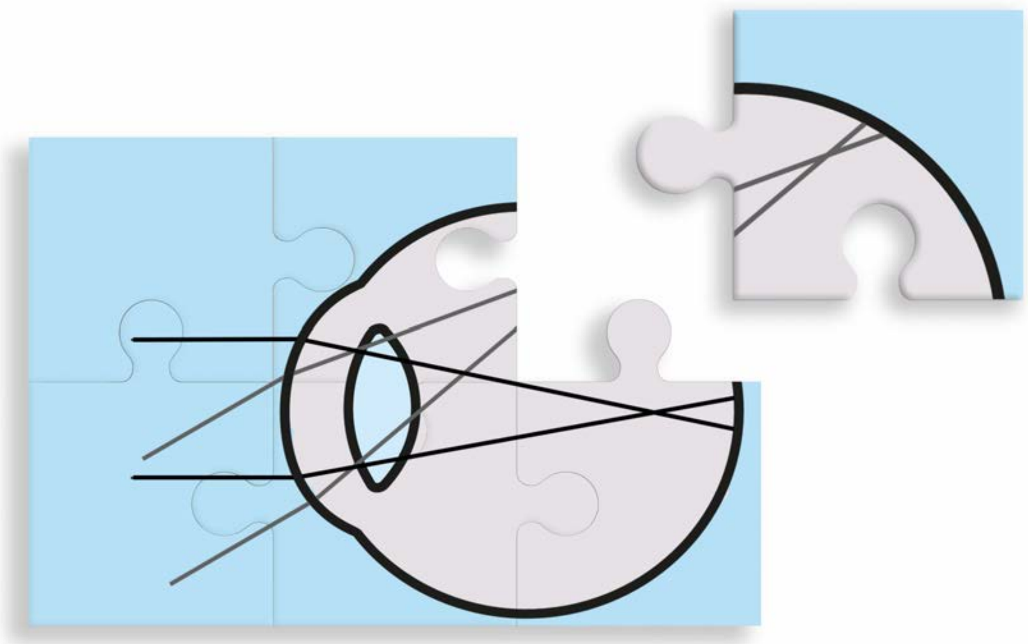
KTH ROYAL INSTITUTE
OF TECHNOLOGY

Doctoral Thesis in Physics

Myopia control and peripheral vision

PETROS PAPADOGIANNIS



Stockholm, Sweden 2021

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Abstract

The rapid rise in myopia prevalence has caused an urgent need for effective myopia control interventions. This thesis investigates the role of the peripheral optics of the human eye in myopia progression. It was initially believed that the axial elongation of the myopic eye is caused only by the defocus signals presented to the central retina. However, studies on animals have proven that ocular growth can be regulated by optical factors beyond the fovea. A common hypothesis nowadays is that peripheral image quality is an important factor for eye growth regulation also in humans. The detection of the sign of defocus by the retina is essential for the control of both accommodation and eye growth. Therefore, the aim of this thesis is to map out visual cues to myopia development by evaluating peripheral vision. Additionally, effective optical properties of multifocal contact lenses for myopia control have been investigated.

Peripheral vision was evaluated by adaptive psychophysical routines in order to find properties in the peripheral image quality that might be used by the eye to detect the sign of defocus. We have shown that peripheral high-contrast detection acuity and contrast sensitivity can be improved by correction of higher-order aberrations and eliminating chromatic aberrations. The measurements proved that asymmetries in peripheral vision under myopic and hypermetropic defocus are mainly due to the monochromatic and not the chromatic aberrations of the eye. Moreover, we found that relative peripheral refraction did not change with increasing accommodation for emmetropes, whereas for myopes a myopic shift was observed. However, in spite of these differences, the two groups showed similar peripheral modulation transfer functions. When subjects were accommodating to an off-axis target, the accommodation amplitude declined and the accommodation response time increased with eccentricity. Finally, we evaluated optical quality and vision with the MiSight multifocal contact lens for myopia control. We believe that the effective optical properties of this lens are the larger peripheral blur and the more asymmetric point spread function, due to the additional astigmatism and coma, and that this leads to the larger accommodative response shown by some of the subjects.

Sammanfattning

Den snabbt ökande förekomsten av myopi (närsynthet) har skapat ett akut behov av effektiva behandlingar. Denna avhandling undersöker vilken roll ögats perifera optik har för myopiprogression. Tidigare trodde man att det var felfokuseringen i bilden på den centrala delen av näthinnan som ledde till den ökade axiala längden i det myopa ögat. Studier på djur har dock visat att ögats tillväxt kan styras av optiska signaler utanför fovea (mitten av gula fläcken). En vanlig hypotes idag är att den perifera bildkvalitén är en viktig faktor för tillväxtreglering även i mänskliga ögon. Näthinnans förmåga att avgöra vilket tecken felfokuseringen har är fundamental för att kunna kontrollera både ögats tillväxt och dess ackommodation. Målsättningen med denna avhandling är därför att kartlägga de visuella ledtrådarna för myopiutveckling genom att utvärdera vår perifera syn. Dessutom har de effektiva egenskaperna hos myopikontrollerande multifokala kontaktlinser undersökts.

Perifer syn utvärderades med adaptiva psykofysiska rutiner för att hitta egenskaper i den perifera bildkvalitén som ögat skulle kunna använda för att avgöra tecknet på felfokuseringen. Vi har visat att perifer högkontrastdetektion och kontrastkänslighet kan förbättras genom att korrigera högre ordningarnas aberrationer och eliminera kromatiska aberrationer. Mätningarna bevisar att asymmetrier i perifer syn mellan negativ och positiv defokus främst beror på ögats monokoromatiska aberrationer och inte på de kromatiska. Dessutom har vi sett att den relativa perifera refraktionen inte förändras för rättsynta, men att den blir mer negativ med ackommodationen för närsynta. Trots denna skillnad uppvisar dock de två grupperna likartad perifer modulationsöverföringsfunktion. Vid ackommodation till objekt utanför optiska axeln minskade ackommodationsamplituden samtidigt som responstiden ökade med ökad excentrisitet. Slutligen utvärderade vi synen med multifokala kontaktlinser, MiSight som utformats för att bromsa närsynthet, och vi tror att de effektiva egenskaperna hos denna lins är att den ger: större perifer suddighet, mer asymmetrisk punktspridningsfunktion på grund av extra astigmatism och koma, samt stimulerar till ökad ackommodativ respons hos vissa av försökspersonerna.

List of papers

Paper 1

AP. Venkataraman, **P. Papadogiannis**, D. Romashchenko, S. Winter, P. Unsbo and L. Lundström, *Peripheral resolution and contrast sensitivity: effects of monochromatic and chromatic aberrations*, J. Opt. Soc. Am. A **36**, B52-B57 (2019).

Paper 2

P. Papadogiannis, D. Romashchenko, P. Unsbo, and L. Lundström, *Lower sensitivity to peripheral hypermetropic defocus due to higher order ocular aberrations*, Ophthalmic Physiol. Opt. **40**, 300-307 (2020).

Paper 3

P. Papadogiannis, D. Romashchenko, S. Vedhakrishnan, B. Persson, A. Lindskoog Pettersson, S. Marcos, L. Lundström, *Foveal and peripheral visual quality and accommodation with multifocal contact lenses*, submitted manuscript, (2020).

Paper 4

D. Romashchenko, **P. Papadogiannis**, P. Unsbo and L. Lundström *Foveal-peripheral real-time aberrations with accommodation in myopes and emmetropes*, submitted manuscript, (2020).

Paper 5

N. Sharmin, **P. Papadogiannis**, D. Romashchenko, L. Lundström and B. Vohnsen, *Parafoveal accommodation response to defocus changes induced by a tuneable lens*, manuscript.

Contents

List of abbreviations and units

2-AFC Two-alternative-forced-choice

AO Adaptive optics

CSF Contrast sensitivity

D Diopter, 1/m

HS Hartmann-Shack

LCA Longitudinal chromatic aberration

logMAR Base-10 logarithm of the minimum angle of resolution in arcminutes

MAR Minimum angle of resolution

MTF Modulation transfer function

RMS Root mean square

TCA Transverse chromatic aberration

Chapter 1

Introduction

The human eye and the brain in a perfect cooperation produce the sense of vision; the most important of our five senses. Vision is a combination of optical input and neural processing. The optical components of the eye focus the rays of light from an object of interest into an image on the retina. There, the light is converted to electrical signals, and these signals are sent to the brain for further processing. The brain receives input from the central and the peripheral visual field simultaneously, and this is essential for proper sight. The normal binocular visual field of a human eye extends to approximately 200° horizontally and 150° vertically. The center of the visual field corresponds to the central retina, the fovea, which is responsible for resolving fine details. The peripheral field is necessary for detecting our surroundings and for orientation and mobility. Peripheral vision becomes even more important for people with reduced or absent foveal vision, for example in patients with macular degeneration.

When the eye fails to focus the light on the retina, myopia (nearsightedness) or hypermetropia (farsightedness) can occur. Compared to a normal-sighted eye (emmetropia, light is focused on the retina), the myopic eye is elongated and the image is focused in front of the retina, whereas the hypermetropic eye is shorter and the image is focused behind the retina. Myopia can be corrected with spectacles, contact lenses or refractive surgery. But, given its increasing prevalence, myopia has become a worrying phenomenon due to its possible sight-threatening complications. Therefore, one of the important topics in visual optics research is development of optical interventions for myopia control and halt the progression of myopia from a young age. Studies in animal models have shown that not only the central, but also the peripheral retina is responsible for ocular growth regulation. Thereby, it is believed that myopia progression in humans is related to peripheral image quality. Furthermore, the most effective optical interventions have been found to be orthokeratology rigid contact lenses, multifocal spectacles and multifocal soft contact lenses, that all manipulate the image quality on the peripheral retina. However, the details of the effective properties of these interventions are not well-understood.

This work focuses on myopia control and peripheral vision and investigates the visual cues that the eye is using to regulate its growth. Chapter 2 gives a brief overview of the anatomical structures of the human eye and the retina. Chapter 3 describes the refractive errors, the higher-order monochromatic and chromatic aberrations and the optical quality over the visual field. Furthermore, the principle of the Hartmann-Shack wavefront sensor is presented. Chapter 4 explains methods for evaluating and quantifying vision and Chapter 5 focuses on the influence of aberrations on peripheral vision and describes adaptive optics for monochromatic aberrations correction. Myopia prevalence and eye growth regulation, as well as myopia control interventions and the effective properties of multifocal contact lenses, are discussed in Chapters 6 and 8. Chapter 7 is focused on the asymmetry in the sensitivity due to myopic and hypermetropic defocus, and Chapter 9 discusses accommodation and aberrations over the visual field. Chapter 10 presents the conclusions of this thesis, and gives an outlook for future work.

Chapter 2

Anatomy of the human eye

Vision is the process through which an image of an object is perceived by the brain. Light from the object of interest propagates to our eyes and reaches the retina after passing through the different optical components of the eye. The light enters the eye through the cornea, it passes through the pupil, then through the crystalline lens and lastly through the vitreous body. Finally, it reaches the retina, where it is converted into electrical signals by the photoreceptors. These electrical signals are sent via the optic nerve to the brain for further processing. In this chapter the anatomical characteristics of the human eye will be presented.

2.1 The structures of the human eye

Figure 2.1 shows a schematic representation of the components of the human eye. The human eye is roughly spherical, it has an axial length of about 24 mm and a refractive power of approximately 60 D. The outer shell of the eye contains the sclera and the cornea. The sclera consists of collagen, it has no blood vessels (except for a few blood vessels on its surface) and it is very durable despite its 1 mm thickness. The sclera forms the supporting wall of the eyeball and is responsible for protecting and holding the eye together. The cornea and the sclera meet at the corneal limbus. The cornea is the transparent surface at the front of the eye and the first refractive surface that the light passes through. It is responsible for two thirds of the eye´s total optical power, i.e. around 40 D, and it has an aspheric surface with average refractive index of 1.376. It mainly consists of the corneal stroma, which is made of collagen fibers and keratocytes, and lies between the corneal epithelium and the corneal endothelium. The cornea has a central thickness of approximately 500 μm which increases to 700μm in the periphery. Since it is important to be transparent, the cornea is avascular and it is oxygenated

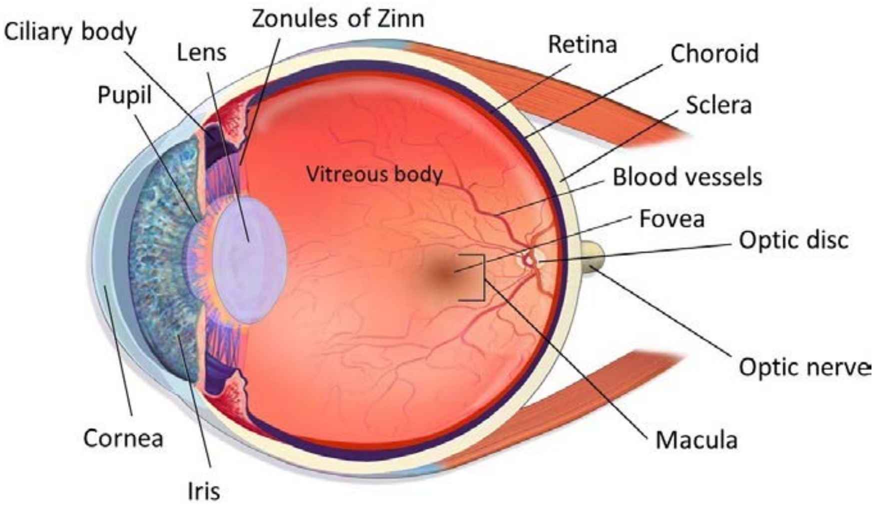

Figure 2.1. A schematic representation of the structures of the human eye. Adapted from Medical gallery of Blausen Medical 2014 [1]

and gets nutrients through the tears via diffusion. It is very durable but also very sensitive to touch.

The iris is the diaphragm of the eye, it is responsible for the color of the eye due to the pigmented cells on its surface, and it separates the posterior from the anterior chamber. It has a circular opening, the pupil, and by controlling the pupil size it controls the amount of light that falls on the retina. The pupil size depends on the light conditions, i.e. it constricts in high light intensities and dilates in lower light intensities. It has a diameter between 2-8 mm and it is the aperture stop of the eye.

After passing through the pupil, the light meets the second refractive component of the eye, the crystalline lens. The crystalline lens is elastic, transparent and avascular. It has one third of the eye´s total power, i.e. approximately 20 D, a biconvex shape and a gradient refractive index between 1.38 and 1.41. The crystalline lens is suspended in place by the zonules of Zinn, a circumferential system of fibrous strands connecting the lens to the ciliary body. The crystalline lens is responsible for accommodation. In the absence of refractive errors, distant observation of an object results in a clear retinal image of the target (i.e. the image is well focused on the retina). When there is a need to see objects that are located at short distances clearly, for instance when we read, the eye should change its refractive power to focus the image of the near object on the retina. This ability is called accommodation and it is achieved by increasing the curvature of the crystalline lens due to the contraction of the ciliary muscle and the relaxation of the zonules of Zinn. This results in a more curved shape of the crystalline lens and thus higher refractive power. Additionally, during the accommodation reflex the eyes also converge and the pupils constrict.

The last structure that the light meets before reaching the retina, is the vitreous body. The vitreous body is a transparent gelatinous mass with a refractive index of 1.336 that fills the space between the crystalline lens and the retina. The retina is the innermost photosensitive layer of the eye, where the rays of light are focused on and converted to electrical signals. The retina consists of several sublayers, and the choroid (a vascular layer that lies between the retina and the sclera) is responsible for the nourishment and oxygenation of the outer layers of the retina.

2.2 Anatomy of the retina

Figure 2.2 shows a schematic representation of the retinal anatomy.The retina has three distinctive areas: the macula, which is a pigmented oval-shaped area near the center of the retina, has a diameter of about 5.5 mm (20°) and provides high acuity vision; the fovea which is a dip located in the center of the macula and gives the highest resolution; and the optic disc (the head of the optic nerve) which has no light perception and is known as the blind spot.

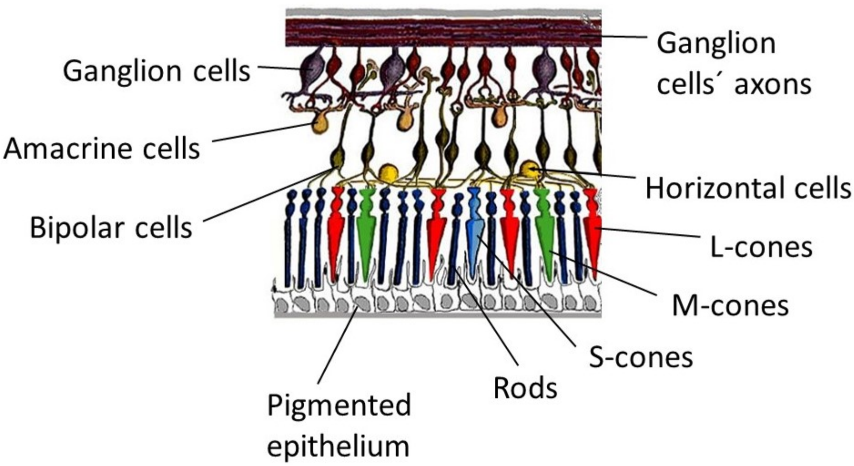

Figure 2.2. A schematic representation of the anatomy of the human retina. Adapted from Webvision [2]

The retina contains five different neuron cells: the photoreceptors, the horizontal, the bipolar, the amacrine and the ganglion cells. The photoreceptors convert the light into electrical signals. There are two kinds of photoreceptors, the rods and the cones. The rods are responsible for night vision, i.e. low light conditions, and they do not help with color vision. Rods are absent from the central fovea, however their density increases with eccentricity. The cones are responsible for day vision, i.e. high light conditions, and they are responsible for color vision. Cones have their highest density in the fovea, however their density decreases and their size increases with eccentricity. There are three types of cones: the S-cones which show their peak sensitivity in short wavelengths (blue color), the M-cones which show their peak sensitivity in medium wavelengths (green color) and the L-cones which show their peak sensitivity in long wavelengths (red color). After the light is converted to electrical signal from the photoreceptors, the signal is transmitted to the ganglion cells via the bipolar and the horizontal cells. The axons of the ganglion cells form the optic nerve which transmits the received information to the brain for further processing.

The area of photoreceptors that are connected to one ganglion cell forms a retinal receptive field. In the fovea each cone is connected to one ganglion cell, and thus ganglion cells located at the center of the retina have the smallest receptive fields. By moving towards the peripheral retina, each ganglion cell is connected to multiple photoreceptors. Thus, the size of the receptive fields increases with eccentricity, which results in a lower sampling density in the periphery.

Chapter 3

Refractive errors and higher-order aberrations

A necessary condition for the proper function of human vision is the formation of a clear image on the retina. This condition is fulfilled by the optical system of the eye. Rays from the objects we see are entering our eyes and are first refracted by the cornea. After that and with the help of the crystalline lens, the rays are focused on our retina. Since the eye is an optical system, it can suffer from refractive errors and higher-order aberrations. This chapter will introduce the different kinds of refractive errors and higher-order aberrations that affect the optical quality of the eye.

3.1 Refractive errors

When the axial length and the refractive power of the eye are in balance, then a clear image from a distant object is formed on the retina (emmetropia, Figure 3.1 top). If this balance is disrupted and the axial length of the eye does not match its refractive power, refractive errors or lower-order aberrations occur (ametropia). The different types of ametropia include myopia (nearsightedness), hypermetropia (farsightedness) and astigmatism and result in blurred vision. In myopia (or myopic defocus), the incident rays from a distant object are focused in front of the retina (Figure 3.1 middle) and in hypermetropia (or hypermetropic defocus) behind the retina (Figure 3.1 bottom).

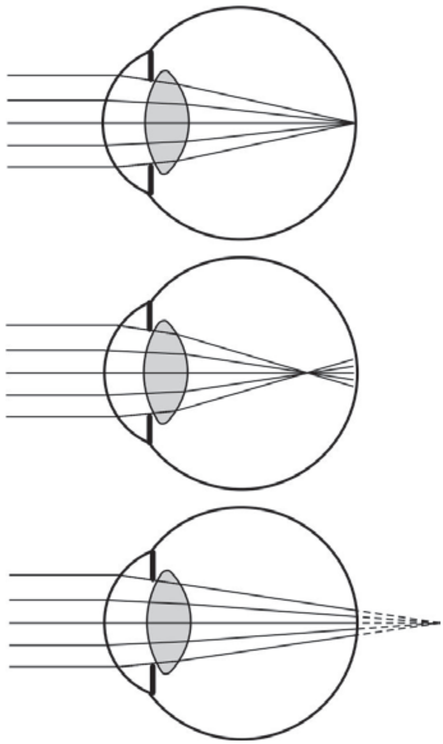

Figure 3.1. A schematic representation of an emmetropic eye (top), a myopic eye (middle) and a hypermetropic eye (bottom).

In astigmatism a blurred image is formed due to the fact that the refractive power in one principal meridian is different compared to the other and as a result the incident rays cannot focus on one point. Regular astigmatism occurs when the two meridians are perpendicular to each other and appears in three different types:

1. With-the-rule astigmatism when the meridian with the greatest power is close to 90°,

2. Against-the-rule astigmatism when the meridian with the greatest power is close to 180° and

3. Oblique astigmatism when the principal meridians are not at 90° and 180° but they are still perpendicular.

The refractive errors of the eye can be measured either by objective methods (retinoscopy, autorefraction) or subjectively (maximization of visual acuity by using trial lenses). Myopia can be corrected with negative spherical lenses, hypermetropia with positive spherical lenses and astigmatism with cylindrical lenses. In case astigmatism coexists with myopia or hypermetropia, sphero-cylindrical lenses are used for simultaneous correction of both refractive errors. Different interventions can be used for lower-order aberrations correction. Spectacles are the most usual intervention but with some disadvantages. In case of very large refractive error, spectacles cause reduction (in myopia) or magnification (in hypermetropia) of the image size. Furthermore, when there is excessive difference in refractive error between the two eyes, spectacle correction causes aniseikonia, that is large size difference of the perceived image between the two eyes. Refractive errors can also be corrected with contact lenses and laser assisted refractive surgery.

3.2 Higher-order aberrations

Higher-order monochromatic aberrations are optical irregularities of the eye which are more complex than refractive errors. Their effect increases with pupil size and they cannot be corrected with spherical or cylindrical lenses. The most common higher-order aberration in the eye is spherical aberration. Spherical aberration occurs due to the fact that peripheral rays (through the edge of the pupil) are focused differently compared to the rays that pass from the center of the pupil, resulting in halos around light sources. Another common higher-order aberration is coma. Coma causes the formation of a comet-shaped image of a point source on the retina when oblique incident rays pass through the optics of the eye.

The higher- and lower-order monochromatic aberrations can be measured with wavefront analysis. The most common principle for wavefront analysis is the Hartmann-Shack (HS) sensor (Figure 3.2). In a HS sensor, a narrow beam of light is sent into the eye through the pupil and focuses on the retina. The focused light acts as a point source which is reflected, and as it passes through the eye it forms an aberrated wavefront due to the ocular aberrations. This aberrated wavefront exits the eye and ends up on a microlens array. The microlens array sub-divides the aberrated wavefront and focuses the sub-divided parts on a corresponding spot on a detector. The displacement of each spot from the reference (flat/aberration free) wavefront spot, represents the local slope of the aberrated wavefront over the pupil. From these slopes the wavefront can be reconstructed and described by Zernike polynomials [3].

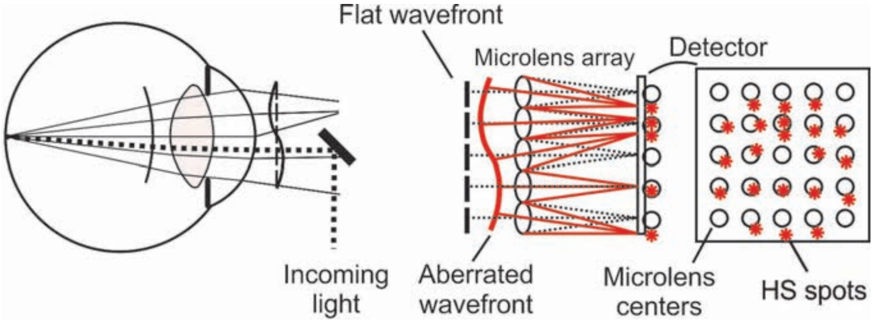

Figure 3.2. A schematic representation of the principle of the Hartmann-Shack wavefront sensor. On the left side, the narrow beam of light that enters the eye (dashed line) and the wavefront that exits the eye are shown. On the right side, the microlens array, the detector and the spot pattern are shown. The aberrated wavefront and the displacements from the reference wavefront are shown in red, whereas in black is the reference wavefront and the corresponding ideal image positions. Adapted from Lundström [4]

3.3 From wavefront aberrations to refraction

Zernike polynomials are the standard metric for reporting wavefront aberrations of the eye, and they can describe both higher- and lower-order aberrations [5, 6]. They are a set of functions that are orthogonal over the unit circle, i.e. the magnitude of one polynomial does not affect any other. The Zernike polynomials are usually defined in polar coordinates (ρ,θ) where ρ is the radial coordinate and θ is the azimuthal angle. The shape of the wavefront over a circular pupil can be described as

$$W(\rho,\theta) = \sum_{m,n} c_n^m Z_n^m(\rho,\theta) \tag{3.1}$$

where (c) is the coefficient that describes the weight of the polynomial in the wavefront (often given in μm), (n) is the radial order, that is the highest power of the radial polynomial and (m) is the angular meridional frequency. By using the second order Zernike coefficients of the wavefront, that is the (c_2^0) which corresponds to defocus, and the (c_2^2), (c_2^{-2}) which correspond to vertical/horizontal and oblique astigmatism respectively, we can determine the refractive error. The refractive correction can be calculated by using the following equations:

$$M = \frac{-4\sqrt{3}}{r_{\text{pupil}}^2} c_2^0, \qquad J0 = \frac{-2\sqrt{6}}{r_{\text{pupil}}^2} c_2^2, \qquad J45 = \frac{-2\sqrt{6}}{r_{\text{pupil}}^2} c_2^{-2} \tag{3.2}$$

where r_{pupil} is the pupil radius. The coefficients and the r_{pupil} should be either all given in *meters* or in μm and *millimeters*, respectively, in order to give the refraction in diopters (D) .

For more accuracy, higher-order Zernike coefficients can be included in the calculation of the refraction (Seidel refraction):

$$
\begin{aligned}
M &= \frac{-4\sqrt{3}}{r^2_{\text{pupil}}} c_2^0 + \frac{12\sqrt{5}}{r^2_{\text{pupil}}} c_4^0 - \frac{24\sqrt{7}}{r^2_{\text{pupil}}} c_6^0 + \ldots , \\
J0 &= \frac{-2\sqrt{6}}{r^2_{\text{pupil}}} c_2^2 + \frac{6\sqrt{10}}{r^2_{\text{pupil}}} c_4^2 - \frac{12\sqrt{14}}{r^2_{\text{pupil}}} c_6^2 + \ldots , \qquad (3.3) \\
J45 &= \frac{-2\sqrt{6}}{r^2_{\text{pupil}}} c_2^{-2} + \frac{6\sqrt{10}}{r^2_{\text{pupil}}} c_4^{-2} - \frac{12\sqrt{14}}{r^2_{\text{pupil}}} c_6^{-2} + \ldots
\end{aligned}
$$

Using the aforementioned equations, the corrective lens can be estimated:

$$C = -2\sqrt{(J0^2 + J45^2)}, \quad S = M - \frac{C}{2}, \quad axis = 0.5 \times \tan^{-1} \frac{J45}{J0} \qquad (3.4)$$

where (S) is the spherical and (C) the negative cylindrical lens components.

3.4 Chromatic aberrations

Chromatic aberrations occur due to dispersion, i.e. the variation in the refractive index of a material for different wavelengths. There are two kinds of chromatic aberrations: longitudinal chromatic aberration (LCA) and transverse chromatic aberration (TCA).

Longitudinal chromatic aberration

Longitudinal chromatic aberration causes the shorter wavelengths to be refracted more than the longer wavelengths. In the eye and in relation to the retina, this causes a myopic shift on the focus for blue wavelengths and a hypermetropic shift on the focus for red wavelengths; assuming that the green wavelengths focus on the retina. Furthermore, LCA occurs along the optical axis and it has been estimated to approximately 2 D for the human eye [7,8]. The LCA occurs both for on-axis and off-axis objects, however it does not increase significantly with eccentricity [9,10].

Transverse chromatic aberration

Transverse chromatic aberration causes the different wavelengths to focus at different points in a vertical plane on the retina. This results in either different image positions on the retina for point sources or different retinal image size for extended objects. TCA is small on-axis and it increases with eccentricity [11, 12].

3.5 Optical quality over the viusal field

The monocular visual field of a healthy human eye extends to approximately 60° nasally, 100° temporally, 75° inferiorly and 60° superiorly [13]. The optical quality of the eye differs across the visual field with the best optical quality to be achieved close to the fovea, whereas with eccentricity it degrades as shown in Figure 3.3. Even in the absence of refractive errors in central vision (emmetropia), the eye experiences a large amount of optical errors in the periphery. It has been found that emmetropic and hypermetropic eyes are relatively myopic in the periphery, whereas myopic eyes have a hypermetropic shift off-axis. Higher-order aberrations also increase with off-axis angles. In terms of refractive errors, off-axis astigmatism is dominant in the periphery and in terms of higher-order aberrations, coma is dominant off-axis. Spherical aberration is more uniform across the visual field and it is, on average, the dominant higher-order aberration on-axis [14, 15].

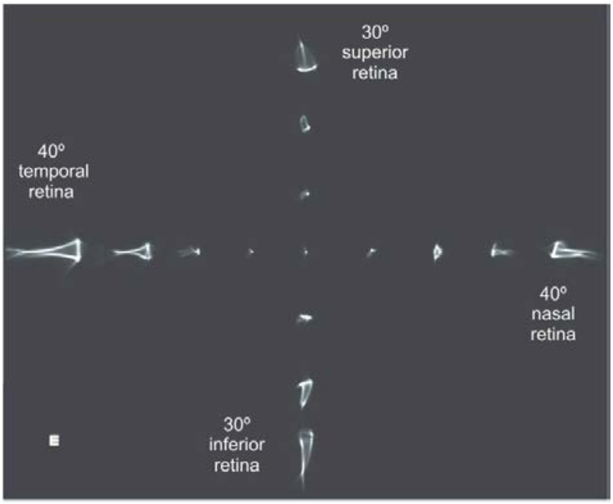

Figure 3.3. Point spread functions of the eye (describes the effect of the ocular imaging system for a point source) for different eccentricities.

Chapter 4

Vision evaluation and quantification

Visual perception is formed by the processing of the visual signal through the different parts of the visual system. Thus, the direct evaluation of vision is a complex task. Methods for vision evaluation include processes related to the electrophysiology and the psychophysics of vision. In this work psychophysical methods were used. Through the comparison of different stimuli parameters (like contrast) with the perceived response of the subject, the different characteristics of the visual system were investigated and quantified. Psychophysical methods have been developed for the understanding of the connection between the visual stimulus, the neural paths and the perceptual output the subject reports. Some common psychophysical methods will be presented in this chapter, as well as two different measures of vision: visual acuity and contrast sensitivity.

4.1 Psychophysics

4.1.1 Psychometric function

The psychometric function or frequency-of-seeing curve, is the way to relate the responses of a subject with the presented stimuli intensity. The psychometric function shows the percentage of the correct answers along the ordinate, and the stimulus intensity along the abscissa. The parameter whose intensity is investigated, depends on the type of the experiment (for example contrast, luminance). The shape of the psychometric function depends on the guess rate, the lapse rate, the threshold and the width of the transition zone:

- The guess rate is the probability that the subject will respond correctly even though the stimulus was not perceived (i.e. stimulus below the threshold),

- The lapse rate is the probability that the subject did not respond correctly even though the stimulus was perceived (i.e. stimulus above the threshold),

- The threshold is the stimulus intensity when the percentage of the correct responses has reached halfway between the guess rate and 100% minus the lapse rate and

- The width of the transition zone depends on the slope .

In the experiments performed for papers 1, 2 and 3, data were fitted with a logistic psychometric function parameterized as:

$$y = \alpha + \frac{1 - \alpha - b}{1 + e^{-(x-c)/d}} \tag{4.1}$$

where α is the guess rate, b is the lapse rate, c is the threshold and d is the width of the transition zone. Since the 2-alternative-forced-choice (2-AFC) method was used in our experiments (see 4.1.2), the guess rate was 0.5. The lapse rate was set to 0.05 and the threshold was estimated at the midway between the guess rate and 0.95 (1-lapse rate=1-0.05=0.95), i.e. 0.725. An example of such a psychometric function is presented in Figure 4.1 below.

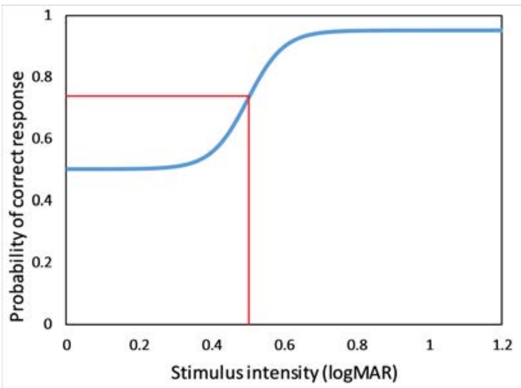

Figure 4.1. Psychometric function for a 2-AFC paradigm. The guess rate is 0.5 and the lapse rate is set to 0.05. The estimation of the threshold (red line) is at the midway between the guess rate and 1-lapse rate, i.e. at 0.725.

4.1.2 The forced-choice method

In the forced-choice method the subject has to choose between two or more alternative answers. By this, a more objective approach is succeeded compared to when the subject has to report if they perceived a stimulus. For instance, in an experiment where the subject is asked if they see the stimulus, the responses can be biased, that means that the subject may want to achieve a very low threshold and subconsciously (or even on purpose) respond ”yes” even though they do not see the stimulus. In this way the experimenter cannot control whether the subject responds correct or not. Whereas by the forced-choice method, since the subject has to make a choice in every trial, the response bias and the guess rate are better controlled. For example, in a 2-AFC experiment, since the alternatives are two, the guess rate is $1/2 = 0.5$. In the case of a 3-alternative-forced-choice experiment the guess rate is $1/3 = 0.33$ etc.

4.1.3 Psychophysical methods

The psychophysical methods aim to determine a threshold, that is the minimum required quantity of a stimuli in order to be perceived. The minimum level of stimulus that can be detected is defined as the absolute threshold, that is the threshold to detect differences between two stimuli in some stimulus parameter such as luminance.

Different kinds of tasks have been established in order to measure the threshold. These are:

- Detection task during which the subject reports if they see the stimulus or not,
- Recognition task where the subject has to name the already visible stimulus and
- Discrimination task that measures the threshold required to distinguish if two stimuli differ.

The different psychophysical methods for choosing the level of the next presented stimuli are [16, 17]:

The method of constant stimuli

In this method, a sequence of predetermined stimuli, with intensity values slightly above or below the threshold, are presented to the subject in random order. Each stimulus intensity value is presented multiple times, and the subject has to report if they see the stimulus. In order to determine the threshold, the percentage of the affirmative answers are plotted against the stimulus property to result in the psychometric function (4.1.1).

The method of limits

In the method of limits, predetermined intensity values of the stimuli are presented either starting with an ascending or with a descending order. The subject´s task is to report whether they started seeing or stopped seeing the stimulus, and the presentation order is then changed. For example, if the experiment starts with a descending stimuli presentation, only when the subject responses with two[1] successive "No, I don´t see the stimulus", the stimuli presentation will stop and the procedure is then repeated in an ascending order instead. In this way the experimenter minimizes the effect of a correct guess.

The method of adjustment

When the method of adjustment is used, the subject can control the intensity of the stimulus parameter that is tested by using a keypad or some other device. In the beginning of every trial, the stimulus is set well above or below the threshold, and the task of the subject is to adjust the intensity of the stimulus parameter that is tested until the visibility of the stimulus is changed. For example, the examiner may aim to check the lowest luminance under which the subject can detect the stimulus. To do this, the trial could start with a bright stimulus and the subject gradually reduces the luminance of the stimulus. The time that the stimulus is not visible any more, the subject reports that they don´t see the stimulus and the value of the luminance is recorded as threshold.

4.1.4 The adaptive methods

In the adaptive methods, the presentation of the next stimulus depends on the observer´s previous responses. By the use of adaptive procedures, the stimulus intensity is kept close to the threshold and thus a smaller range of stimuli is required.

An example of adaptive methods is the staircase method, which could be described as a developed version of the method of limits. In the staircase method the stimuli series starts with a descending order of the examined parameter. When the subject responds that they see the stimulus, then the intensity of the parameter is decreased by one step for the next trial. The descending order continues until the subject reports that the stimulus

[1]The number of "No" responses depends on the set-up of the staircase

cannot be perceived. Then the directionality changes to ascending, and the intensity of the parameter is increased by one step. In this way the intensity of the stimulus is kept close to the threshold.

The Ψ-method

The Ψ-method is a Bayesian adaptive method that assumes a specific form of the psychometric function (like Weibull, Logistic), a guess rate value according to the experimental method that is used (for example for a 2-AFC task the guess rate is set to 0.5) and a value for lapse rate. The threshold and the slope are estimated for each trial, based on all previous trials. After each trial, the Ψ-method updates the two-dimensional posterior probability distribution based on Bayes´theorem, across a range of possible values for the threshold and slope. The intensity of the stimulus for the next trial is chosen to be likely to give most new information of the threshold and slope. The termination of the procedure used in this work is based on a predetermined number of 40 trials. [18]

4.2 Visual acuity

Visual acuity measures the ability of the eye to resolve or detect details of a high contrast image at a given distance. It can be assessed by asking the subject to identify different black optotypes on white background (e.g. letters, illiterate E, landolt C) with varying size, or to distinguish the orientation of a grating with varying spatial frequency.

One common metric for visual acuity is logMAR, which is the logarithm (log-) of the minimum angle of resolution (-MAR). The MAR (measured in arcminutes) is the smallest detail size one can resolve. Better visual acuity corresponds to lower logMAR values.

The best visual acuity is achieved in the fovea due to higher neural sampling compared to the peripheral retina. Theoretically , one cone transfers information to one ganglion cell and thus the spatial distribution of the neurons determines the resolution limits. Normal foveal visual acuity corresponds to 0 logMAR or better (i.e. negative values). The relation between the visual acuity expressed in logMAR, decimal notation and spatial frequency is as follows: 0 logMAR corresponds to 1.0 decimal visual acuity and to 30 cycles/degree spatial frequency.

The visual acuity decreases with eccentricity for two reasons:

1. The density of the ganglion cells drops fast with off-axis angles and

2. The aberrations of the optical system of the eye increase in the periphery.

When the optical errors in the periphery are corrected, the distribution of the ganglion cells is the limiting factor for resolution acuity. In fact, detection acuity (i.e. task that demands the stimulus to be perceived but not resolved, measured in minimum angle of detection) in the periphery is better than resolution acuity, whereas in the fovea both acuities are the same [19, 20]. This is due to the Nyquist limit; when the Nyquist limit is not satisfied, i.e. that the stimulus frequency should be less than half the sampling frequency of the ganglion cells in order to be resolved, the stimulus will undergo aliasing (Figure 4.2). Aliasing means that the stimulus can still be detected but it will not be resolved. When the contrast of the presented stimulus in the periphery is high, resolution acuity is usually not affected by the ocular optical errors whereas detection acuity is [21, 22].

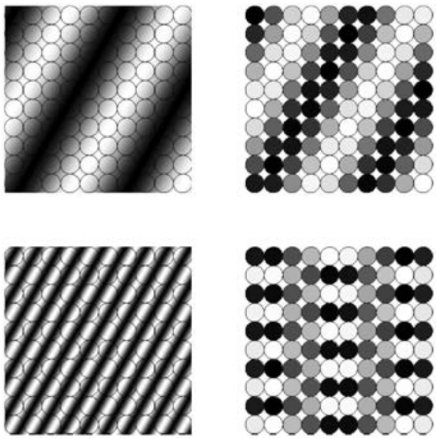

Figure 4.2. Aliasing in the peripheral visual field. A grating stimulus with low spatial frequency (top left) can be detected and resolved (top right) because its spatial frequency is lower than half the sampling frequency of the ganglion cells receptive field (circles). The high spatial frequency grating (bottom) cannot be resolved due to insufficient sampling, but can be detected due to aliasing.

4.3 Contrast sensitivity

Contrast sensitivity quantifies vision through measuring the lowest contrast needed (i.e. the threshold) for the detection or the resolution of a stimulus. Then, the contrast sensitivity is given by:

$$\text{Contrast sensitivity} = \frac{1}{Contrast_{\text{threshold}}} \tag{4.2}$$

By measuring contrast thresholds for different spatial frequencies, we can derive the contrast sensitivity function (CSF).

The shape of the CSF is affected by neural and optical factors, and the highest foveal contrast sensitivity is achieved between 3-6 cycles/degree. The magno cells dominates the close-to-threshold detection, whereas the parvo cells dominates detection in higher contrast, when the magno cells saturate [23]. The decrease in contrast sensitivity for spatial frequencies lower than 2 cycles/degree is due to the lateral inhibition and the center-surround antagonistic mechanisms of the ganglion cells receptive fields. The decrease in contrast sensitivity above 5 cycles/degree is mostly due to optical factors. The contrast sensitivity decreases with decreasing luminance; the spatial frequency of the contrast sensitivity peak as well as the cut-off spatial frequency shift towards lower values [24,25]. Eccentricity also affects the CSF. It is known that the size of receptive fields of the ganglion cells increases with off-axis angles. Thus, the contrast sensitivity in the periphery peaks for lower spatial frequencies. In Figure 4.3 the CSF function for different eccentricities is presented. The high spatial frequency cut-off is closely related to the visual acuity.

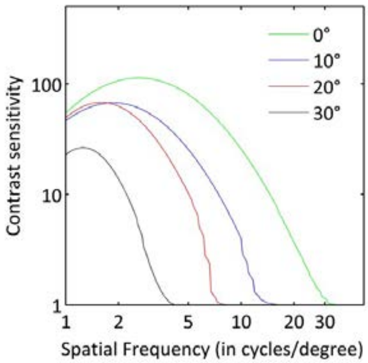

Figure 4.3. The contrast sensitivity function for different eccentricities for one subject under monochromatic adaptive optics correction. The green curve represents the foveal CSF, the blue 10° off-axis, the red 20° off-axis and the black 30° off-axis. The graph is plotted with data from Rosén et al. [26]

Stimulus choice

The neurons across the visual path are sensitive to different spatial frequencies, contrast, luminance levels, thus the stimulus for the evaluation of visual acuity and contrast sensitivity should be chosen carefully. Since gratings are well defined in both contrast and spatial frequency, they are a good choice of stimulus. Gratings consist of sinusoidal alternating bright and dark bars and in order to be described, the following parameters should be defined:

- The spatial frequency in cycles/degree,
- The contrast of the grating determined from Michelson contrast as

$$\text{Contrast} = \frac{L_{\text{max}} - L_{\text{min}}}{L_{\text{max}} + L_{\text{min}}}$$

  where L_{max} is the maximum and L_{min} the minimum luminance of the grating and
- The orientation of the grating, i.e. the angle of the grating in relation to the horizontal axis.

In this work, Gabor gratings within a Gaussian envelope were used. An example of these gratings is shown in Figure 4.4. The grating acuity (in cycles/degree) is given by the highest spatial frequency that can be resolved by the subject, and from this the MAR is calculated (30/grating acuity).

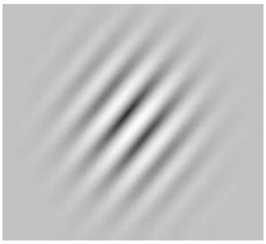

Figure 4.4. A Gabor grating with oblique orientation. This stimulus pattern was used for vision evaluation in this thesis.

Chapter 5

Influence of aberrations on peripheral visual function

Neural sampling of the retina is the densest in the fovea. Thus, even small optical errors that occur in central vision can reduce the visual performance [27, 28]. Although optical quality of the eye is the limiting factor of foveal vision, in the periphery this is not always the case. As mentioned in previous chapter, it is well known that visual acuity and contrast sensitivity are reduced in the periphery. Neural sampling is the reducing factor for peripheral high-contrast resolution, whereas for high-contrast detection and low-contrast resolution the reducing factor is optics [20, 21].

The optical errors of the eye are increasing with increasing eccentricity. But how are monochromatic and chromatic aberrations affecting our peripheral vision? This question will be answered in this chapter. Methods for peripheral optical errors correction will be presented, as well as the results of the peripheral vision function evaluation as obtained from experiments performed for Paper 1.

5.1 Peripheral optical errors correction for off-axis vision evaluation

As in the fovea, refractive errors in the periphery can be corrected by using spherical and cylindrical spectacle lenses. But since higher-order aberrations in the periphery are often large, further correction is needed. Correction of monochromatic higher-order aberrations can be succeeded by an adaptive optics (AO) system. The concept of AO correction is based on the modification of the incoming wavefront to compensate for the monochromatic aberrations of the eye. The main components of an AO system for vision evaluation are a wavefront sensor (usually a HS sensor), a control system, a deformable mirror and a screen. Such an AO system is presented in Figure 5.1. In Papers 1 and 2, a custom-built AO system with a HS sensor was used for peripheral monochromatic higher-order aberrations correction [29]. In combination with a stimuli presentation apparatus, vision evaluation was achieved. At first, the aberrated wavefront that exits the eye is measured by the HS sensor (Chapter 3, section 3.2) and the monochromatic aberrations are calculated. Then, the control system adjusts the shape of the deformable mirror to modify the wavefront from the visual stimulus and compensate for the monochromatic aberrations of the eye. In such a way, close to diffraction-limited vision can be achieved. The AO system was operating in a continuous closed-loop and thus the measurement and the correction of the monochromatic aberrations were continuous during the vision evaluation. For the correction of the peripheral refractive errors trial lenses were used, and the deformable mirror was responsible mainly for monochromatic higher-order aberrations correction. For the assessment of the correction during the vision evaluation, the residual aberrations were monitored by the root mean square error (RMS). The residual RMS is the square root of the sum of the squares of the residual Zernike coefficients, and it shows the deviation from the perfect wavefront. Furthermore, the residual Zernike coefficients were recorded during the vision evaluation for post-processing of the image quality on the retina.

5.2 Effects of aberrations on peripheral vision

The optical quality of the eye decreases with eccentricity. This is not only due to refractive errors, but also due to increasing higher-order monochromatic aberrations and TCA (LCA is more uniform across the visual field). As a consequence, vision is affected. Studies have shown that peripheral refractive error correction has no or small influence on high-contrast resolution acuity in the periphery [30, 31] but improves detection acuity and low-contrast resolution acuity [21, 32]. Additionally, Artal et al. found that the detection of high-contrast drifting sinusoidal gratings was improved with peripheral correction, whereas discrimination-of-direction performance was less dependent on refraction [33]. Lundström et al. went a step further and corrected both peripheral refractive errors and higher-order aberrations. Their results indicate that peripheral optical correction can not improve high-contrast resolution acuity of individuals with normal vision [20]. In contrast, off-axis refractive error correction can increase high-contrast resolution acuity performance in subjects with central visual field loss [34, 35]. The effect of induced defocus on peripheral high-contrast resolution and detection acuity was investigated by Wang et al. They found that detection acuity was significantly dependent on defocus, whereas resolution acuity

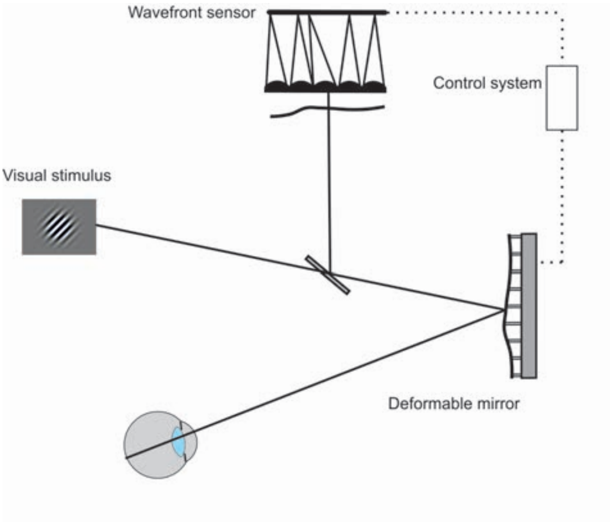

Figure 5.1. The main components of an AO system for vision evaluation. The monochromatic aberrations are measured by the wavefront sensor and the aberrated wavefront is reshaped by the deformable mirror as it directed from the control system. In this way monochromatic aberrations correction is achieved.

was not affected up to a large amount of imposed defocus [36]. Rosén et al., however, found that peripheral low-contrast resolution acuity is affected by defocus [21] and that combined AO and refractive correction for eccentric higher- and lower-order aberrations can improve low-contrast resolution acuity, compared to when only peripheral refractive errors were corrected [29].

Peripheral detection acuity is affected also by TCA. Cheney et al. suggest that TCA is the dominant limiting factor for peripheral detection acuity. However, the presented stimuli was produced by interference directly on the retina, and thus the contrast was very high and LCA was absent [37]. This could exaggerate the effect of TCA. In a later study, Winter et al. evaluated detection acuity using a more natural stimuli. They found that induced TCA (under full monochromatic errors correction) decreased grating detection acuity in the peripheral visual field [38].

In Paper 1, the effects of monochromatic and chromatic aberrations on peripheral vision functions were investigated for different grating orientations. We found that AO correction for monochromatic aberrations combined with chromatic aberrations elimination improved high-contrast detection acuity both for gratings parallel and perpendicular to the horizontal meridian at 20° nasal visual field. Also, in the case of detection contrast sensitivity both orientations showed improvements with full monochromatic and chromatic correction. Furthermore, detection acuity and contrast sensitivity improved the most when perpendicular gratings were tested. In Figure 5.2, the monochromatic Modulation Transfer Function (MTF) curves from the wavefront measurements obtained throughout the vision evaluation of one subject are presented (Paper 1). It can be seen that the image quality for horizontal gratings is better compared to the image quality for perpendicular gratings, when higher-order aberrations are present (dashed curves). This is due to the asymmetric blur of coma and remaining astigmatism that has the same directionality as the horizontal gratings. The difference in MTFs explains the better scores in detection acuity and contrast sensitivity for horizontal gratings. When monochromatic lower- and higher-order aberrations were corrected, the MTF curves for both grating orientations are very similar (continuous curves).

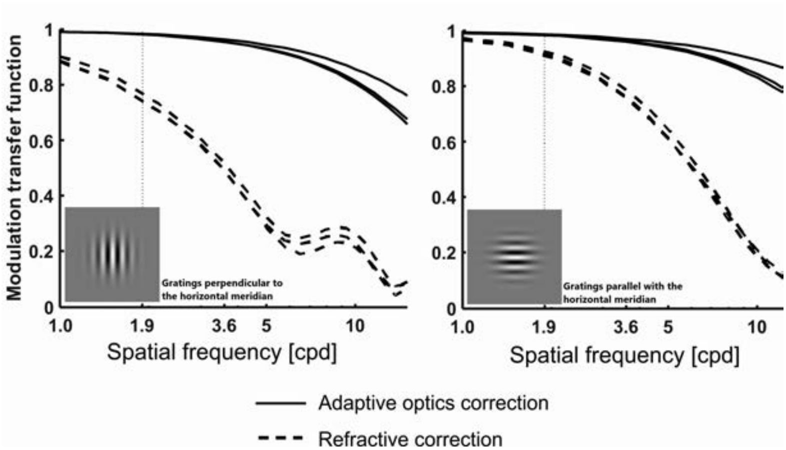

Figure 5.2. Peripheral monochromatic Modulation Transfer Function (MTF) curves for one subject. The continuous curves represent the condition under which monochromatic lower- and higher-order aberrations were corrected, whereas the dashed curves represent the condition under which only refractive errors were corrected.

To avoid the meridional effect, i.e. the preference to a certain stimulus orientation due to optical and neural characteristics (asymmetric aberrations, orientation of receptive fields), oblique gratings were also evaluated. Oblique gratings have close to equal visibility, which makes them more suited for 2-AFC tasks [39]. When oblique gratings were tested, there was no improvement in low-contrast resolution acuity with full optical correction on average. Our findings on individual level, however, indicate that when the natural higher-order aberrations are large, then optical correction can improve low-contrast resolution acuity also for oblique gratings.

Chapter 6

Myopia

Myopia comes from the Greek word « $\mu\upsilon\omega\pi\acute{\iota}\alpha$ », which means "squinting, contracting the eyes", and refers to the habit of the uncorrected myope to slightly close their eyes in order to see the distant objects better (due to increasing depth of focus). As explained in Chapter 3, myopia occurs when the optical system of the eye focuses the parallel rays of a distant object in front of the retina causing a blurred retinal image. It is a common vision problem with millions of people being myopic across the globe, and its onset and progression are connected to genetic and environmental factors. Myopia usually starts developing in childhood and it is related both to foveal and peripheral vision. The global prevalence of myopia as well as the role of foveal and peripheral vision in myopia development will be discussed in this chapter.

6.1 Prevalence of myopia

Myopia is often misjudged as a minor issue due to the fact that it can be easily corrected and its effects on vision can be mitigated, however, it is a major global problem. Today, more than 2.5 billion people are estimated to be myopic. According to the World Health Organization (WHO), by 2050 this number is estimated to reach 5 billions (half of the global population) with almost 1 billion high myopes [40].

In urban East Asian countries, myopia has epidemic dimensions [41]. In preschool children in Taiwan it has been found that 12% of 6-year-olds are myopic. In school children, and especially in some countries, the prevalence of myopia is even higher. In Taiwan and Singapore almost 35% of 8-year-old children are myopic. In Shangai 52% and in Guangzhou 30% of 10-year-olds are myopes. The prevalence of myopia is around 50-60% among 12-year old children, with the highest prevalence to be observed in Singapore (62%) and

Hong Kong (53.1%). Among young adults (18-24 years old), the prevalence is around 80-96.5%, with approximately 20% of them being high myopes. The highest percentages have been found in South Korea with a prevalence of 96.5% followed by Shanghai (95.5%).

In non-Asian countries the prevalence of myopia is lower [41]. In Sweden, England, Northern Ireland and Poland the prevalence of myopia among 12-13-year-olds is 49.7% [42], 29.9%, 17.7% and 14.2% respectively. In Australian 12-year-old children (Sydney) the prevalence of myopia reported to be 18.9%. The lowest prevalence (4%) among children (5-15-years-old) has been reported in South Africa. In young adults aged 19-22 years, myopia was present in 20.4% in Australia and 12.8% in Denmark. In Norway 35% reported to be myopic among young adults between 20-25 years old, but a more recent study reports that the prevalence of myopia in students aged 16–19 years is 12.7% [43].

6.2 Heritability and environmental factors

Genetics and heritability are related to myopia onset and development. Studies have shown that the likelihood to become myopic is higher for children with myopic parents compared to children with non-myopic parents [44]. Zadnik et al. found that even before the onset of myopia, the axial length of children with myopic parents was longer than children with one or no myopic parents [45]. Studies with twins also support the heritability of myopia with monozygotic twins showing higher concordance rates of myopia compared to dizygotic twins [46]. The heritability of myopia, however, cannot explain the rapid increase of myopia worldwide.

Environmental factors have a key role in myopia onset and development. Studies have shown relation between myopia and the level of education in the population [47, 48]. Many years of studying could possibly lead to myopia due to the demanding near work while reading [49]. Although not entirely clear, near-work has been associated with myopia due to optical changes in the eye because of accommodation [50].

Another environmental factor is outdoor activity. The more time children spend outdoors, the less chances they have to develop myopia [51, 52]. And when myopia occurs, time spend outdoors is a prophylactic factor against myopia progression [53]. Furthermore, a study in school children in Taiwan reported that an additional of 80 minutes daily spent outdoors resulted in 50% reduction in incidence of myopia [54]. Outdoor activity is associated with high light levels. Read et al. found that children who had greater daily light exposure, showed significantly slower axial elongation compared to children who were exposed to less outdoor light [55]. However, the acting mechanism of high light levels is not entirely clear. Animal studies suggest that the increased dopamine production under high light levels acts as a inhibitory factor for axial elongation [56], but an alternative hypothesis is that the contraction of the pupil due to high light levels results in increased depth of focus and thus clearer retinal image which does not trigger eye growth (explained more in the following section) [57]. Finally, another hypothesis related to outdoor activity is that since outdoor activity does not demand high accommodation due to distant stimuli, lag of accommodation present for close targets is reduced and thus axial elongation is not triggered [58].

6.3 Optical regulation of eye growth

At birth our eyes are hypermetropic, i.e. the image of a distant object is formed behind the retina in the unaccommodated eye [59]. Through the process of emmetropization during childhood, the hypermetropia is reduced. Emmetropization is the process during which the eye grows in order to bring the focal plane of the eye on the retina. Although the exact mechanisms of emmetropization are still unclear, it is known that the eye is using visual feedback from its refractive state; hypermetropia that occurs at birth triggers axial elongation. If the eye continues to elongate after emmetropization, myopia occurs [60].

Animal studies have shown that depending on the location of the image relative to the retina, axial elongation can be stopped or triggered. Experiments in chickens and monkeys whose vision was defocused either with negative (image behind the retina) or positive (image in front of the retina) spectacle lenses, showed that their visual system was altering their refractive state by accelerating or slowing axial elongation in order to compensate for the imposed defocus [61, 62]. This applies both in the fovea and in the periphery of the retina. Originally it was believed that only foveal optical errors could regulate eye growth, but it is proved that also peripheral image quality can modify ocular growth even in the presence of a sharp foveal image. Benavente-Pérez et al. applied bifocal contact lenses in juvenile marmosets eyes. The bifocals had a plano-center zone and +5 D or -5 D peripheral zones. They found that the marmosets whose peripheral visual field was defocused positively developed hypermetropia whereas the negatively defocused animals developed myopia. They concluded that eye growth can be manipulated by peripheral image quality [63].

In Figure 6.1 is a schematic representation of an eye showing peripheral hypermetropic and myopic defocus while the foveal image is in focus. In the left case where hypermetropic defocus blurs the peripheral image, a growth signal is sent to the eye and axial elongation occurs. In the right picture the peripheral image is instead blurred by myopic defocus, and a signal to stop axial growth is sent.

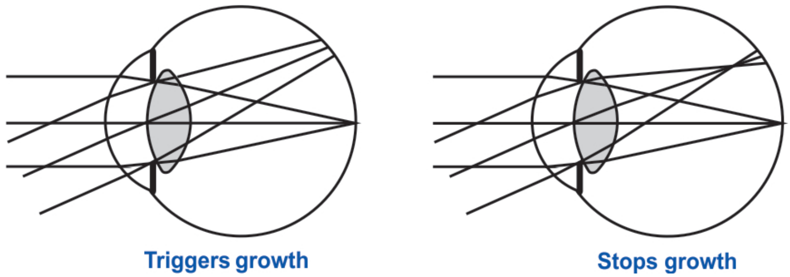

Figure 6.1. Schematic representation of eyes with foveal emmetropia: peripheral hypermetropia (left) and peripheral myopia (right) are shown. Peripheral hypermetropic blur triggers axial elongation whereas peripheral myopic blur stops axial growth.

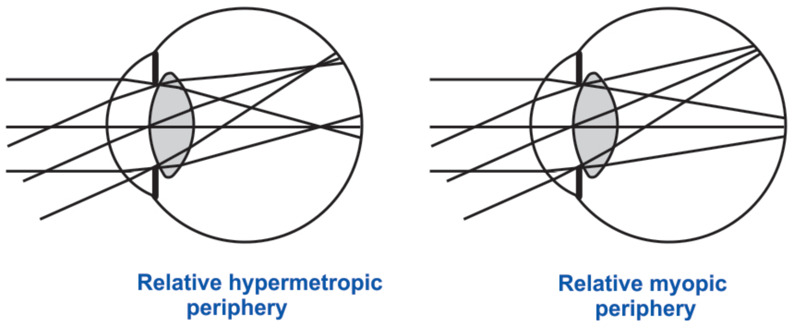

Figure 6.2. A foveally myopic eye with relative hypermetropic periphery (although the peripheral image is still in front of the retina) on the left, and a foveally hypermetropic eye with relative myopic periphery (although the peripheral image is still behind the retina) on the right.

As mentioned in Chapter 3 (section 3.5), even foveally emmetropic eyes suffer from refractive errors in the periphery. Assuming a foveally emmetropic eye, relative peripheral hypermetropia occurs when the peripheral image is focused behind the retina, whereas relative peripheral myopia occurs when the peripheral image is focused in front of the retina. In addition to this, relative peripheral refraction can have more expressions, i.e. foveally myopic eyes are less myopic off-axis and thus their periphery is relatively hypermetropic compared to the fovea (although the peripheral image is still located in front of the retina without correction). Thus, the dioptric correction needed is more negative in the fovea than in the periphery. Similarly, foveally hypermetropic eyes tend to be less hypermetropic eccentrically, resulting in a relatively myopic periphery compared to the fovea (although the peripheral image is still focused behind the retina without correction). Thus, peripheral correction would be less positive than foveal. Such eyes are presented in Figure 6.2.

Several studies report relative peripheral hypermetropia in myopic eyes and relative peripheral myopia in hypermetropic eyes. Mutti et al. reported relative peripheral hypermetropia $+0.80 \pm 1.29$ D at 30° nasal visual field in myopic children aged 5 to 14 years and -1.09 ± 1.02 D relative peripheral myopia in hypermetropic children of the same age range [64]. Lee et al. also found relative peripheral myopia and relative peripheral hypermetropia for hypermetropes and myopes respectively, across the central 60° horizontal field. However, their results do not indicate that relative peripheral refraction is the causing factor of myopia, but is more likely related to the shape of the eye [65]. Therefore, the role of peripheral optics in myopia onset and development is not entirely clear, and relative peripheral refraction is not the only factor that affects peripheral image quality.

Chapter 7

Asymmetries due to the sign of defocus

As mentioned in Chapter 6, the retina has the ability to differentiate between myopic (positive) and hypermetropic (negative) defocus and accordingly to regulate the growth of the eye. Experiments have shown that this ability is present not only in the foveal, but also in the peripheral retina of animals [63], and it is believed that eye growth is related to peripheral image quality also in humans [66]. The mechanism with which the retina registers the sign of defocus and detects when the image is located in front of or behind the retina is not entirely understood. It is therefore interesting that humans show asymmetric behavior in their sensitivity to defocus. These asymmetries will be discussed in this chapter.

7.1 Asymmetry in the sensitivity to defocus

To better understand the content of this chapter, the term ”asymmetry in the sensitivity to defocus” should be defined. By asymmetry in the sensitivity to defocus we mean the unequal performance of a subject during a vision evaluation task (for example visual acuity) due to the dependence on the sign of defocus. In simple words, subjects show an unequal reduction in vision when they are blurred with positive lenses (myopic defocus) compared to when they are blurred with negative lenses (hypermetropic defocus) of the same optical power.

7.2 Foveal asymmetry in the sensitivity to defocus

Asymmetry in the sensitivity to defocus has been found for foveal vision by Radhakrishnan et al [67]. They evaluated visual acuity in 12 myopic and 12 non-myopic subjects under cycloplegia. During the experiment, myopic (positive) and hypermetropic (negative) defocus was induced with defocusing lenses up to ±3 D in 0.25 D steps. They report that the myopic subjects performed better (better visual acuity values were measured) when they were defocused with negative lenses compared to when they were defocused with positive lenses, indicating an asymmetric reduction in vision. For non-myopes this was not the case: a symmetric reduction in vision was observed when equal amounts of positive and negative blur was induced.

Similarly, Guo et al. performed foveal visual acuity measurements in one myopic and one emmetropic subject, under monochromatic conditions [68]. High- and low-contrast vision was evaluated with induced myopic (positive) and hypermetropic (negative) defocus out to ±1.33 D. The subjects were measured with and without adaptive optics correction for higher-order aberrations. For both subjects they found asymmetries in the sensitivity to the sign of defocus, with worse vision for myopic (positive) defocus when compared to the same amounts of induced hypermetropic (negative) defocus. When adaptive optics were used, both subjects showed less asymmetric profiles.

A possible reason for better performance when hypermetropic (negative) defocus is induced, is the interaction of spherical aberration with the different signs of defocus. In Figure 7.1 the effect of a positive and a negative lens when placed in front of an eye with positive spherical aberration is shown. In the upper eye, pure spherical aberration is presented. In the middle eye the interaction of spherical aberration with a positive lens is shown: placing a positive lens in front of the eye results in shifting the disc of least confusion further away from the retina. Thus, the image quality is becoming worse when compared to the upper eye. In the bottom eye, the negative lens interacts with spherical aberration in a way that shifts the disc of least confusion closer to the retina resulting in a better image quality. When adaptive optics are used, spherical aberration is corrected. Thus, the image quality is affected only by the induced defocus. As a result more equal reduction in vision is observed. Also other higher-order aberrations and LCA give an asymmetric depth of focus that can affect the sensitivity to defocus.

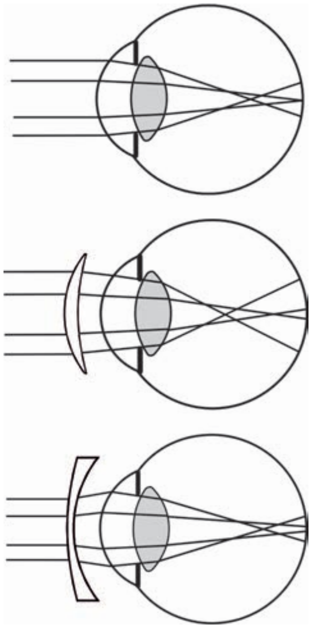

Figure 7.1. A schematic representation of an eye with positive spherical aberration (top picture) and the interaction of spherical aberration with induced positive (middle picture) and negative (bottom picture) defocus. When positive defocus is induced, the disc of least confusion is moved further away from the retina, whereas with induced negative defocus the disc of least confusion is shifted closer to the retina.

7.3 Peripheral asymmetry in the sensitivity to defocus

The different effects of imposed myopic (positive) and hypermetropic (negative) defocus were investigated by Rosén et al. for peripheral vision. They evaluated low-contrast resolution acuity in 16 emmetropic and 16 myopic subjects at 20° nasal visual field. In general, myopes were more sensitive to myopic (positive) defocus than to hypermetropic (negative) defocus, whereas emmetropes showed more similar thresholds between the two defocus states (positive-negative). We wanted to repeat the aforementioned measurements but under controlled optical conditions, and thus in Paper 2 we evaluated peripheral vision for different signs and magnitudes of defocus with and without higher-order monochromatic and chromatic aberrations present. We also found asymmetries in the sensitivity to the sign of defocus in the 20° nasal visual field for myopes and non-myopes, but our main goal was to unravel the reason of these asymmetries. We showed that it is not

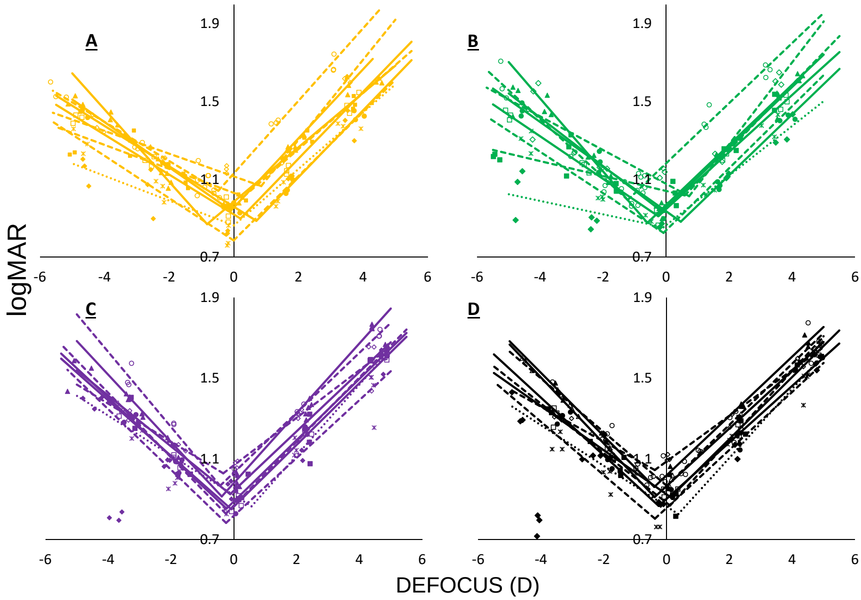

Figure 7.2. Peripheral low-contrast (10%) resolution grating acuity in log-MAR plotted against defocus in diopters. Each graph represents one condition and includes all subjects participated in the experiment. In Figure 7.2.A chromatic and higher-order monochromatic aberrations are present, in Figure 7.2.B higher-order monochromatic aberrations are present while chromatic aberrations were eliminated, in Figure 7.2.C higher-order monochromatic aberrations are corrected while chromatic aberration is present and in Figure 7.2.D both chromatic and higher-order monochromatic aberrations are corrected. Myopes are presented with dashed lines and emmetropes with solid line. The dotted line represents the hypermetropic subject. The outliers in 7.2.C and 7.2.D are due to spurious resolution phenomenon.

the chromatic aberrations of the eye, but the higher-order monochromatic aberrations that are the main reason of the asymmetric behavior. This is demonstrated in Figure 7.2 where the curves from all subjects that participated in the experiments are presented. In Figure 7.2.A chromatic and higher-order monochromatic aberrations are present, in Figure 7.2.B higher-order monochromatic aberrations are present while chromatic aberrations are eliminated, in Figure 7.2.C higher-order monochromatic aberrations are corrected while chromatic aberrations are present and in Figure 7.2.D both chromatic and higher-order monochromatic aberrations are corrected. It can be seen that in the absence of higher-order monochromatic aberrations, the subjects showed a more equal reduction in vision when myopic (positive) and hypermetropic (negative) defocus was induced.

We also found that the group of myopes (dashed lines Figure 7.2) tended to be more asymmetric compared to the group of emmetropes (solid lines in Figure 7.2) in all conditions. This could mean that higher-order aberrations cause a more asymmetric peripheral depth of focus for myopes. A fact that indicates that this asymmetry can be important for myopia control.

Chapter 8

Myopia control

The continuous increase in the prevalence of myopia [40] is a worrying phenomenon. It is not just ¨a pair of glasses¨ problem. It is more than that. Myopes have a higher likelihood to develop glaucoma [69], retinal detachment [70], cataract [71] and myopic maculopathy [72]; conditions that can be fatal for vision. It has been found that there is a 40% lower risk to develop myopic maculopathy by reducing myopia progression by 1 D in childhood [73]. Myopia should be managed from a young age, since the earlier it occurs the more likely it is to progress fast. This chapter will present different interventions for myopia control, and will focus on multifocal contact lenses and the active mechanism for myopia control.

8.1 Myopia control interventions

Many different interventions, including pharmaceutical and optical methods, now aim to control myopia progression. Atropine, a pharmaceutical cycloplegic agent, in low concentration has been found to slow down the myopia progression and the increase in axial length, although its action mechanism is not yet understood. Yam et al. investigated the 1-year effect of 0.05%, 0.025% and 0.01% concentration atropine in myopic children aged 4 to 12 years [74]. They compared the results with a group that was receiving placebo treatment and they found that after 1 year the mean spherical equivalent change was -0.27±0.61 D, -0.46±0.45 D, -0.59±0.61 D and -0.81±0.53 D in the 0.05%, 0.025%, 0.01% atropine groups and placebo group respectively. The respective mean increase in axial elongation was 0.20±0.25 mm, 0.29±0.20 mm, 0.36±0.29 mm, 0.41±0.22 mm. Although 1% atropine has been found to be even more effective in myopia control, it is not a common choice due to the fact that it causes photophobia.

Treatments with orthokeratology rigid contact lenses are also effective in significantly reducing the progression of axial growth probably by manipulating the peripheral image quality. Santodomingo-Rubido et al. compared axial elongation between children wearing orthokeratology contact lenses and children wearing single-vision spectacles. A total of 61 children from 6 to 12 years old participated in this study. The authors found that after a 2-years period, the orthokeratology group (consisted of 31 children) had 32% less axial elongation when compared to the single-vision spectacles group (consisted of 30 children) [75]. Additionally, Hiraoka et al. in a 5-year follow-up study, investigated the effect of orthokeratology on axial length growth in a group of 43 subjects. They found that the increase in axial length was 0.99±0.47 mm for the orthokeratology group whereas for the control group (single-vision spectacles) the increase was 1.41±0.68 mm [76].

Furthermore, spectacle approaches for myopia control have been found to slow myopia progression probably by reducing the accommodative demand. Cheng et al. randomized 135 children between 8-13 years old and investigated the effect of bifocal and prismatic bifocal spectacles in myopia progression, while using single-vision spectacles as control [77]. They found that myopia progression over 3 years was -2.06±0.13 D, -1.25±0.10 D and -1.01±0.13 D on average for the single-vision lens, the bifocal and the prismatic bifocal group respectively. The respective average axial length increase was 0.82±0.05 mm, 0.57±0.07 mm and 0.54±0.06 mm. The efficacy of Defocus Incorporated Multiple Segments (DIMS) spectacle lenses in myopia control was recently investigated by Lam et al [78]. The principle of DIMS spectacle lenses is to add myopic defocus in the peripheral visual field. A total of 160 children completed the study, aged between 8-13 years, divided in two groups according to their treatment: a DIMS spectacles group (79 children) and a single-vision spectacles group (81 children). The myopic progression over 2 years was on average -0.41±0.06 D in the DIMS spectacles group and -0.85±0.08 D in the single-vision spectacles group. In the DIMS spectacles group the mean axial growth was 0.21±0.02 mm whereas in the single-vision spectacles group 0.55±0.02 mm.

Finally, multifocal soft contact lenses with a center distance design (i.e. with a central zone that provides clear distant vision) have been shown to control the progression of myopia by presenting two simultaneous images; one image on the retina and one in front of the retina to create a myopic blur, while looking at a distant target with relaxed accommodation. In Figure 8.1 a schematic representation of a contact lens with a center-distance design and its effect principle are presented. Sankaridurg et al. investigated the impact on myopia progression of two lens designs that induced myopic defocus both in the center and in the periphery, and two lens designs that provided extended depth of focus by manipulating higher-order aberrations and modulate retinal image quality. In total 508 children between 8-13 years old participated in the study. Single-vision contact lenses were used as control. The 2-years progression of myopia was -1.12 D for control and between -0.78 D to -0.87 D for the test contact lenses. The corresponding axial elongation was 0.58 mm and from 0.41 mm to 0.46 mm [79]. Chamberlain et al. evaluated the effectiveness of MiSight lenses, a soft contact lens with a center-distance design (Figure 8.1) approved to be sold for myopia control [80]. They compared myopia progression in 109 children (8-12 years old) randomised to either wear the MiSight multifocal (test group) or single-vision contact lenses (control group). The 3-year average progression in myopia was as follows: -0.51 D for the test group and -1.24 D for the control group and the axial growth was 0.30 mm and 0.62 mm for the test and the control group respectively.

The effective properties of multifocal contact lenses for myopia control are not yet well-understood. Thus, we chose to evaluate and try to understand the effective properties of MiSight contact lens; the only intervention for myopia control available on the Swedish market.

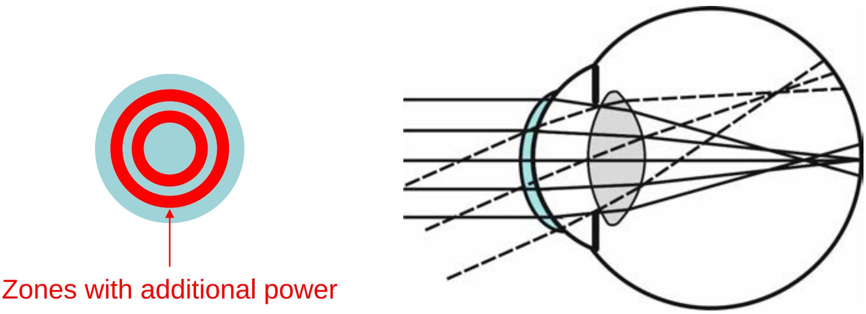

Figure 8.1. A schematic representation of a center-distance design of a multifocal contact lens (left side) and its effect principle (right side). The red color represents the zones with the additional power.

8.2 Impact of multifocal contact lenses on foveal and peripheral visual quality and accommodation

Accommodation as well as foveal and peripheral vision in young myopic eyes can be affected by multifocality [81–84]. Ruiz-Pomeda et al. evaluated accommodation and vision in 41 children wearing MiSight contact lenses and in 33 children wearing single-vision spectacles. They found no statistically significant difference between the two groups in the amplitude of accommodation (MiSight: 13.88±3.58 D, Spectacles: 12.40±2.55 D), in the accommodative response at 0.33 m (MiSight: 1.08±0.61 D, Spectacles: 1.24±0.75 D) and in the distant (MiSight: -0.06±0.06 logMAR, Spectacles: -0.07±0.07 logMAR) and near (MiSight: 0.4±0.06 M, Spectacles: 0.39±0.03 M) visual acuity [85]. Sha et al. found worse monocular accommodation facility when they compared MiSight lenses (11.7±4.8 cycles per minute) with two other contact lenses designs (Prototype 1 14.5±3.9 and Prototype 2 14.0±4.3 cycles per minute) for myopia control [86], and Chamberalain et al. reported similar visual acuity between MiSight and single-vision contact lenses (-0.03±0.06 vs. -0.05±0.07 logMAR) [80].

In Paper 3, we evaluated the impact on accommodation and on foveal and peripheral vision after a short-term application of MiSight contact lenses, and we compared the results to those of Acuvue Moist multifocal contact lenses used for presbyopia; single-vision spectacles were used as control. Acuvue Moist contact lenses have a center-near design (provides clear near vision through the central zone, Figure 8.2). Additionally, the effect on foveal and peripheral image quality was investigated.

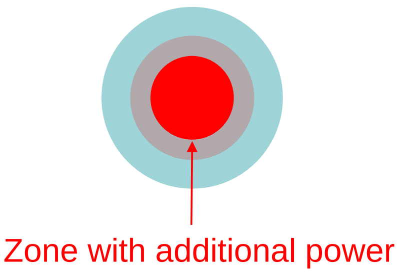

Figure 8.2. A schematic representation of a center-distance design of a multifocal contact lens for presbyopia. The red color represents the zone with the additional power.

When compared to spectacles, the MiSight multifocals decreased the peripheral low-contrast resolution acuity whereas foveal far and near visual quality was similar. The majority of the subjects showed an increase in accommodative response, whereas accommodative facility and near point of accommodation tended to be worse. Finally, astigmatism when viewing the far and the near target, and foveal coma showed greater values. With Acuvue Moist contact lenses, foveal near visual acuity and peripheral low-contrast resolution acuity were similar, whereas foveal visual quality for far was decreased when compared to control. A reduction in accommodative response and facility was observed, whereas astigmatism when viewing the far and the near target was similar to spectacles. Our foveal findings are in agreement with earlier studies, and the peripheral effects were expected from the optical design of the lens. We therefore believe that the active mechanisms of MiSight contact lenses in myopia control are the larger peripheral blur, the more asymmetric point spread function due to the additional astigmatism and coma, and that this leads to the increased accommodative response shown by some of the subjects.

Chapter 9

Accommodation and aberrations over the visual field

The accommodation reflex is responsible for focusing near targets on the retina. It is driven by central vision, but peripheral vision can also evoke it to some extent. During accommodation the shape of the crystalline lens changes, and thus the aberration profile of the eye is affected. The study of accommodation in relation with myopia is of great importance, both because myopia is associated with near work and because myopes show different aberration profiles compared to emmetropes. This chapter focuses on accommodation over the visual field. The effect of accommodation on peripheral aberrations as well as the peripheral stimulation of accommodation are presented.

9.1 Lag of accommodation and myopia

Association has been found between near work and the development and progression of myopia [87]. It has been hypothesized that the inadequate accommodative response to near targets, i.e. the lag of accommodation, can affect the progression of myopia in humans. Lag of accommodation results in hypermetropic retinal defocus, that may trigger axial elongation [61, 62]. Myopes tend to have larger lags of accommodation when compared to emmetropes. Gwiazda et al. measured accommodative responses in myopic and emmetropic children for different accommodation demands and they found that myopes were accommodating significantly less than emmetropes at near distances [88]. Although some studies propose that accommodative lag promotes eye growth [89–91], other studies found no relation between the lag of accommodation and axial elongation. Chen et al. evaluated the association between accommodation and myopia progression in Chinese myopic children, and they found no correlation [92]. Albeit some studies did not find any correlation between the lag of accommodation and myopia progression, lag of accommodation cannot be disregarded when it comes to myopia.

9.2 Accommodation and aberrations beyond the central visual field

Accommodation affects the aberration profile of the eye. Studies have investigated mainly the foveal but also the peripheral refractive state of the eye during accommodation. Smith et al. measured oblique astigmatism and field curvature for accommodation up to 5 D and eccentricity up to 60° in emmetropic subjects, and they found that these aberrations increased with accommodation level but statistically significant increases are observed only beyond 40° off-axis [93]. Peripheral refraction out to ±45° horizontal visual field for 2 m, 0.5 m and 0.25 m viewing distances was measured for emmetropic subjects by Tabernero and Schaeffel, and they concluded that accommodation did not cause any changes between central and peripheral refraction [94]. Calver et al. evaluated peripheral refraction out to ±30° of the horizontal visual field, for myopes and emmetropes at 2.5 m and 0.4 m of target distances. They found increasing astigmatism with increasing off-axis angles, but no significant difference between myopes and emmetropes was observed, except at 30° nasal visual field [95]. Lundström et al. investigated how accommodation affects the peripheral image quality in myopes and in emmetropes. They measured aberrations at ±40° and ±20° horizontal and vertical visual field respectively, for 0.5 D and 4 D target distances. They concluded that when compared to emmetropes, myopes showed lower relative peripheral myopia, they had larger asymmetry in relative peripheral refraction over the visual field and their relative peripheral myopia did not change or decreased with accommodation [96]. Whatham et al. determined the influence of accommodation on peripheral refraction in myopes by measuring the refractive error at three different distances (2 m, 0.40 m and 0.30 m) and up to 40° nasal and temporal retina. Their results indicated that myopes experienced hypermetropic shifts in the foveal and near-peripheral retina with higher accommodation demands, whereas in larger eccentricities refraction either remained unchanged or showed a myopic shift. Also, accommodation increased astigmatism significantly in the farthest off-axis angles [97]. The peripheral optical errors across the central 42°×32° of the visual field of emmetropic subjects for 0.3 D and 4 D of stimuli distances, were measured by Mathur et al. They found mostly myopic relative peripheral refraction for both accommodation demands, a slight change with accommodation in the astigmatic components as well as for most of the higher-order aberrations and a significant negative shift with accommodation in the 4th-order spherical aberration across the visual field. [98]. In conclusion, the previous studies are not in agreement on how accommodation affects the peripheral image quality in myopes compared to emmetropes, which motivates studies under more controlled conditions.

In Paper 4 we therefore investigated simultaneously foveal and peripheral (20° nasal visual field) optical quality during accommodation in order to achieve a better understanding of peripheral ocular aberrations when the eye accommodates. We found no change in the relative peripheral refraction with increasing accommodation for the emmetropic subjects (in agreement with Tabernero and Schaeffel [99], Calver et al. [95], Mathur et al. [98]), whereas myopes showed a more myopic relative peripheral refraction (in agreement with Whatham et al. [97]). In spite of the differences in relative peripheral refraction between myopes and emmetropes, both foveal and peripheral MTFs were similar for the two groups.

9.3 Parafoveal accommodation

Accommodation is driven by cones and thus foveal vision is more responsible for the accommodation reflex than peripheral vision. However, off-axis stimuli can also trigger accommodation to some extend. And since peripheral optics of the eye are linked to myopia development and progression, accommodation beyond the fovea can be of fundamental interest for myopia. Semmlow and Tinor investigated off-axis accommodation for $\pm 6^{\circ}$ from the fovea, and they reported a reduction in accommodative response with eccentricity [100]. Gu and Legge evaluated accommodation for stimuli eccentricities up to 30°, and they found that accommodation magnitude dropped 50-75% when 1° off-axis was compared to 30° off-axis [101]. Hartwig et al. measured accommodation to targets up to 15° in myopic and emmetropic subjects. They also concluded that although peripheral stimuli evokes accommodation, the accommodative response diminishes with increasing peripheral angles, and they support that there is some evidence that off-axis accommodation may be slightly less effective in myopes than in emmetropes [102]. In Paper 5 we evaluated nonocular parafoveal and perifoveal accommodation in myopes and emmetropes, up to $\pm 8^{\circ}$ of eccentricity, using annular stimuli. We concluded that the accommodative response time increased and the accommodation amplitude decreased with increasing off-axis angles (in agreement with Semmlow and Tinor [100]), and that beyond 7° of eccentricity, accommodation became negligible.

Chapter 10

Conclusions and outlook

This thesis is focused on peripheral image quality and vision with the aim to find visual cues to myopia development. Psychophysical methods were used to evaluate peripheral vision to understand how different levels of correction can improve vision and how the eye detects the sign of defocus. Additionally, the stimulation of accommodation and the optical aberrations over the visual field were studied. Finally, the short-term effects on foveal and peripheral vision of a special contact lens for myopia control (MiSight) were investigated to unravel its effective properties.

Improvements in both high-contrast detection and contrast sensitivity were observed in the peripheral visual field when compensating for higher-order monochromatic aberrations and/or for chromatic aberrations. Stimuli containing high spatial frequencies perpendicular to the visual field meridian benefit more from the optical correction. Additionally, when low-contrast resolution acuity was evaluated with induced myopic or hypermetropic defocus, an asymmetry with respect to the sign of defocus was observed with lower sensitivity to hypermetropic defocus. This asymmetry did not change significantly when chromatic aberrations were eliminated. However, when higher-order aberrations were corrected, the subjects showed similar reduction in vision both with myopic and hypermetropic defocus.

Myopes and emmetropes show different characteristics of the optics in the peripheral eye depending on the level of accommodation. When the change of relative peripheral refraction with accommodation was studied, no difference was found for emmetropes, whereas myopes showed a myopic shift. Nevertheless, similar foveal and peripheral MTFs between the two groups were observed. Regarding the stimulation of accommodation with perifoveal monocular targets, the accommodation amplitude decreases with increasing target eccentricity and at 7° and beyond it becomes absent.

Finally, the MiSight multifocal contact lens produced similar foveal visual quality compared to spectacles, in spite of the increased astigmatism and coma. However, a reduction in low-contrast resolution acuity was observed in the peripheral visual field.

These findings can help further understanding of peripheral vision and the cues that the eye is using to regulate its growth. This thesis has focused on the asymmetry in the point spread function caused by higher-order aberrations with the refractive errors corrected. The effect of peripheral astigmatism was not investigated as it is similar for all eyes, emmetropic as well as myopic. However, astigmatism could change the asymmetry, and further research on the interaction between astigmatism and higher-order aberrations is needed.

The results of this thesis are also important for the improvement of myopia control interventions. For example, a reduction of the peripheral depth of focus may make myopia interventions more efficient as it enhances the peripheral contrast reduction of the optical intervention for distant compared to nearby targets. Animal studies on form-deprivation have shown that low image contrast for different target vergences causes exaggerated eye growth. A large change in the peripheral image contrast for different target distances is thereby a possible clue for eye growth. It may therefore be more effective to control myopia by inducing pure peripheral myopic defocus without higher-order aberrations that extend the depth of focus. Similarly, lens designs with aberrations that induce a more asymmetric point spread function may also help the eye to differentiate between myopic and hypermetropic defocus.

Summary of the original work

This Thesis is based on the five papers listed below. The author was the main responsible for Papers 2 and 3, including the design of the study, the execution of the experiments, the analysis of the data and the writing of the papers. In Paper 1 the author was involved in planning and performing the measurements as well as in preparing and calibrating the experimental adaptive optics system. In Paper 4 the author contributed to the design and execution of the experiments. In Paper 5, the author took part in developing the original idea and the design of the study and performed the pilot measurements. The author also discussed the results and contributed to the writing of Paper 1, 4 and 5.

Paper 1: Peripheral resolution and contrast sensitivity: effects of monochromatic and chromatic aberrations

This paper investigates the effects of different levels of optical correction of the image quality in 20° nasal visual field. When vision was evaluated in green light conditions (chromatic aberrations elimination) combined with adaptive optics for higher-order aberrations correction, both high-contrast detection and contrast sensitivity thresholds were improved.

Paper 2: Lower sensitivity to peripheral hypermetropic defocus due to higher order ocular aberrations

This paper describes the effect of monochromatic and chromatic aberrations on the asymmetric sensitivity to the sign of defocus in the peripheral visual field. When chromatic aberrations were eliminated, the asymmetry did not change. However, when adaptive optics were used for higher-order aberrations correction, significantly more symmetric profiles were observed.

Paper 3: Foveal and peripheral visual quality and accommodation with multifocal contact lenses

This study presents the short-term effects of multifocal contact lenses on foveal and peripheral vision. The investigated multifocal contact lenses were the MiSight contact lenses designed for myopia control and the Acuvue Moist contact lenses designed for presbyopia. The MiSight lenses produced similar foveal results compared to spectacles despite the increased astigmatism and coma. In the periphery, they reduced the low-contrast resolution acuity. When compared to spectacles, Acuvue Moist decreased accommodative response and reduced foveal high- and low-contrast resolution acuity whereas peripheral thresholds were more similar to spectacles.

Paper 4: Foveal-peripheral real-time aberrations with accommodation in myopes and emmetropes

This study shows that relative peripheral refraction with accommodation remained the same for emmetropes and became more myopic for myopes. However, despite the differences in relative peripheral refraction between emmetropes and myopes, the MTFs with natural pupil sizes were similar between the two groups both foveally and peripherally, and did not change with accommodation.

Paper 5: Parafoveal accommodation response to defocus changes induced by a tuneable lens

In this paper accommodation beyond the foveal visual field was studied. The findings indicate that the monocular accommodative amplitude decreases with increasing eccentricity, and becomes absent at 7° and farther. Additionally, increased accommodative response times with increasing off-axis angles were observed.

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