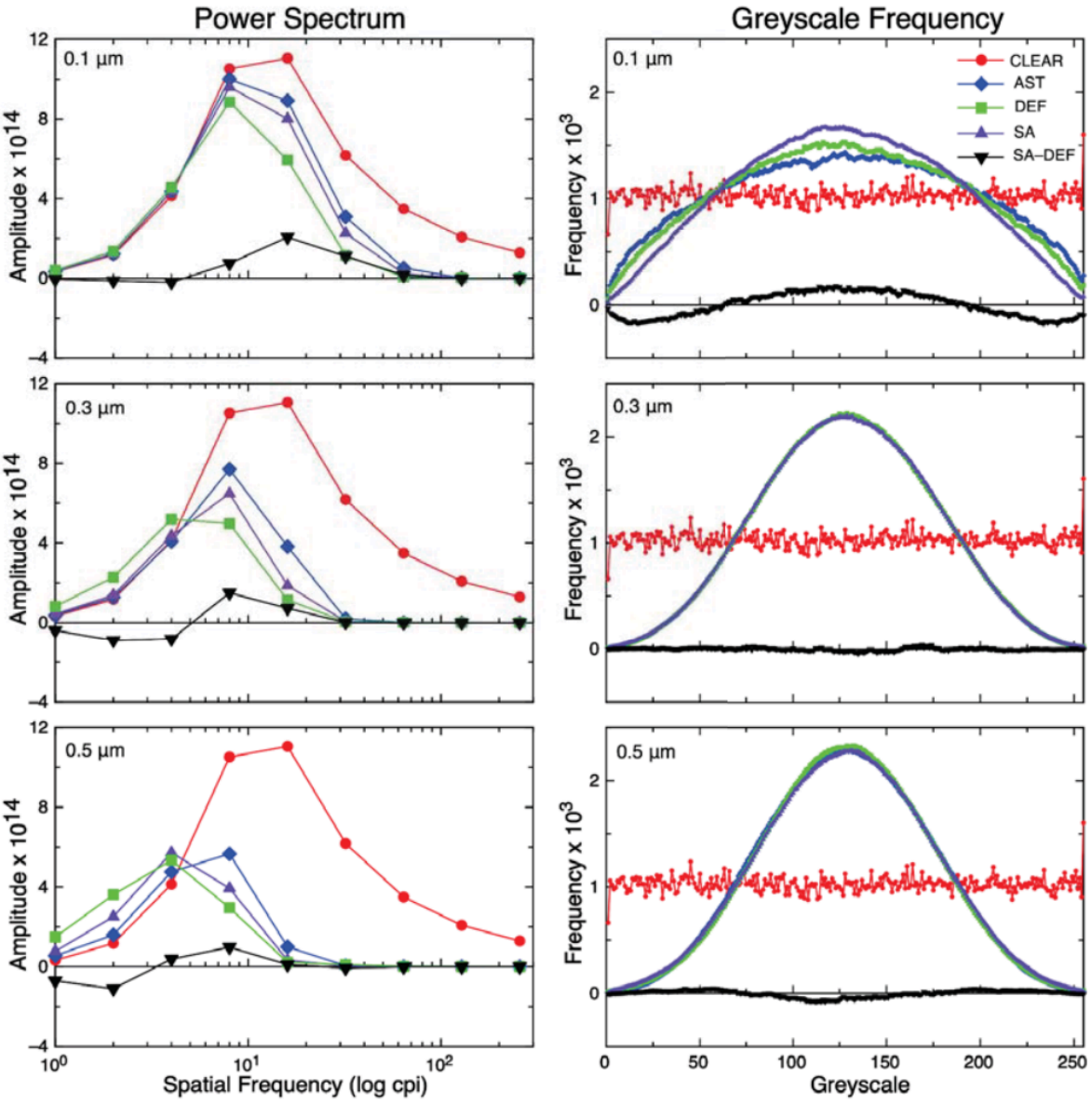
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Appendix I: Image Statistics



Appendix II: ARVO Poster 2019

Cross-Retinal pERG Responses to Simulated Optical Blur in Myopia

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Background

- Myopes show decreased peripheral sensitivity to blur[1] that may be correlated to a sub-optimal retinal function in the near-peripheral retina. Peripheral deficiencies in blur sensitivity may interfere with normal emmetropization.
- Retinal image focus provides a feedback signal for eye growth control during normal emmetropization.[2-3] Disruption of this process by abnormal image focus or abnormal use of this signal causes myopia.
- The electroretinogram (ERG) measures the electrical activity generated by retinal cells in response to a stimulus. Previous studies have shown abnormal ERG responses in both animal models of myopia and humans with myopia. ERG studies in humans have shown reduced amplitude and delayed latency in myopia, more so in the peripheral retina.[4-6]
- Chin et al[7] found a sign-dependent retinal response to defocus blur, located in the near peripheral retina. Retinal responses to blur across the retina in myopia have not been previously measured.

Purpose

- ***To use pERG to evaluate the near-peripheral retinal decoding system for different types of optical blur in myopic eyes.***

Hypothesis

- Adults with myopia will show impaired retinal responses (decreased amplitude) to optically blurred stimuli in the near-peripheral retina.

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Acknowledgements / Commercial Relationships

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Commercial relationships: No commercial relationships.

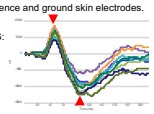
Methods

Stimuli and Procedures

- Retinal responses were recorded (dominant eye) using DTL active electrodes, 9mm gold-cup reference and ground skin electrodes.
- Outcome variables of the pERG:

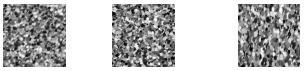
  N95 (amplitude)

  P50 (amplitude)



- Viewing target: customized blurred images ("dead leaves") displayed on CRT monitor via MATLAB. Images convolved with optical blur:

(i) **Defocus** (ii) **Spherical Aberration (SA)** (iii) **Astigmatism (J45)**



blur amount: (0.1, 0.3 and 0.5μm)

(iv) **Combination of Astigmatism and Defocus**

blur amount: (0.071, 0.213 and 0.354μm)

- Three different image areas were blurred



0 degrees: The entire image was blurred, with no clear central area,
6 degrees: The entire image was blurred except for a central disk of 6deg radius
12 degrees: The entire image was blurred except for a central disk of 12deg radius.

Analyses

- Mixed model ANOVA each parameter: within subject factors: blur type {Defocus, J45, SA, J45+Defocus}, blur amount {0.1, 0.3, 0.5}, eccentricity {12, 6, 0} and between subjects factor: refractive groups {Myopes, Emmetropes}.

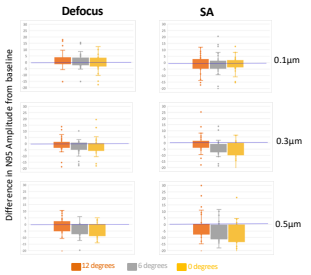
Subjects

- 20 young adults (mean age 24 ± 1 years), BCVA 0.0 LogMAR or better
- Refraction (SE each eye) range: +0.75 to -8.00 (<1.50DC):
  - Myopes (n=12; Mean SE: -2.59 ± 1.38D)
  - Emmetropes (n=8; Mean SE: -0.03 ± 0.04D)

Results

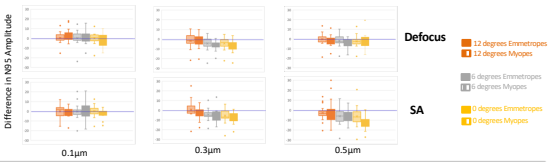
Group Data: Effect of Amount of Blur and Blur Eccentricity

- Significant effect was found of the **blur amount** on N95 responses for each type of blur (Defocus: F=50.775, p<0.001; SA: F=37.774, p<0.001; J45: F=11.061, p<0.001; J45+Defocus: F=25.714, p<0.001).
- Significant effect of blur **eccentricity** was found on N95 responses for all types of blur (Defocus: F=26.094, p<0.001; SA: F=28.640, p<0.001; J45: F=5.478, p=0.008; J45+Defocus: F=5.346, p=0.009). Posthoc analyses showed significant effect of eccentricity for 0.3um and 0.5um of Defocus and SA.
- Significant interactions for **eccentricity** and the **amount of blur** for Defocus (F=3.672, p=0.014), SA (F=4.836, p=0.03), and J45 (F=3.375, p=0.020), but not for the J45+Defocus (F=0.399, p=0.808).



Effect of Refractive Group

- No significant difference between refractive groups (F=0.048, p=0.828).



Conclusions

- pERG may be used to evaluate retinal responses to varied amounts of optical blur and different peripheral eccentricities.
- Differences in retinal responses with blur eccentricity suggest distinct retinal zones for blur decoding.
- No differences in retinal responses were found among these groups of myopes and emmetropes.

Appendix III: ARVO Abstract 2020

ARVO 2020

View Abstract

CONTROL ID: 3357539
SUBMISSION ROLE: Abstract Submission

AUTHORS
AUTHORS (LAST NAME, FIRST NAME): Jeong, Emily[1]; Bex, Peter J.[2]; Otero, Carles[3]; Vera-Diaz, Fuensanta A.[1]
INSTITUTIONS (ALL): 1. New England College of Optometry, Boston, MA, United States.
2. Northeastern University, College of Science, MA, United States.
3. Anglia Ruskin University, Cambridge, United Kingdom.
Commercial Relationships Disclosure (Abstract): Emily Jeong: Commercial Relationship: Code N (No Commercial Relationship) | Peter Bex: Commercial Relationship: Code N (No Commercial Relationship) | Carles Otero: Commercial Relationship: Code N (No Commercial Relationship) | Fuensanta Vera-Diaz: Commercial Relationship: Code N (No Commercial Relationship)
Study Group: (none)

ABSTRACT
TITLE: Perceptual responses to peripheral optical blur in myopia and emmetropia.
ABSTRACT BODY:
Purpose: Blur signals play an important role in emmetropization. The purpose of our study is to measure sensitivity and sources of sensitivity differences to different types and levels of simulated optical blur across the visual field. We hypothesize that myopic individuals will show increased intrinsic blur and perceptual criteria, and this will increase with eccentricity.

Methods: Thirty (24.88±1.39yrs) healthy adults with myopia (n=16, SE: -3.20±2.85D) or emmetropia (n=14, SE: +0.07±0.20D) with best-corrected VA of 20/20 or better and no binocular or accommodative dysfunction participated. Blur discrimination thresholds were measured monocularly (dominant eye) with an adaptive 4AFC task. Participants observed dead leaves stimuli 50cm from a screen with a blur annulus at either 0°, 6°, or 12° eccentricity. Images were convolved with Spherical Aberration (SA), Defocus (Def), Astigmatism (Ast), or Defocus+Astigmatism (Def+Ast) kernels. Blur pedestal levels (0.01, 0.03, 0.09, 0.27, or 0.81 μm), and increments were applied to one quadrant of the image. Participants chose which of the four quadrants appeared blurriest. Blur discrimination thresholds were fit with a two-parameter (intrinsic blur and perceptual criteria) dipper function. Mixed model analyses and pairwise t-tests were used to compute the effects of blur and eccentricity.

Results: Intrinsic blur showed an overall effect of eccentricity, with higher levels of blur at the more peripheral conditions and were overall significantly higher in myopes ($P<0.010$, $\eta2=0.092$). One-way ANOVAs showed higher intrinsic blur in myopes for SA (0deg: $F=11.457$, $P=0.002$; 6deg: $F=7.203$, $P=0.012$; 12deg: $F=6.203$, $P=0.019$), Def+Ast at 6deg ($F=10.229$, $P=0.003$) and Ast at 6deg and 12deg (6deg: $F=9.343$, $P=0.005$; 12deg: $F=5.749$, $P=0.023$). Perceptual criteria showed an overall effect of eccentricity with higher levels of blur at more peripheral conditions for Def ($P<0.001$, $\eta2=0.243$) and Def+Ast ($P<0.001$, $\eta2=0.279$), but not for SA or Ast. No main significant interaction between eccentricity and refractive group was found for blur threshold in any type of blur.

Conclusions: Intrinsic blur was higher in myopes and more pronounced in the periphery for SA, Ast, and Def+Ast, indicating that myopes have more difficulty discriminating these types of blur. This effect was not found for Def. Perceptual criteria are also eccentricity-dependent, but no differences between refractive groups was found.

(No Image Selected)
Layman Abstract (optional): Provide a 50-200 word description of your work that non-scientists can understand. Describe the big picture and the implications of your findings, not the study itself and the associated details.: Myopia (nearsightedness) is a major public health concern due to its increasing prevalence and potentially blinding consequences. Although the exact mechanisms that cause myopia are not well understood, it is known that blur signaling is an important feedback signal involved in eye growth and myopia. Consequently, disruption of blur signals can result in myopia. The purpose of our study was to

measure participant's ability to perceive different types of simulated optical blur. Our results indicate that individuals with myopia have a decreased ability to discriminate certain types of blur, particularly in the periphery of their vision.

DETAILS

PRESENTATION TYPE: #1 Poster, #2 Paper

CURRENT REVIEWING CODE: 1200 Physiological optics: Refractive error myopia/ocular dimensions - VI

CURRENT SECTION: Visual Psychophysics/Physiological Optics

Clinical Trial Registration (Abstract): No

Other Registry Site (Abstract): (none)

Registration Number (Abstract): (none)

Date Trial was Registered (MM/DD/YYYY) (Abstract): (none)

Date Trial Began (MM/DD/YYYY) (Abstract): (none)

Grant Support (Abstract): Yes

Support Detail (Abstract): AAO Career Development Award, Vera-Diaz (PI), NIH/NEE R01 EY029713, Bex (PI)

TRAVEL GRANTS and AWARDS APPLICATIONS

AWARDS: ARVO Members-in-Training Outstanding Poster Award|ARVO and ARVO Foundation Travel Grants

AFFIRMATIONS

Affirmations: Affirmation of compliance with ARVO's Statement for Use of Animals.

Affirmations: Affirmation of compliance with ARVO policy on registering clinical trials.

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