The influence of optics, peripheral refraction and posture on refractive error development

A thesis submitted to
The University of Manchester
for the degree of a
Doctor of Philosophy
in the Faculty of Life Sciences.

2011

Andreas Hartwig

Contents

word count: 52 419

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Abstract

The aim of the present project was to analyse the link between peripheral posture, optics, optics and refractive error progression. Preliminary studies were conducted to ensure that peripheral aberrometry is valid for further analysis.

The repeatability of the IRX-3 for peripheral aberrometry was as good as for central measurements and the recalculation of elliptical pupils did not seem to be necessary for measurements up to 20 degrees eccentricity. Higher order aberration measurements were comparable to other studies.

Eye and head movements as well as working distance did not differ significantly between myopes and non-myopes. However, there was some evidence, that forward bending of the head during reading increases in association with higher refractive error progression rates.

The link between central higher order aberrations and refractive error development was analysed by comparing higher order aberrations between isometropes and anisometropes. This analysis did not show any significant association of higher order aberrations on the development, as no major differences were found between the two groups. For central vision, changes in biometric parameters during accommodation were analysed. It was found that biometric parameters change similarly in myopes and non-myopes.

Peripheral accommodation was found to differ between myopes and emmetropes indicating that there might be an influence of peripheral refraction on myopisation. However, association between peripheral refraction or peripheral aberrations and refractive error progression were not significant. The reason for this observation might be the low refractive error progression (0.04 $\pm$ 0.29 D in myopes and -0.12 $\pm$ 0.38 D in emmetropes) during one year in the study population.

Declaration

I herby declare that no portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Copyright statement

Abbreviations

al.	Alii
ATR	Against the rule
B.C.	Before Christ
c	Cycles
COAS	Complete Ophthalmic Analysis System
d	Distance
D	Dioptres
deg	Degree
F	Focal point
g	Gram
HOA	Higher order aberration
Hz	Hertz
I	Inferior
IOL	Intra ocular lens
LASIK	Laser-assisted in situ keratomileusis
LOA	Lower order aberration
mm	Millimetre
MRI	Magnet Resonance Imaging
n	Optical refractive index
N	Nasal
N	Front Nodal Point
N'	Back Nodal Point
nm	Nanometre
OD	Oculus dexter (right eye)
OS	Oculus sinister (left eye)
RMS	Root mean square
S	Superior
T	Temporal
V	Vergence
WTR	With the rule

Acknowledgements

There are plenty of persons who were around during my time in Manchester and contributed in various ways to my project.

First of all there are my supervisors Dr. Hema Radhakrishnan and Dr. Ian J. Murray. Both managed to guide me through the PhD in a perfect way. From my perspective they could not have done any better, they were always helpful and always encouraging.

Dr. Emma Gowen was my advisor and all her advice was very helpful.

The discussions with Prof. Neil Charman had a big impact of on me.

Without Prof. David Henson I probably would not have come to Manchester for the PhD. My first contact to the University of Manchester was through Prof. Henson. He was very helpful and offered various possibilities of projects.

The highlight of my PhD was probably my visit to Queensland University of Technology, Brisbane, Australia. I thank Prof. David Atchison for hosting me for several weeks in his lab. It was a great and useful time.

Also I would like to thank my friends at the university, in particular Amit Jinabhai as well as Ana Hernandez Trillo and Michael Read.

I am endlessly thankful to my parents Maren and Wilfried Hartwig. There are no words to describe their endless support!

In summary the last three years were great. I would not have wanted to miss any day of this period. Thanks to everybody including all study-participants who was involved and thank you to everyone who made daily life at university interesting for me.

Acti iucundi labores!

Cicero

Chapter 1

Introduction

1.1 The project

The prevalence of myopia is increasing dramatically around the world. Figure 1.1 provides a rough overview about myopia prevalences. (Section 1.2.3 provides further discussion on myopia prevalence.) In total, about 1.6 billion humans are affected by myopia and calculations propose that 2.5 billion individuals will be affected by the year 2020 (Holden *et al.*, 2010). However, due to varied definitions of myopia, the prevalence varies. But it can be summarised that myopia is the most common human eye condition in the world (Pararajasegaram, 1999) and a leading cause for blindness (Fredrick, 2002). Myopia is not only a significant health problem, as it is associated with an increased risk for visual loss, but also has an economical impact, as health care costs increase with increasing prevalence (Young, 2009).

It has been agreed that myopia is a multifactorial problem (see Mutti, 2010 and Charman, 2011a for reviews). However, genetics and environmental factors have been identified as major causes for the increased myopia prevalence. Amongst the environmental factors peripheral vision seems to one factor that holds most potential to influence myopisation. But it is likely that not only peripheral vision in the field of environmental factors has an impact on myopisation.

Chapter 1 summarises the work that has been done in the field of myopia research. Also it gives an overview of optical principals and describes terms and relationships that are described in the following chapters. Chapter 2 to 12 describe the research studies that were conducted to get a better understanding of the development of myopia as part of the PhD.

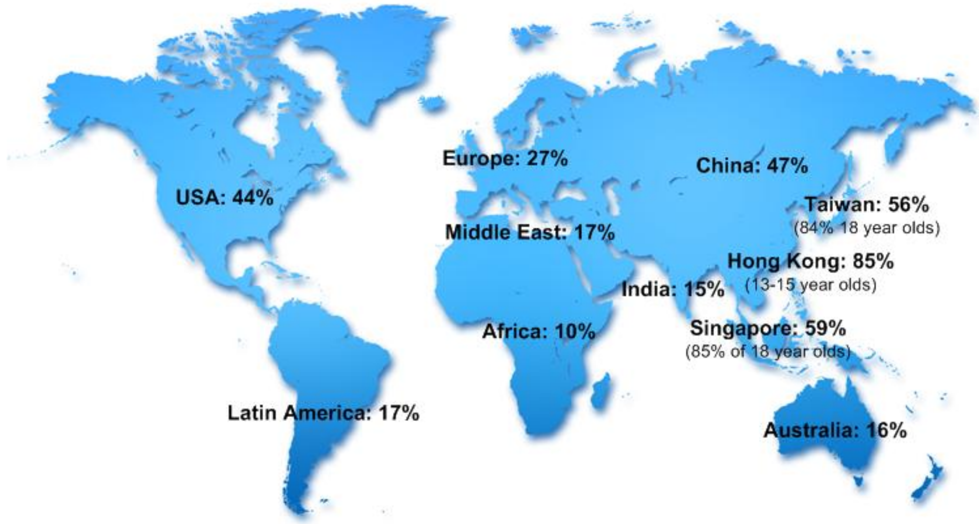

Figure 1.1 – Prevalence of myopia around the world. (Source: Holden *et al.*, 2010)

1.2 Basic optics

1.2.1 Introduction

Optics is classically divided into two sub areas: geometric optics and physical optics. It is split into these two parts because light shows different characteristics. On the one hand light behaves like rays. Therefore geometric optics is also called ray optics. Geometric optics is used for describing aberrations and constructing optical systems. On the other hand aspects like diffraction cannot be explained by ray optics. Hence physical or wave front optics explain the habits of light described as diffraction or interference. Wave front optics is based on the observations firstly made by Huygene.

1.2.2 The optical elements of the human eye and their functions

1.2.2.1 Introduction

The human eye (Figure 1.2) is considered to be a lens system, which consists of the cornea and the crystalline lens. The cornea is responsible for about $^2/_3$ of the total refractive power in this optical system. This is due to the fact, that the difference between the refractive indices of air ($n = 1.0$) and the cornea ($n = 1.376$) shows the highest value. In an emmetropic eye, this lens system allows light from infinity to refract so that the focal point of cornea and lens combined lies exactly on the retina. An approximation of the relationship between eye length and ametropia is that a difference of 1 mm would cause an ametropia of about 3.0 D.

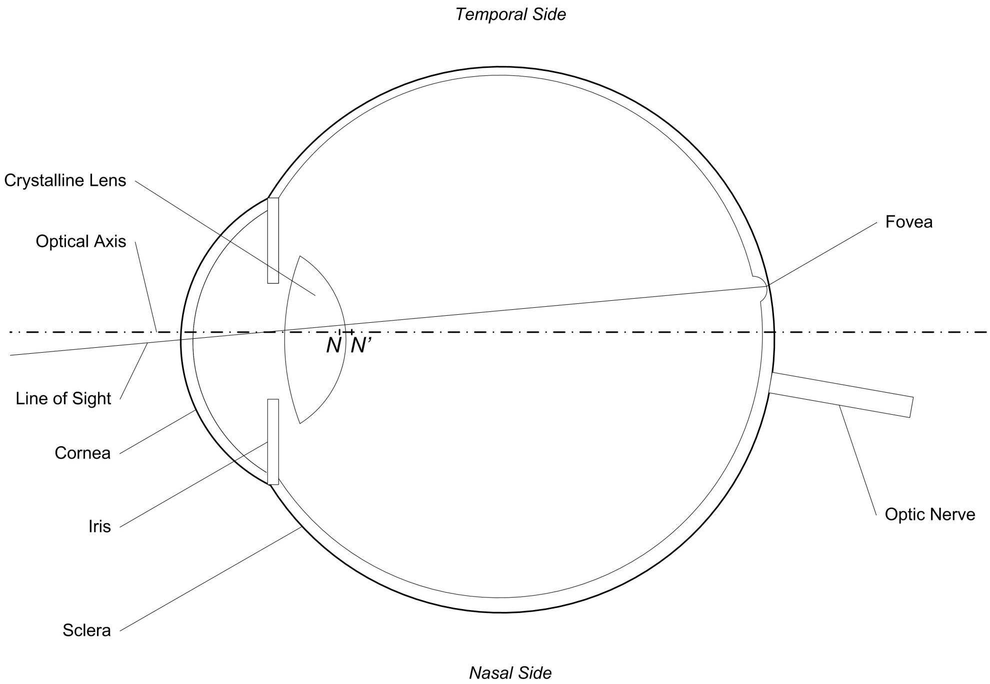

Figure 1.2 – Schematic representation of the human eye. Horizontal point of view. The nodal points N and N' are marked as they are often used as reference points.

1.2.2.2 Cornea

The outer layer of the eye is divided into two parts: cornea and sclera. The sclera is the opaque and dense part that gives the shape of the eye. The cornea is the transparent part that provides about $^2/_3$ of the optical power of the relaxed eye. Any corneal irregularities have an impact on the optical performance (Kiely *et al.*, 1982; Atchison and Smith, 2000a p. 3-4; McMahon *et al.*, 2001). The front surface of the cornea has the highest refractive contribution compared to the other refractive surfaces in the human eye. It is covered by the tear film which is essential, because it smooths the corneal surface and is essential for a clear retinal image. The average anterior corneal radius is slightly less than 8.0 mm which varies for different meridians. It was found that longer eyes have flatter corneas (Chang *et al.*, 2001, see also chapter 4). A change of 0.1 mm in corneal curvature results in a change in refractive power of 0.6 D of the whole eye (Bennett and Rabbetts, 1989). Usually the radius of curvature flattens with eccentricity from the centre. Therefore the shape of the cornea is aspheric. This fact plays an important role in the optical balance of spherical aberration between the cornea and the crystalline lens.

The asphericity of the cornea is specified by Q and is given without units. Corneal asphericity in terms of Q is usually negative, which indicates a flattening ellipse. The flattening of the cornea contributes to a reduction of spherical aberration (Kiely *et al.*, 1982; Carney *et al.*, 1997; Atchison and Smith, 2000a p.11-16; Cuesta *et al.*, 2003; Miranda *et al.*, 2009b). Kiely *et al.* (1982) gave a mean corneal asphericity in a population of 176 patients of -0.26 ± 0.18. The asphericity in this group ranged from -0.76 to +0.47. On the basis of a regression calculation between corneal radius and asphericity the authors established a relationship between a steep corneal centre and a more rapid flattening. Carney *et al.* (1997) found a statistically significant relation between the corneal asphericity and the refractive error. With increasing myopia they found the cornea to flatten less.

Different types of conic functions are given in Table 1.1. Sometimes corneal asphericity is expressed by a p-value or by the eccentricity e instead of Q. Values are converted by equation 1.1 or 1.2. The asphericity can be significantly influenced by refractive surgery (LASIK) (Anera *et al.*, 2003; Atchison, 2006a) and orthokeratology (Mathur and Atchison, 2009).

Q > 0	ellipsoid with the major axis in the X-Y plane
Q = 0	sphere
-1 < Q < 0	ellipsoid with the major axis in the Z plane
Q = -1	paraboloid
Q < -1	hyperboloid

Table 1.1 – Classification of corneal asphericity.

$$p = (1 + Q) \tag{1.1}$$

$$e = -\sqrt{Q} \tag{1.2}$$

The anterior corneal asphericity has been analysed extensively, whereas posterior corneal asphericity has not been studied in detail (Smith, 1995).

1.2.2.3 Pupil

Based on a dynamic system the pupil regulates the amount of light getting into the eye. Whilst the surroundings are illuminated the pupil is small and less light can get into the eye. With decrease of illumination the pupil dilates. Furthermore the pupil-size decreases with accommodation which increases the depth of focus. The amount of pupil-size-change declines for constant light levels with age resulting in a smaller pupil diameter. Even though ocular aberrations increase with age the decrease in pupil size reduces their effect on retinal image quality, although retinal illuminance is reduced (Calver *et al.*, 1999; Charman, 2010).

The average pupil diameter ranges between 2.5 and 4.0 mm. In darkness, the pupil might have a diameter of about 8.0 mm (Atchison and Smith, 2000b).

1.2.2.4 Crystalline lens

Directly behind the pupil the crystalline lens is situated consisting of the nucleus and the surrounding cortex comparable to an onion like structure. The name 'crystalline lens' is misleading as the lens does not show a crystalline structure as it consists of proteins. Whereas the refractive index of the nucleus appears to be constant (ranges between 1.39 and 1.41), the outer region, which tends to be one third of the lens, shows a gradient refractive index. This means that the refractive index varies throughout the cortex (for review, see Pierscionek, 2010). Due to changes in lens surface curvature (see section 1.2.2.8) and change in position (Ostrin *et al.*, 2006), the optical power of the lens increases for near vision. The gradient refractive index also changes with accommodation (Pierscionek, 2010).

Throughout life the crystalline lens grows and the mass increases approximately logarithmically (Weale, 1982). Also with increasing age the elasticity and the gradient refractive index changes due to permanent lens growth during the lifetime (Glasser and Campbell, 1999; for review, see Augusteyn, 2008). However, the eye does not become myopic with age, which would be the consequence of continuous lens growth as the lens becomes thicker (Koretz *et al.*, 1989). Also the anterior and posterior radii of curvature decrease with age (Pierscionek and Weale, 1995). It is assumed that a decrease in refractive index of the nucleus compensates the growing effect so that the eye does not become myopic with age (Pierscionek, 2010). Even though, compensation mechanisms occur as described above, the overall prescription of the eye changes throughout life. Also, light sensitivity changes during an individual's lifetime due to opacification of the lens (Liou and Brennan, 1997; Smith and Atchison, 2001; Popiolek-Masajada and Kasprzak, 2002; Jones *et al.*, 2005; Atchison, 2006b).

1.2.2.5 Retina

From the optical point of view, the aspheric retina (Atchison *et al.*, 2005a) is the last section in terms of image formation of the eye containing rods and cones, which convert electromagnetic radiation from roughly 380 to about 780 nm into neurological impulses. The retina of each eye forwards visual information via roughly one million nerve fibres to the brain (Saude, 1993). The duality of rods and cones allows not only colour vision but also vision in relative darkness. Cones are responsible for the visual processing of colours and rods are responsible for monochromatic vision. To allow a detection of different colours, three types of cones are present in the human retina, whereas only one rod-type exists. The L-cones are sensitive for long wavelengths and detect therefore red light. M-cones are appropriate for middle wavelengths (green) and S-cones for short wavelengths (blue) (Atchison and Smith, 2000a).

Curcio *et al.* (1990) analysed the fine details of retinae of eight donor eyes. They found a mean foveal peak cone density of 199 000 $\frac{cones}{mm^2}$ and a rod density of 176 000 $\frac{rods}{mm^2}$ on average. Furthermore, they calculated a ratio of 20:1 for the total number of rods to the total number of cones. The comparison between the right and left eye showed a similar topography of rods and cones, but the topography was not identical. No obvious trends were found for a cell reduction with age.

The sampling of rods and cones along the horizontal meridian of the retina can be seen in Figure 1.3. Cones have their maximum density at the fovea for high resolution vision. Rods have their maximum density at about 15 degrees on each side from the fovea and are very sensitive in low light conditions. Not only the type of receptor plays a role for the kind of vision, but also the neural network which combines information from different receptors, which additionally varies with retinal location. For instance only a few cones are combined for further processing, but about 100 rods are combined, which allows the cones higher spatial resolution than the rods. The neurological impulses from the rods and cones are forwarded by the optic nerve for processing by the visual cortex and midbrain. So it can be reasoned that the retina is the starting point of visual processing (Atchison and Smith, 2000a p. 5-7).

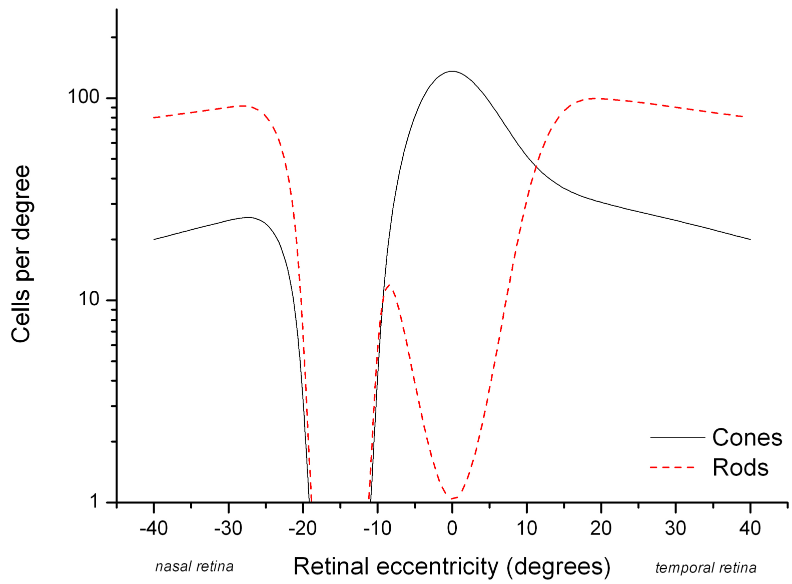

Figure 1.3 – Cells per degree in the human retina along the horizontal meridian. At about -15 degrees (nasal retina) there are no receptors due to the optic nerve head (papilla), therefore it is also called the blind spot. (Source: Freeman and Hull, 2003, p. 517)

1.2.2.6 Optical quality

In a human eye aberrations and diffraction limit the image quality on the retina. Beside the optical quality of the cornea and crystalline lens, the pupil contributes significantly to the image quality (Campbell and Green, 1965). Figure 1.4 shows that aberrations predominantly affect the retinal image quality where pupil size is 4.0 mm or more. With increasing pupil size, the impact of aberrations also increases. At a pupil diameter between 2.0 and 3.0 mm aberrations and diffraction are usually balanced resulting in good retinal image quality during daylight conditions (Liang and Williams, 1997; Freeman and Hull, 2003).

Not only the optical elements of the eye are crucial for the quality of the image perception, the retinal photoreceptors (rods and cones), the optic nerve and the brain also contribute to the visual perception, which is finally

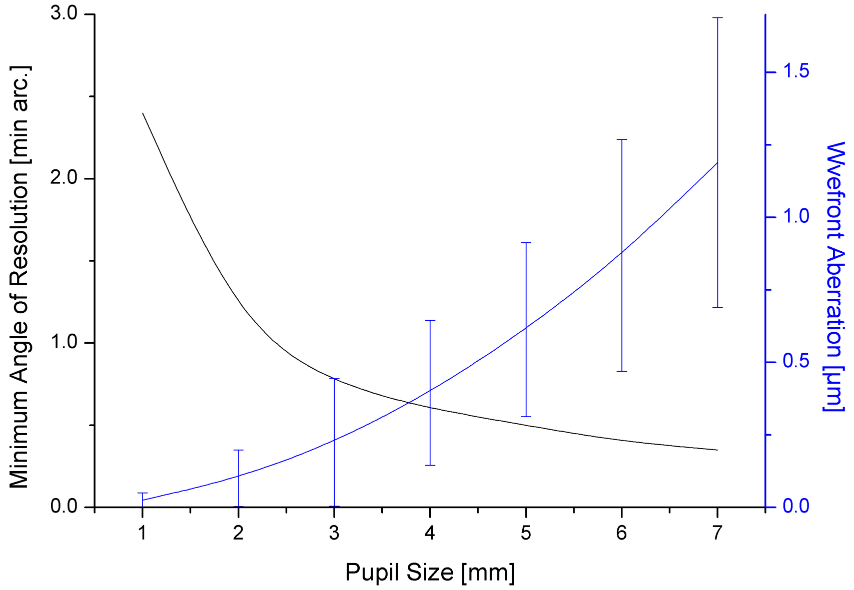

Figure 1.4 – Impact of pupil diameter on diffraction (black) and aberrations (blue). Diffraction-limitation is based on green light (555 nm). Data for aberration are based on aberrometry measurements on 28 subjects. The error bars show ± 1 standard deviation (Hartwig, 2007). The small study population of 28 subjects and the different study populations for diffraction and aberration might be the reason for the shift in pupil diameter to approximately 3.8 mm instead of 2.0 to 3.0 mm. (Source: Freeman and Hull, 2003, p. 518)

perceived. Campbell and Green did some fundamental research on visual resolution in the 1960s. For example, they analysed the resolution of the retina and brain by measuring the threshold for sinusoidal interference fringes. Interference fringes were used because their contrast is not influenced by most aberrations. They utilized a neon-helium laser with wavelength 632.8 nm. The spatial frequencies of the laser fringes formed on the retina were up to 35-40 $^{c}/_{deg}$. Their results are plotted in Figure 1.5 and show that contrast sensitivity, which is the reciprocal of threshold contrast, decreases exponentially from 10 $^{c}/_{deg}$ onwards with increasing spatial frequency (Campbell and Green, 1965; Campbell and Gubisch, 1966).

In their work about the spatial resolution capacity of the fovea Hirsch and Curcio (1989) summarised that the foveal lattice of cells does not necessarily limit visual acuity. Other factors such as central optics or neural processing could have an impact on the visual acuity. Later Schwiegerling (2000) calculated a theoretical limit of high contrast visual acuity. He performed

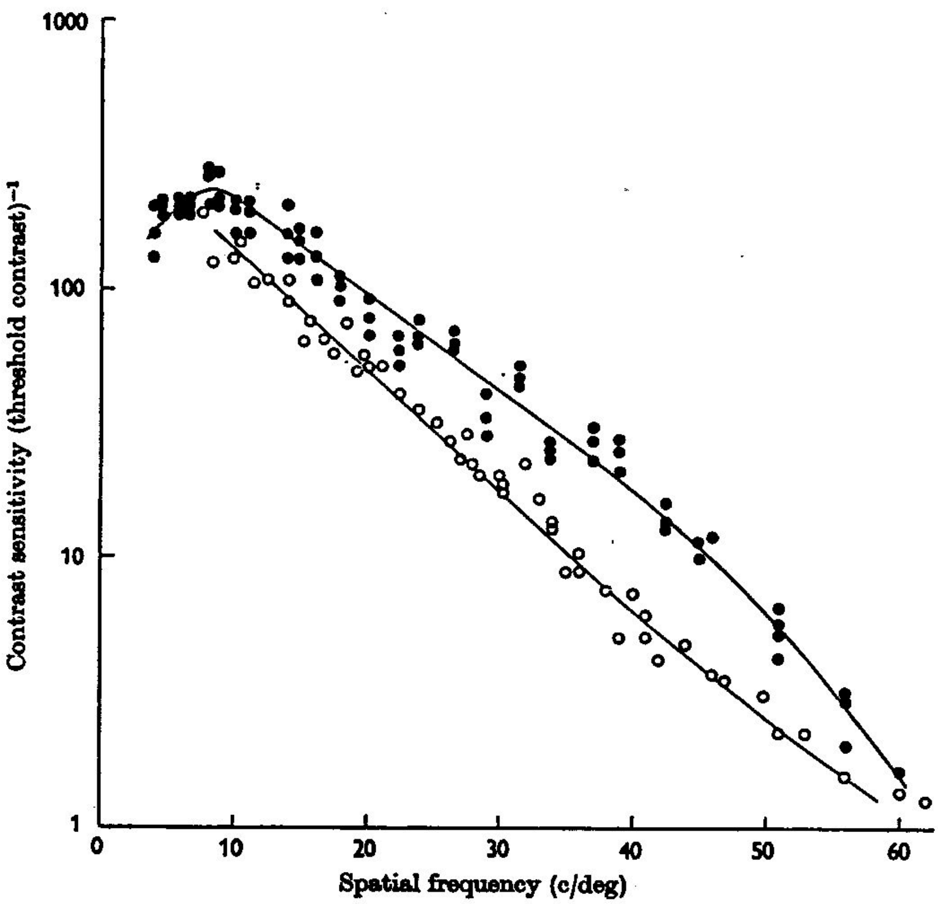

Figure 1.5 – Contrast sensitivity versus special frequency shown for two subjects. The smooth curves have been added by visual judgement. (Source: Campbell and Gubisch, 1966)

ray tracing on a schematic eye and calculated the limiting spatial frequency by superimposing the modulation threshold function over the modulation transfer functions for 2.0 mm, 4.0 mm and 6.0 mm pupils of chromatic aberrations. The modulation transfer functions give the limit of the eye's optics when forming an image on the retina for certain pupil sizes and were limited to chromatic aberrations and diffraction at a single wave length. The modulation threshold function gives the minimum contrast necessary for the retina and brain to detect a sinusoidal grating. The result of this approach from Schwiegerling is shown in Figure 1.6. The intersections between the superimposed modulation threshold function and the modulation transfer functions predict the approximate limit for visual resolution. According to Figure 1.6 the approximate values are 50 $^{c}/_{deg}$ for a 2.0 mm pupil, 100 $^{c}/_{deg}$ for a 4.0 mm pupil and 120 $^{c}/_{deg}$ for a 6.0 mm pupil. These values can be converted into metric Snellen notation by the rule of thumb that 30 $^{c}/_{deg}$ equals 6/6 Snellen notation. Hence 50 $^{c}/_{deg}$ equals 6/3.8, 100 $^{c}/_{deg}$ 6/1.9 and 120 $^{c}/_{deg}$

6/1.5. Schwiegerling (2000) reasoned that refractive surgery that incorporates the correction of aberrations could theoretically improve retinal image quality. Charman and Chateau (2003) reviewed this topic and came to the conclusion that correction of higher order monochromatic aberrations would not improve photopic vision, but it could have a positive influence on mesopic and scotopic vision.

Recently Schallhorn *et al.* (2008) reviewed the outcome of conventional LASIK refractive surgeries and wavefront-guided LASIK. They concluded that the visual acuity does not improve as suggested by Schwiegerling (2000), when refractive surgery corrects aberrations. They found that higher order aberrations increase with a wavefront-guided LASIK refractive surgery, even though it was corrected for during the surgery.

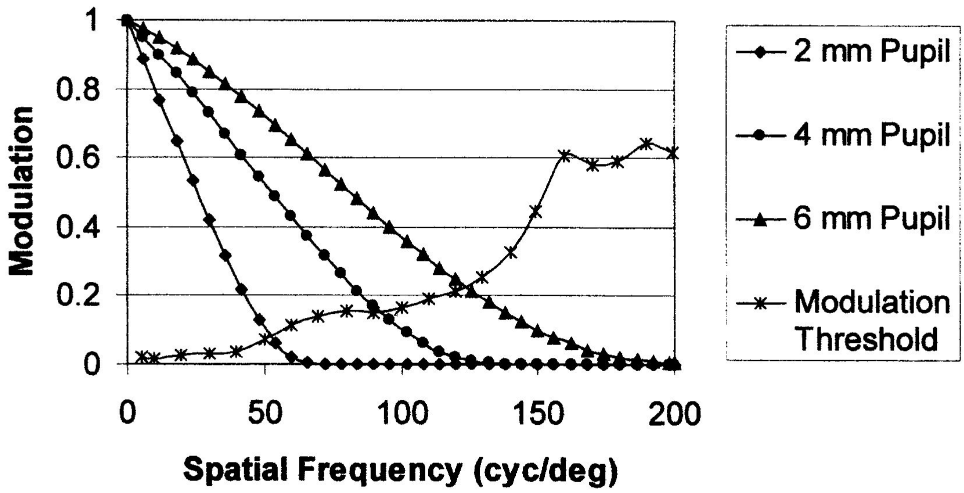

Figure 1.6 – Estimate of theoretical visual acuity based on modulation transfer function for 2.0 mm, 4.0 mm and 6.0 mm pupil diameter and their intersections with modulation threshold which give the limiting spatial frequency. (Source: Schwiegerling, 2000)

1.2.2.7 Emmetropisation

During the process of emmetropisation the refractive state is reached in adolescence by growing of the ocular components where parallel light rays come to a focus on the retina. The far point of an emmetropic eye lays in infinity. This situation is shown in Figure 1.7 and the dependency on age is shown in Figure 1.8. Emmetropisation is a sophisticated process as various components (for instance, corneal curvature, lens curvature, lens thickness and axial length) change during eye growth (Augusteyn, 2008) to achieve a clear image on the retina. Most substantial changes occur within the first three years (Mayer *et al.*, 2001) and in normal eyes no substantial refractive changes tend to occur after the age of 16 years (Gordon and Donzis, 1985). The decrease in spherical equivalent in childhood is mainly achieved by a reduction in lens thickness (Zadnik *et al.*, 1995).

Several studies in humans and animals have shown that emmetropisation is an active process partly based on visual feedback (Hubel and Wiesel, 1962; Wildsoet, 1997; Norton, 1999; Gilmartin, 2004; Wallman and Winawer, 2004; Buehren *et al.*, 2005; Mutti *et al.*, 2005). Different definitions about the range of emmetropia exist, but generally the interval between -0.50 D and +0.50 D is identified as emmetropia, especially for research studies Hirsch, 1964; Lam and Goh, 1991; Saw *et al.*, 1996; Mutti *et al.*, 2002; Atchison *et al.*, 2005a; Hartwig, 2007. Bradley *et al.* (1999) found in rhesus monkeys that greater amounts of hyperopia at birth are followed by a faster increase of axial length. Interestingly, chicken eye growth is also well coordinated after optic nerve section, which means that emmetropisation is mainly controlled by the eye and the process is not exclusively controlled by the brain (Troilo *et al.*, 1987; Wildsoet and Pettingrew, 1988). However, it remains unanswered what guides axial growth of the eye. Until now, it is not clear if the effectiveness of emmetropisation varies due to genetic factors or if different sensitivities for emmetropisation exist that change with environmental factors (Morgan and Rose, 2005). Furthermore, it is uncertain if both eyes are linked for emmetropisation or if each eye runs the process of emmetropisation on its own. This question is supported by animal studies as monocular occlusion in rhesus macaque monkeys leads to myopia but not in stumptailed macaque (Lawrence and Azar, 2002). As emmetropisation is functional after optic nerve section, it can be assumed that no link exists.

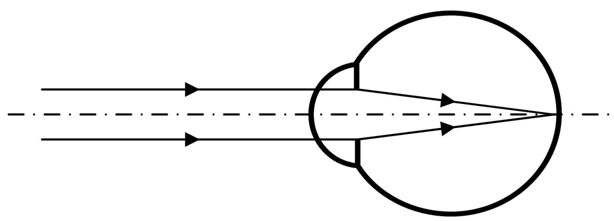

Figure 1.7 – Emmetropic eye: focus of light from infinity lies on the retina.

1.2.2.8 Accommodation

Fundamentals The mechanisms of accommodation were first described by Helmholtz (1867, p. 103-125). Helmholtz described four biometric changes

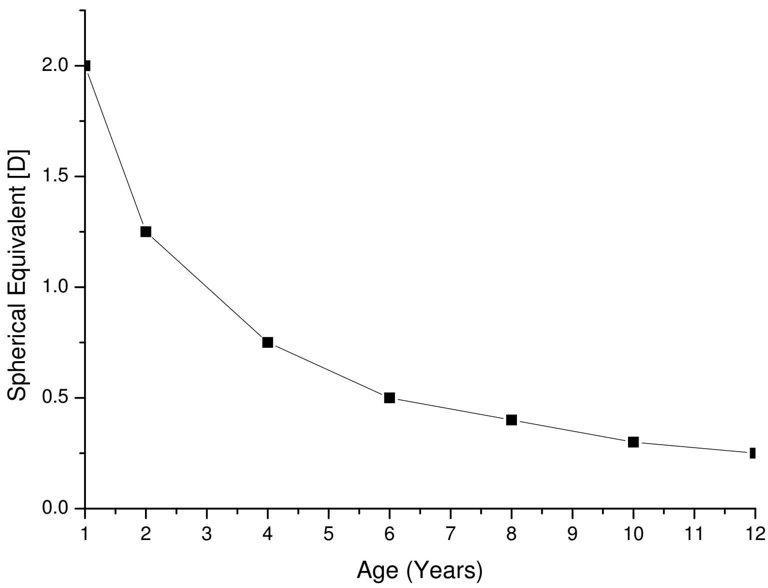

Figure 1.8 – Polynomial fit for mean spherical equivalent versus age as a summary of various studies. (Source: Mayer *et al.*, 2001)

that occur with accommodation:

1. reduction of pupillary diameter with accommodation
2. the anterior lens surface moves towards the cornea
3. the radius of the anterior crystalline lens surface becomes steeper
4. only a minimal movement of the posterior lens surface

These descriptions are nowadays widely accepted, even though some authors question the theory of Helmholtz (e.g. Schachar *et al.*, 1993). Accommodation enables the eye to see clearly at various distances. To achieve good near vision accommodation is supported by vergence and change in pupil size. The accommodative state is usually identical in the two eyes. Only cones drive accommodation which means that accommodation becomes less effective under dim and low light conditions (Charman, 2010). Accommodation is maintained by the ciliary body, which is mainly parasympatheticly innervated (Schmidt *et al.*, 2000, p. 285). The ciliary body is attached to the crystalline lens by zonular fibres. In a relaxed accommodative state the circular ciliary muscle is wide and the tension executed by zonular fibres is high, so that the crystalline lens is in a flat shape. For near vision, the ciliary body contracts and the crystalline lens can get into its steeper shape due to lower zonular fibre tension. Therefore the central thickness of the crystalline lens increases. The anterior and the posterior surface of the lens do not change their radii of curvature equally. The change of the anterior surface was shown to be 4.7 times greater than the change of the posterior surface (Dubbelman *et al.*, 2005). By rule of the thumb, $^1/_3$ of accommodation is contributed by the posterior surface and consequently $^2/_3$ by the anterior surface (Garner and Yap, 1997; Weale, 2003; Dubbelman *et al.*, 2005; Rosales *et al.*, 2006). However, an increase in refractive power is not only achieved by a change of curvature, but also by the change of refractive index. Gullstrand (1911) assumed in the early 1900s that accommodation is linked to a change in refractive index. Dubbelman *et al.* (2005) finally proved that the increase in power of the crystalline lens is not only achieved by a change in curvature, but also by a change in refractive index distribution in the accommodated crystalline lens. Based on refractive index maps, Jones *et al.* (2007a) showed that the refractive index of the lens decreases by 0.38% for a 6.5 D stimulus in a cohort of six patients. However, the change in refractive index was not statistically significant with the small number of subjects in the study.

Until now, the mechanisms which drive accommodation are not well understood. There is strong evidence that minor changes of corneal curvature contribute to an increase of optical power (Buehren *et al.*, 2003b; Read *et al.*, 2007). Also, it has often been shown that accommodation is linked to convergence and pupil constriction (Charman, 2008). Accommodation works very quickly and precisely and is not a trial-and-error mechanism (Zhu *et al.*, 2005). Even though the mechanisms that control accommodation are not understood in detail, it is widely accepted that accommodation is mainly, but not entirely controlled by image quality at the fovea (Charman, 2005). Two questions arise, first, it has not been shown yet if the brain influences accommodation or if the process of accommodation is only controlled by the eye. This could perhaps be demonstrated by optic nerve sections. Second, accommodation and emmetropisation might use the same signals to reach a stable refractive state and clear vision, therefore, both systems are likely to be linked and controlled by the eye itself. However, in a recent review, Charman (2011b) summarised that the sense of accommodation and emmetropisation is a clear retinal image, but both mechanisms differ in aspects such as peripheral involvement.

Due to hardening of the crystalline lens, its ability to change the power starts to decline appreciably between the age of 40 and 45. It comes down to zero at about the age of 60 (Donders and Moore, 1864; Charman and Tucker, 1978; Grosvenor, 2002). Figure 1.9 shows the amplitude of accommodation in relation to the age measured by Donders more than 100 years ago. Current amplitude of accommodation measurements show a similar distribution (Charman, 2008). The process of decreasing accommodation ability is called presbyopia and defined as a subjective amplitude of accommodation below three dioptres. Analysis of magnetic resonance images (MRI) of the eye showed that the maximum contraction of the ciliary body does not change with age (Strenk *et al.*, 1999). The change in ciliary ring diameter over age can be seen in Figure 1.10. Even though the number of subjects (25) was small in this study, the results are informative because they support the theory that lens hardening causes presbyopia as the ciliary body keeps constricting even for presbyopic patients.

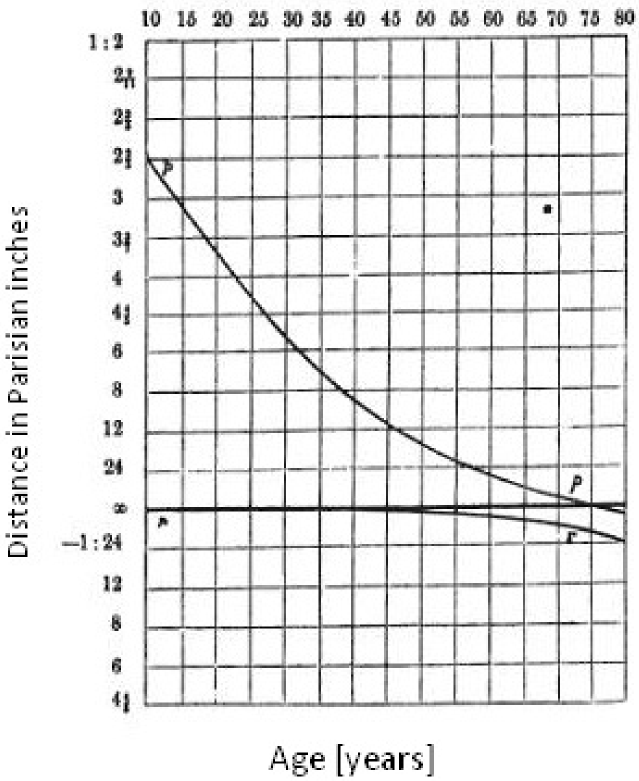

Figure 1.9 – Amplitude of accommodation during lifetime. The abscissa shows the age and the ordinate shows the distance in Parisian inches (one Parisian inch equals approximately 27.0 mm). (Source: Donders and Moore, 1864)

Kirschkamp *et al.* (2004) compared radii of curvature, axial separations and alignment in unaccommodated and accommodated eyes of nine subjects. Their results are shown in Table 1.2. Interestingly, the anterior chamber depth

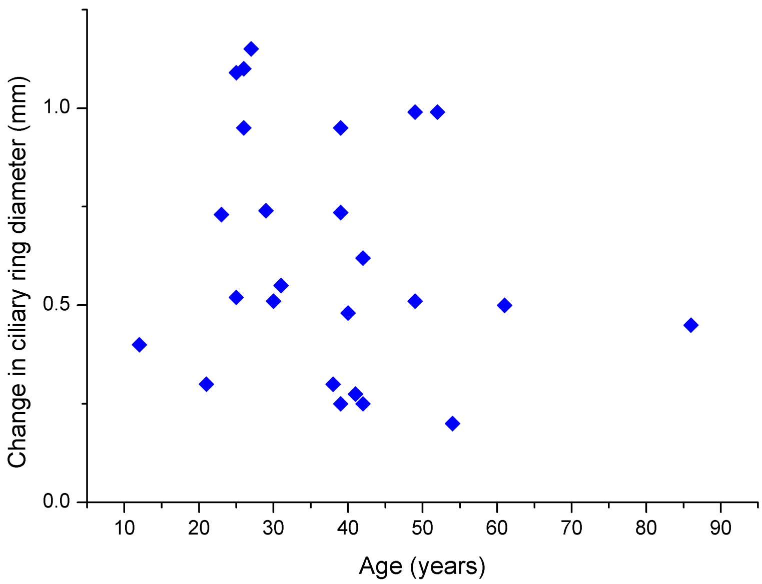

Figure 1.10 – Change of ciliary ring diameter with 8.0 D of accommodation stimulus as a function of age. Even for a 86 years old subject the ciliary ring diameter changes with accommodation. (Source: Strenk *et al.*, 1999)

and the lens thickness changed by the same magnitude (0.2 mm) in opposite directions. Both values reached statistical significance for a paired two-tailed t-test. Changes in ocular alignment with accommodation could not be shown. The refractive error of the subjects was not mentioned. It would be worthwhile to know, if these differences are linked to the type and magnitude of ametropia.

As suggested by Erickson (1984), Kirschkamp *et al.* (2004) analysed their data by vergence analysis. They used ray tracing to calculate a ray from the retina back to the cornea, using optical distances (see formula 1.3) instead of normal distances.

$$V = \frac{n}{d} \tag{1.3}$$

whereas V is vergence, n is refractive index and d is measured distance.

This revealed a different result in comparison to the above-mentioned results (Table 1.2). As it can be seen from Table 1.3, vergence of anterior chamber decreases by -1.5 D and also the vergence of crystalline lens thickness decreases by -0.2 D. In contrast to the vergence of the anterior chamber, the vergence of the lens thickness was not statistically significant different between unaccommodated and accommodated states (Kirschkamp *et al.*, 2004).

Vergence analysis allows the total effect of each optical component to be summed. The given accommodation stimulus was 4.0 D. Therefore there is a

Parameter	Unaccommodated	Accommodated	p-value
Radii of curvature (mm)			
Cornea	7.9 ± 0.2	7.9 ± 0.2	0.7344
Anterior crystalline lens	12.3 ± 0.8	8.6 ± 1.2	< 0.0001
Posterior crystalline lens	-6.1 ± 0.2	-5.3 ± 0.2	0.0001
Axial separation (mm)			
Anterior chamber depth	3.6 ± 0.2	3.4 ± 0.2	0.0005
Crystalline lens thickness	3.7 ± 0.1	3.9 ± 0.1	0.0004
Vitreous depth	16.3 ± 0.4	16.3 ± 0.4	0.2986
Ocular alignment			
Eye rotation (degrees)	5.7 ± 1.6 T	5.8 ± 1.3 T	0.6493
Crystalline lens tilt (degrees)	0.2 ± 0.8 T	0.3 ± 0.8 N	0.1389
Crystalline lens decentration (mm)	0.1 ± 0.1 N	0.1 ± 0.1 N	0.1133

Table 1.2 – Changes in ocular parameters with accommodation. The table shows mean values with 95% confidence intervals and p-values for a paired two-tail t-test. The direction of change in alignment is indicated by N (nasal) and T (temporal). (Source: Kirschkamp *et al.*, 2004)

difference of 0.3 D, which is not explained. The fact that Kirschkamp *et al.* (2004) do not consider the change in refractive index of the crystalline lens might be a reason for the difference.

Components of accommodation Heath (1956) suggested that there are four components of accommodation.

1. *Reflex accommodation:* This type of accommodation is driven by the quality of the retinal image. Heath (1956) describes reflex accommodation with the fact that a young emmetrope is able to see a distant object clearly through a low-power minus lens due to accommodation.

2. *Proximal or psychic accommodation:* In this case accommodation is caused by just thinking of a near object. This shows that also the mind can control accommodation.

3. *Convergence accommodation:* Heath (1956) summaries that convergence stimulates accommodation due to fusion disparity.

4. *Tonic accommodation:* If no visual target is presented to the eye, a slightly myopic refractive error is observed. This phenomenon is also

Ocular component	**Change in vergence contribution**	**p-value**
Cornea	0.0 ± 0.2	0.8116
Anterior chamber	-1.5 ± 0.3	< 0.0001
Anterior crystalline lens surface	3.1 ± 0.8	< 0.0001
Crystalline lens thickness	-0.2 ± 0.2	0.0914
Posterior crystalline lens surface	2.1 ± 0.6	0.0001
Vitreous depth	0.2 ± 0.3	0.2946
Refractive error (accommodation)	3.7 ± 1.1	0.0002

Table 1.3 – Mean values of vergence contributions during accommodation for individual ocular components together with 95% confidence intervals. The p-values were calculated by one sample two-tailed t-test. (Source: Kirschkamp *et al.*, 2004)

described as night myopia (Charman, 1986) and observed as instrument myopia (Hennessy, 1975). See also section 1.2.3.5.

These components of accommodation show that several possibilities exist that can control the process of accommodation. Presumably some components have a strong influence and other components have a weak influence, but all components seem to interact to provide an adequate refractive state.

Overview of processes that might influence accommodation The processes that drive accommodation are of interest in the field of myopia research, because there might be parallels between accommodation and emmetropisation. Comparing accommodation and emmetropisation, during accommodation the eye is able to focus the retinal image within a very short period. Emmetropisation is supposed to bring the retinal image in focus over a period of years rather than a fraction of a second as in accommodation. Therefore, knowledge of the underlying processes in accommodation could provide further information about the process of emmetropisation and therefore also myopisation (Radhakrishnan *et al.*, 2007; Langaas *et al.*, 2008).

Marran and Schor (1998) applied a detailed study to the question, if accommodation is controlled monocularly or binocularly and if accommodation is accomplished consensually. Their results showed that aniso-accommodation (unequal binocular accommodation) is generally possible, even to a physiologically significant state, which means > 0.50 D. Furthermore, they reasoned that a mechanism exists which controls accommodation of both eyes independently. In contrast Charman (2008) summarised in a review that the accommodative state is usually similar in both eyes.

Also, it is still unclear, if emmetropisation is driven monocularly or binocularly? There is evidence for a monocular processes (Troilo *et al.*, 1987; Wildsoet and Pettingrew, 1988), which is supported by the occurrence of anisometropia (Fledelius, 1984; Dadeya *et al.*, 2001; Weale, 2003). It would also be helpful to know, if special areas of the retina and therefore only one type of cones are responsible for emmetropisation and accommodation control (Campbell, 1954). These questions are related because Wald (1967) found that the centre of the fovea is free of S-cones. The S-cone free area was specified as 7-8 min of arc. Wald (1967) reasoned that the S-cone free zone contributes to seeing fine details. Hence the outer ring of S-cones might contribute to other vision tasks, during sports for example, which possibly involves peripheral vision (Lingelbach and Jendrusch, 2005). Every lens causes longitudinal chromatic aberration, including cornea and crystalline lens. To reduce blur, the information of blue light, which would focus in front of the retina is excluded. Rucker and Kruger (2001) dealt with the influence of colour on accommodation in detail. Their experiment showed that some patients were able to accommodate based on S-cones, but a high variability between the subjects occurred. It has to be summarized that no clear conclusion was possible, that one type of cones contributes most to accommodation, but the performance of accommodation changes, when the longitudinal chromatic aberration is influenced by removing parts of the spectrum. It was assumed that accommodation is controlled in conjunction with chromatic aberration by binocular processes like vergence (Rucker and Kruger, 2001, 2004; Kruger *et al.*, 2005). Another study revealed a change in sensitivity for long wavelengths. Interestingly the sensitivity increased with the amount of myopia (Rucker and Kruger, 2006).

López-Gil *et al.* (2007) studied monochromatic third-order aberrations and could not find a relation between accommodation and monochromatic aberrations. Their experimental results in 26 subjects were comparable to the outcome of a theoretical consideration.

Long periods of nearwork which imply the use of accommodation have been correlated with myopia progression for a long time (Goldschmidt, 1968; Angle and Wissmann, 1980; Richler and Bear, 1980; Zadnik *et al.*, 1994). But no scientific work that has been published recently has shown a relationship between nearwork and myopia. In fact recently published work provided results that conflict with the relationship between nearwork and myopia (Mutti *et al.*, 2002; Morgan and Rose, 2005; Ip *et al.*, 2008c). In this context the findings of Walker and Mutti (2002) are interesting. They observed a hyperopic shift in the mean relative peripheral refractive error from $+0.27 \pm 1.58$ D at baseline to $+0.64 \pm 1.65$ D spontaneously after a 3.0 D nearvision stimulus was given. They measured different values after one and two hours of sustained nearwork, but it has to be questioned if optical components or imprecise accommodation influenced the results. Allen and O'Leary (2006) measured a wide range of accommodative functions to set these results in relation to refractive error, age of onset of myopia and progression of myopia. The key accommodative functions to distinguish between stable and progressing myopes were accommodative facility and lag of accommodation. The results show that accommodative facility is significantly lower in myopes than in non-myopes for distance vision, but not for near vision. Binocular lag of accommodation correlated with refractive error and progression of myopia. They also found a significant correlation between refractive error and amplitude of accommodation.

The fact that a difference in accommodative facility between myopes and non-myopes could only be found for distance vision, but not for near vision (Allen and O'Leary, 2006) corresponds to the finding of Rose *et al.* (2008a) who found that time spent on outdoor activities rather than indoor activities is an important factor for refractive error development. These findings imply that the focus for research questions need to be drawn to distance vision tasks rather than near vision tasks.

Adams and McBrien (1992) reported a high prevalence of myopia in clinical microscopists. Interestingly the images of the binocular microscopes were nominally placed at infinity. Therefore no accommodation is required to see the image clearly. From that point of view accommodation could be ruled out as a reason for myopia development. But instrument myopia which is induced by accommodation might occur and hence accommodation might play a role, especially a peripheral influence (Hennessy, 1975).

These conflicting arguments show that several questions need to be answered. However, at the moment it seems to be that the influence of peripheral stimuli on accommodation holds some potential as discussed in the following section.

Accommodation to peripheral stimuli Early approaches ruled out that accommodation could be influenced by peripheral stimuli. By analysing the luminance threshold level that is required for accommodation, Campbell (1954) reasoned that only cones are responsible for accommodation and observed that peripheral stimuli did not elicit an accommodative response. Also Crane (1966), Toates (1972) and Charman (2005) supported that the foveola is responsible for the accommodation response.

Several other authors have shown that peripheral stimuli can cause accommodation responses under different conditions, which implies that not only cones, but also rods could contribute to accommodative responses (Figure 1.3). Earliest of these was Whiteside (1957) who used narrow white annuli in a dark field as stimuli and found that, with fixation at the centre of the annuli, accommodation was stimulated for annular radii up to at least about 2.5 degrees. A more comprehensive study was conducted by Bullimore and Gilmartin (1987a,b), who used targets consisting of uniform white disks against a black background: the disk radii subtended angles between 0.5 and 10 degrees. Subjects fixated the centre of each disk and the slope of the accommodation response/stimulus curve was determined for the stimulus range of 0.0 to 4.0 D. The slope varied from 0.9 for the case where the retinal target eccentricity for the disk edge was 0.5 degree, to about 0.25 for the 10 degrees eccentricity. The slope was found to fall approximately linearly with the minimum angle of resolution for the retinal location on which the edge contour fell (Charman, 1986): these results appear to be broadly compatible with depth of focus and blur detection data (Wang and Ciuffreda, 2004, 2005; Wang *et al.*, 2006). A further study of this general nature was that of Gu and Legge (1987) who used black disks in a uniform white field as targets and varied the accommodation stimulus with negative lenses. Using disk radii of 1, 7, 15 and 30 degrees they found that there was an accommodative response for all the disks, even when the stimulus edge had an eccentricity of 30 degrees.

As different opinions about the influence of peripheral stimuli on accommodation exist, it can be summarised that certain stimuli can influence the state of accommodation. The size of the target and the viewing distance might play a role as well as the state of the target's surface.

1.2.3 Myopia

1.2.3.1 Fundamentals

Myopia was identified as early as the period of 384 – 322 B.C. by Aristotle, but even today the reasons for myopia development are not clear. In myopes the system of eye-length and optical refraction does not match so that the focal point of infinite light lies in front of the retina. The eye tends to be too long according to the power of cornea and crystalline lens (see Figure 1.11; Cheng *et al.*, 1992; Scott and Grosvenor, 1993; Carney *et al.*, 1997; Siegwart and Norton, 1999; Touzeau *et al.*, 2003; Gilmartin, 2004; Atchison *et al.*, 2006c; Mutti *et al.*, 2007; Olsen *et al.*, 2007; Chen *et al.*, 2009; Qiao-Grider *et al.*, 2010).

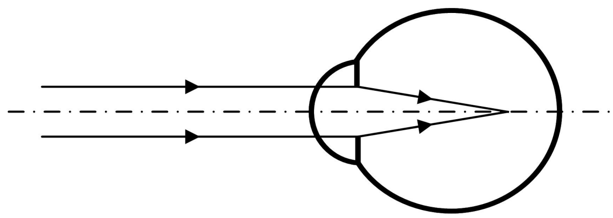

Figure 1.11 – Myopic eye: the focal point lies in front of the retina.

Myopia prevalence has increased dramatically, especially in some Asian regions (Figure 1.1). Ten to 20% of the population of western countries are effected by myopia and 60-80% in eastern countries (Saw, 2003; Lin *et al.*, 2004; Morgan and Rose, 2005; Rose *et al.*, 2008b). It was observed that prevalence rates are higher in urban regions in Asia like Singapore or Hong Kong (Saw, 2003). But there are also exceptions: the prevalence of myopia in Denmark for example is nearly as high as in Asian countries (Fledelius, 1983; Gilmartin, 2004). However, it was reported that the prevalence of myopia in Chinese children living in Canada is comparable to Chinese children living in Asian countries (Cheng *et al.*, 2007).

There is also a change in prevalence rate with age. In Taiwanese schoolchildren the prevalence rate is 12% in six year old children and 84% in 16 to 18 years old teenagers, for example (Lin *et al.*, 1999). High prevalence rates of myopia were also found in Hong Kong for different age groups (Lam and Goh, 1991; Goh and Lam, 1994). More meaningful are the results by Wu and Edwards (1999). They compared the prevalence of myopia in three generations. Therefore they measured the refractive state of Chinese schoolchildren between 7 and 17 years of age and gathered the refractive states of their parents and grandparents by questionnaires. The calculated prevalence and odds ratio for myopia are shown in Table 1.4. The odds ratio is noticeable high in the third generation compared to the first generation.

The disparate distribution in eastern and western countries and the impact of myopia has attracted many researchers to have a closer look at myopia and not at hyperopia, as myopia can be a major disabling refraction associated with

Generation	$\mathbf{1}^{st}$	$\mathbf{2}^{nd}$	$\mathbf{3}^{rd}$
Prevalence of myopia	5.8%	20.8%	26.2%
Odds ratio of getting myopia	0.06	0.26	0.35

Table 1.4 – Prevalence and odds ratio for myopia in three generations of a Chinese population. (Source: Wu and Edwards, 1999)

pathologies. Especially high myopia, which is usually defined as higher than 6.0 D, predisposes the eye to severe pathological conditions like retinal detachment and can lead to blindness (Rosenfield and Gilmartin, 1998, p. 4-5; Tano, 2002; Vongphanit *et al.*, 2002; Wong *et al.*, 2003; Saw *et al.*, 2005b; Saw, 2006; Ripandelli *et al.*, 2008). An appealing question for further research is, whether European and American countries will reach similar myopia prevalence as seen in Asia. Myopia also contributes to quality of life and economical aspects in respect to health costs and spectacles manufacturing (Rose *et al.*, 2000; World Health Organisation, 2000; Weale, 2003).

1.2.3.2 Myopia development

There have been several approaches to categorise the development of myopia based on age of onset. Some factors determining myopia development and progression are age-of-onset, ethnicity, and visual environment (Grosvenor, 1987; Rosenfield and Gilmartin, 1998, p. 3-8; Gilmartin, 2004). Grosvenor (1987) reviewed a couple of possibilities and came to the conclusion that four age-related types are useful, which are congenital myopia, youth-onset myopia, early adult-onset myopia and late adult-onset myopia. The proposal from Grosvenor (1987) is not used very often nowadays, because four groups did not show any benefit. The age-of-onset is only divided in early and late onset of myopia. Thirteen years of age is the cut-off between the two groups (Hirsch, 1964; Zadnik *et al.*, 1999). However, a study by Grosvenor and Scott (1991) in 79 young adults revealed that the onset of myopia does not influence the changes that happen to refractive components of the eye.

For the purpose of research, animal models have been utilised to understand the process of myopisation in humans. Although it is unclear if induced myopia in animals is comparable to physiologic myopia in humans. Various studies in monkeys (Smith *et al.*, 2005), chickens (Troilo *et al.*, 1987; Wildsoet, 1997) and tree shrews (Norton, 1999) identified emmetropisation as an active process, which matches axial length and optical power of the cornea and lens for a clear retinal image.

1.2.3.3 Risk factors for myopia development

Two groups of risk factors have been discussed over the last several years (Goldschmidt, 2003; Young, 2009). First genes seem to have an influence on myopisation and second environmental factors are likely to have an impact. Genetic factors are known to influence myopia development. Several loci on chromosomes for high myopia have been identified (Young *et al.*, 1998b,a; Pacella *et al.*, 1999; Heath *et al.*, 2001; Paluru *et al.*, 2003) and Hammond *et al.* (2001) showed that the genetic effects account for up to 86% of the spherical equivalent (myopia and hyperopia) in their study population, which consists of 506 twin pairs aged from 50 to 79 years. Some other studies support these findings (Sorsby *et al.*, 1966; Lyhne *et al.*, 2001; Chen *et al.*, 2007). However, Angi *et al.* (1993) calculated a heritability of 8% to 14% on monozygote and dizygote twin children aged from 3 to 7 years.

It was observed that the eyes of non-myopic children of myopic parents have got a longer axial length compared to non-myopic children of non-myopic parents (Zadnik *et al.*, 1994). Very simple arguments can question the genetic aspect: is myopia really inherited by genes or is it due to habits of the myopic parents? Myopic parents might tend to hold their child closer to themselves than emmetropic or hyperopic parents might do. Or myopic parents might start earlier to share, for example, books with their child (Mutti *et al.*, 2002).

Strong evidence was found for the genetic influence on the development of high myopia (Guggenheim *et al.*, 2000; Farbrother *et al.*, 2004). However, low myopia and genetics are not so well linked. The influence of the PAX6 gene, which is a major eye development gene, is discussed controversially. On the one side it was shown that PAX6 genes regulate eye growth and influence low myopia development (Hammond *et al.*, 2004). Whilst another study ruled out the influence of PAX6 (Simpson *et al.*, 2007). However, Young (2009) summarised that multiple genes might be involved in myopia development, rather than a single gene.

Genetics alone cannot explain the development of low myopia. In particular the dramatic increase in myopia prevalence in the far east and in urban populations (Saw, 2003; Ip *et al.*, 2008b). Furthermore, identical twins should have identical refractions, which they do not have and usually there is also a difference between the two eyes of an individual (Goldschmidt, 2003). Zadnik *et al.* (1994) found a higher prevalence of myopic children when both parents were myopic (12.2%) compared to just one parent (8.2%) and no myopic parents (2.7%), but reasoned that a combination of genetics and environmental effect influences myopia development.

It has been shown that patients with predisposition for obesity due to a gene variant can be influenced by physical activity (Rampersaud *et al.*, 2008). This example indicates that genetic information can override external information. Therefore, the growth of the eye might be guided by genetic information and also by environmental factors. It is widely accepted that genetic information does not change after birth. Recent research concluded that genes are stable throughout the life, but the methylation of genes is not stable. This implies that methylation as part of a gene might be influenced by environmental factors (see Szyf *et al.*, 2008 for review).

In terms of environmental factors, nearwork has been discussed for years as a trigger for myopia. Weale (2003) thought of increased zonular fibres tension, which is obtained by the prolate eye shape, decreasing the crystalline lens power (Weale, 2003; Gilmartin, 2004). Nearwork is cited again and again as a risk factor of myopia (Rosenfield and Gilmartin, 1998). This is based on the idea, that accommodation causes myopisation. In that case the use of bifocal or progressive lenses should reduce myopisation. Unfortunately this approach was unsuccessful (Zadnik, 1997; Saw *et al.*, 2001; Mutti *et al.*, 2002; Saw *et al.*, 2002a,b,c). Thus the question arises if environmental factors others than close work contribute to myopia development or if a connection between emmetropisation and accommodation as mentioned before exists.

Central and peripheral aberrations have also been discussed as a risk factor for myopisation (see Charman, 2005 for review). Kwan *et al.* (2009) compared central aberrations between myopes and non-myopes. They also compared central aberrations between more myopic and less myopic eyes in anisometric subjects and could only find a correlation between particular aberrations (spherical aberration) and refractive error. On the basis of the theory that peripheral vision might have an influence on myopia development and progression (Hoogerheide *et al.*, 1971; Smith *et al.*, 2005), Mathur *et al.* (2009b) extended the experiment to analyse the peripheral aberrations in myopes and emmetropes. They found a modest difference in particular aberrations (coma and spherical aberration). However, they pointed out that differences in aberrations between the two groups are small compared to differences in refractive error and astigmatism.

1.2.3.4 Approaches to influence myopia development

Various approaches have been used to reduce the progression of myopia. Examples are: orthokeratology, use of progressive addition lenses, special design of spectacle or contact lenses, pharmaceutical agents. A short overview is provided below (for review, see Saw *et al.*, 2002c or Morgan, 2003).

The role of the correction method itself has been discussed as a possibility of influencing myopia progression for a long time. Attention was especially drawn to contact lenses. So far, soft contact lenses seem to have no relevant impact on myopisation (Horner *et al.*, 1999; Walline *et al.*, 2008; Marsh-Tootle *et al.*, 2009). RGP lens studies showed that myopia progression can be reduced (Stone, 1976; Perrigin *et al.*, 1990), increased (Baldwin *et al.*, 1969) or be without effect (Katz *et al.*, 2003) with this mode of correction. Shen *et al.* (2010) reasoned that soft contact lenses fail to have an effect on myopia progression due to the performance of the peripheral optics. RGP orthokeratology lenses seem to be capable of reducing myopia progression, as it was shown that growth rate of the vitreous chamber depth reduced significantly. Based on the annual growth rate of the vitreous chamber, Cho *et al.* (2005) and Walline *et al.* (2009) showed a reduction in myopisation using orthokeratology lenses. Cho *et al.* (2005) compared orthokeratology wearers with wearers of glasses after two years. In the orthokeratology group the vitreous chamber elongated 0.16 mm and in the spectacle group vitreous chamber depth increased by 0.34 mm. Similar results were found by Walline *et al.* (2009), who compared soft contact lens users with orthokeratology users. Vitreous chamber depth increased by 0.35 mm and 0.15 mm over two years, respectively.

The theory that extended periods of accommodation might cause myopisation led to the idea of using bifocal or progressive addition lenses to prevent myopia progression. Some studies were able to show a reduced progression with bifocals or multifocals (Leung and Brown, 1999; Fulk *et al.*, 2000; Gwiazda *et al.*, 2003; Hasebe *et al.*, 2008; Cheng *et al.*, 2010). Other studies could not show this effect (Parssinen *et al.*, 1989; Edwards *et al.*, 2002). The positive effect of bifocal or multifocal lenses were associated with children with near esophoria in some studies (Goss, 1986; Brown *et al.*, 2002). It has been suggested to use base-in prisms in combination with bifocal or multifocal lenses to reduce myopia progression (Cheng *et al.*, 2010).

Sankaridurg *et al.* (2010) showed in a subgroup of their study-population that a significantly reduced myopia progression was achieved with spectacle lenses that were designed to reduce peripheral hyperopia.

A daily instillation of pharmaceutical agents like atropine, for example, has been advocated to control the development of myopia in children. The theory is based on the assumption that myopisation is caused by over-accommodation. Atropine paralyses the ciliary body and reduces accommodation. Therefore clear near vision is only possible with reading glasses. Due to constant mydriasis, light sensitivity increases and side effects of the pharmaceutical agents occur. Studies showed that the regular instillation of pharmaceuticals delays myopia progression. During the instillation period myopia progresses slower than in the control group. However, after the treatment myopia progresses more quickly (Grosvenor, 1996; Rosenfield and Gilmartin, 1998; Tong *et al.*, 2009).

Recent studies showed that myopia progression rates change within a year. For example Deng *et al.* (2010) found that myopes and non-myopes spend more time outdoor during the summer break. They concluded that this could be a reason for reduced myopia progression during the summer break. This was supported by Donovan *et al.* (2011) as they showed in a group of 98 myopes that progression is higher during the winter period than in the summer period. Mean progression in summer was -0.25 $\pm$ 0.24 D and -0.57 $\pm$ 0.33 D in winter. Additionally, Deng and Gwiazda (2011) found a small but statistical significant differences in refractive error depending on the season of birth: children born in summer were less hyperopic (0.43 $\pm$ 1.60 D) than children born during the winter period (0.87 $\pm$ 1.43 D).

1.2.3.5 Night myopia

Even though night myopia is not associated with an increased axial length or increased power of the crystalline lens, it is worth mentioning here to understand the whole context of myopia, as night myopia seems to be linked to accommodation as it might be caused by involuntary accommodation (Koomen *et al.*, 1951).

Night myopia seems to appear during vision in scotopic or mesopic conditions. The theory of night myopia is the absence of an accommodation stimulus in low illumination leads to an accommodative response of about 1.0 D. It appears to be that light levels between 10^{-6} and 3 cd/m^2 lead to myopic shifts (Charman, 1996).

The existence of the phenomenon of night myopia is controversial. In a review, Charman (1996) summarised the existence of night myopia and estimated the magnitude of night myopia to about 1.00 D. Otero and Duran (1941) measured night myopia and concluded the magnitude of night myopia is between 1.50 D and 2.00 D. In a similar experiment, Wald and Griffin (1947) estimated the magnitude of night myopia to be 0.60 D. In an article three years later Koomen *et al.* (1951) showed night myopia to be around 1.50 D. In a recent study Artal (2010) could not find any myopic shifts during mesopic vision.

Using an adaptive optic system Artal *et al.* (2011) tried to find reasons for night myopia under scotopic conditions. They ruled out that night myopia is driven by chromatic aberrations or spherical aberrations. But they could find evidence that involuntary accommodation causes night myopia, which contradicts some early findings (Koomen *et al.*, 1951; Tousey *et al.*, 1953).

1.3 Eye shapes

Three kinds of eye shape are usually discussed in the literature: prolate, spherical and oblate (Figure 1.12). Mean difference between anterior-posterior and transverse diameter were shown in a study by Wang *et al.* (1994) cited by Weale (2003). For myopic eyes they found a mean difference of +1.56 mm, for emmetropic eyes -0.29 mm and for hyperopic eyes -0.98 mm. From these numbers it can be concluded that myopes have prolate, emmetropes more or less spheric and hyperopes oblate eyes (Logan *et al.*, 2004; Stone and Flitcroft, 2004; Charman, 2005; Atchison *et al.*, 2006c). Atchison *et al.* (2006c) gave the approximate proportion of enlargement of a myopic eye as 1:2:3 which is horizontally, vertically and axially, respectively. These findings are in contrast to Cheng *et al.* (1992), who used MRI to analyse the eye shape. They found that myopic eyes are horizontally longer than axial. In myopic eyes, the axial length increases at a rate of about 0.36 mm per dioptre (mean of different studies) (Carroll, 1981; Atchison *et al.*, 2004; Chau *et al.*, 2004; Singh *et al.*, 2006). A recent study from Berntsen *et al.* (2008) using the COAS aberrometer showed that the temporal retina is prolate and the nasal retina is spherical in myopic eyes. The mean difference between 30 degrees nasal and 30 degrees temporal retina was +0.45 D. Berntsen *et al.* (2008) reasoned that the asymmetry is caused by the difference in cylinder (J_{180}). An asymmetry between nasal and temporal retina was also found in other studies (Seidemann *et al.*, 2002; Atchison, 2003; Atchison *et al.*, 2003, 2005b), but not as high as the results from Berntsen *et al.* (2008). All studies have in common that changes in the nasal retina were greater than in the temporal retina. In a different study, Atchison *et al.* (2006b) analysed peripheral refractions along the horizontal and the vertical meridian. In the horizontal field they found similar results to those above. For the vertical visual field they found that contrary to other studies (Seidemann *et al.*, 2002; Schmid, 2003) the peripheral refractive error is independent of the axial refractive state. In particular for vertical peripheral refraction Seidemann *et al.* (2002) found that the lower visual field is more myopic than the upper visual field and reasoned an analogy with lower field myopia which was found in chicks (Schaeffel *et al.*, 1994; Seidemann *et al.*, 2002). Lower field myopia in animals was interpreted by Hodos and Erichsen (1990) as an ability for better sight at the ground. The theory of lower field myopia in humans has not been verified in detail in further studies.

Walker and Mutti (2002) found a change in eye shape with accommodation. During accommodation eyes tend to become more prolate. Other studies showed a change in axial length with accommodation (Drexler *et al.*, 1998b; Mallen *et al.*, 2006; Read *et al.*, 2010).

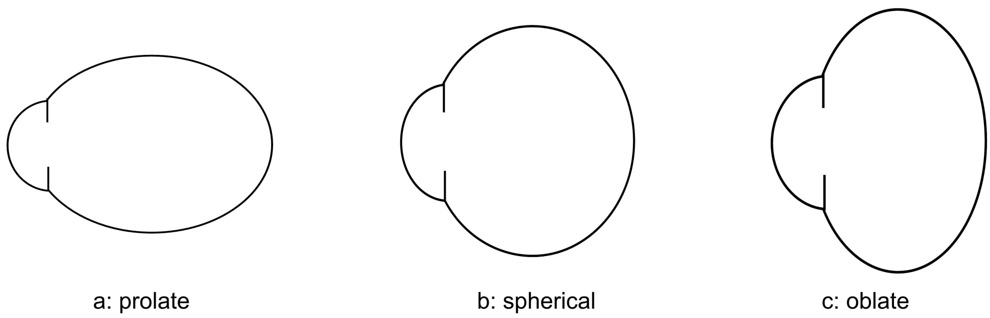

Figure 1.12 – Prolate eye shape, which is mainly seen in myopic eyes, spherical shape seen in emmetropic eyes and oblate shape seen in hyperopic eyes.

1.4 Model eyes

Model eyes or schematic eyes are useful, for instance, to gain better understanding of optical effects of the eye, of processes as emmetropisation or of the impact of vision correction as contact lenses or glasses. Many model eyes have been introduced during the last hundred of years (for reviews, see Smith, 1995 and Atchison and Smith, 2000a p. 250-258). By predicting the overall aberrations of an eye as well as the aberrations of particular components of the eye, model eyes are very helpful to improve for example refractive surgery or the design of intraocular lenses (Charman, 2010). The first model eye was possibly introduced by Christian Huygens. This model eye was represented by two hemispheres, where the first hemisphere represents the cornea and the second hemisphere the retina. The hemispheres were filled with water and in-between a diaphragm was placed. The radius of the retinal hemisphere had a radius three times of the corneal radius hemisphere. A few further model eyes were introduced, but the schematic eye introduced by Gullstrand lead to recognition until today as it is based on comprehensive analysis of biometric ocular data. Later this eye was modified by Emsley (Smith, 1995).

Model eyes are divided into two groups: paraxial and non-paraxial. Whereas paraxial models have only the ability to predict on-axis aberrations, non-paraxial models are also able to deal with off-axis aberrations. Recent schematic eyes also take account of changes with age (Smith, 1995; Smith and Atchison, 2001; Norrby, 2005; Atchison, 2006b; Bakaraju *et al.*, 2008b). There are only a few model eyes which have an aspheric crystalline lens surface and a gradient index lens (Liou and Brennan, 1997; Atchison, 2006b), which allow to make realistic conclusions about the human eye.

For most model eyes it is essential to keep in mind that model eyes are still restricted to a rotational symmetry around the optical axis, whereas the elements of a human eye are not centred to an axis. Atchison (2006b) addressed the fact of misalignment in the model eye presented below.

In 1997 Liou and Brennan (1997) developed the first model eye to give additional data on chromatic aberrations. As far as possible they based their model eye on empirical biometric data and modelled values which were not empirically available. The equivalent power of the Liou-Brennan model eye is 60.35 D, which is close to the commonly accepted value of 60.00 D. The axial length of the model eye is 23.95 mm. In comparison to 24.0 mm for males and slightly less than 24.0 mm for females the schematic eye is in good concordance with empirical data.

Smith and Atchison (2001) based their model eye on the Gullstrand Exact Schematic Eye. The property of the lens in the Gullstrand Exact Eye was changed to obtain a model eye with aspheric surfaces and a gradient lens index similar to that of Liou and Brennan (1997). The crystalline lens surfaces were therefore made aspheric and the model lens that composed of four surfaces was reduced to two surfaces with a gradient refractive index between them.

The Dubbelman schematic eye discussed by Norrby (2005), for example, takes into account that the crystalline lens becomes thicker and more curved in its unaccommodated state with increasing age. That means that age and the amount of accommodation influences the calculations for the parameters of the schematic eye. This eye is chiefly based on data collected by Dubbelman *et al.*, during research on Scheimpflug images (Dubbelman and Van der Heijde, 2001; Dubbelman *et al.*, 2005, 2006). These data resulted in a virtually aberration-free model for a variety of pupil sizes. Like the Liou and Brennan (1997) as well as the Smith and Atchison (2001) model eyes the Dubbelman model also failed to take into account the fact that there is a crystalline lens tilt of 0.2 degrees temporally and a decentration of 0.1 mm nasally and a discrepancy of the fovea, which is 5.7 degrees off axis (Kirschkamp *et al.*, 2004). The Dubbelman eye exhibits negative spherical aberrations, whereas wavefront measurements of 532 eyes showed positive spherical aberration (Wang and Koch, 2003). Wang and Koch (2003) found that human eyes become hyperopic with age, namely 4.0 D between 20 and 70 years. The Dubbelman eye exhibits an increase of 1.9 D in the same period of time.

Atchison (2006b) introduced two new schematic eyes. These model eyes were specially constructed to represent myopic eyes and concentrate on changes due to the refractive state. Atchison (2006b) proposed a model eye based on the results of biometric research by various authors (Liou and Brennan, 1997; Dubbelman and Van der Heijde, 2001; Atchison *et al.*, 2004, 2005a; Atchison and Smith, 2005; Dubbelman *et al.*, 2005; Jones *et al.*, 2005; Dubbelman *et al.*, 2006). Furthermore these models allow to change the refractive index distribution of the crystalline lens. Atchison added formulae to calculate the vertex radius of curvature of the anterior cornea by taking into account the spherical refraction. The first model features centred surfaces and the second model contains a tilt of the lens as well as a tilt and decentration of the retina, which were proposed by Norrby (2005). With these models Atchison (2006b) implemented new ways of performing peripheral refractions on schematic eyes. The centred version is very useful for predicting the impact of different shaped lenses or contact lenses on the peripheral defocus. The second model shows comparable values for peripheral refraction in the horizontal meridian. For the vertical meridian the empirical data shows more symmetry than the results from the model.

Bakaraju *et al.* (2008b) compared different schematic eyes simulating emmetropic eyes (the following eyes were compared: Lotmar, 1971; Kooijman, 1983; Liou and Brennan, 1997; Escudero-Sanz and Navarro, 1999; Atchison, 2006b) among each other and with in-vivo data. For small pupil diameters all eyes compared showed good performance in comparison to real eyes. The

Liou and Brennan (1997) and Atchison (2006b) models showed good results, especially for large pupils. Bakaraju *et al.* (2008b) reasoned that the Liou and Brennan (1997) and Atchison (2006b) schematic eyes benefit from the fact that they took the asphericity of different surfaces into account. Hence, these schematic eyes performed very realistically in matters of spherical aberration and coma.

Bakaraju *et al.* (2008b) also compared the above mentioned model eyes for peripheral refraction. The models of Lotmar, Kooijmann and Escuderro-Sanz and Navarro showed hyperopic shifts in the horizontal periphery whereas the Liou-Brennan and Atchison models showed myopic shifts in the horizontal periphery, which accords with other studies (Gustafsson *et al.*, 2001; Seidemann *et al.*, 2002; Atchison *et al.*, 2006b). All model eyes compared in this study appear to overestimate the peripheral image quality.

1.5 Aberrations and aberrometry

1.5.1 Fundamentals

Aberrations are usually measured using a Hartman-Shack aberrometer (Liang *et al.*, 1994) and are described as wavefront aberrations and in terms of Zernike polynomials (Thibos *et al.*, 2002a). The advantage of wavefront aberrations is that the whole area of the pupil is analysed.

Zernike polynomials consist of the Zernike expansion mode Z_n^m and the Zernike expansion coefficient c_n^m. The type of aberration is described by the expansion mode and the amount of aberrations is indicated by the Zernike coefficient, which describes the difference between an ideal and the measured wavefront in micrometers. To get an overview of the impact of more than one coefficient, they can be summed up as the root-mean-square (RMS) (see Formula 1.4, Thibos *et al.*, 2002a). RMS is an estimation of the total aberrations of the eye. For 3 mm pupils an average RMS is around 0.04 to 0.1 μm. For 6 mm pupils RMS lies between 0.2 and 0.5 μm (Howland and Howland, 1977; Walsh *et al.*, 1984; Navarro *et al.*, 1998; Porter *et al.*, 2001; Atchison and Scott, 2002; Thibos *et al.*, 2002b).

$$RMS = \sqrt{\sum_{n,m} (c_n^m)^2} \tag{1.4}$$

The wavefront aberrations are divided into lower and higher order aberrations. Lower order aberrations (LOA) are the well known values of sphere / defocus (Z_2^0) and cylinder / astigmatism (Z_2^{-2} and Z_2^2). Higher order aberrations contain aberrations such as spherical aberration and coma, for example (Charman, 2005). Piston (Z_0^0) and Tilt (Z_1^{-1} and Z_1^1) belong to the lower order aberrations, but usually are not referred to, as Piston does not affect monochromatic image quality and Tilt affects only the image position and not the image quality. Lower order aberrations blur the retinal image more than higher order aberrations. Figure 1.13 shows an overview of the Zernike aberrations up to the fourth order.

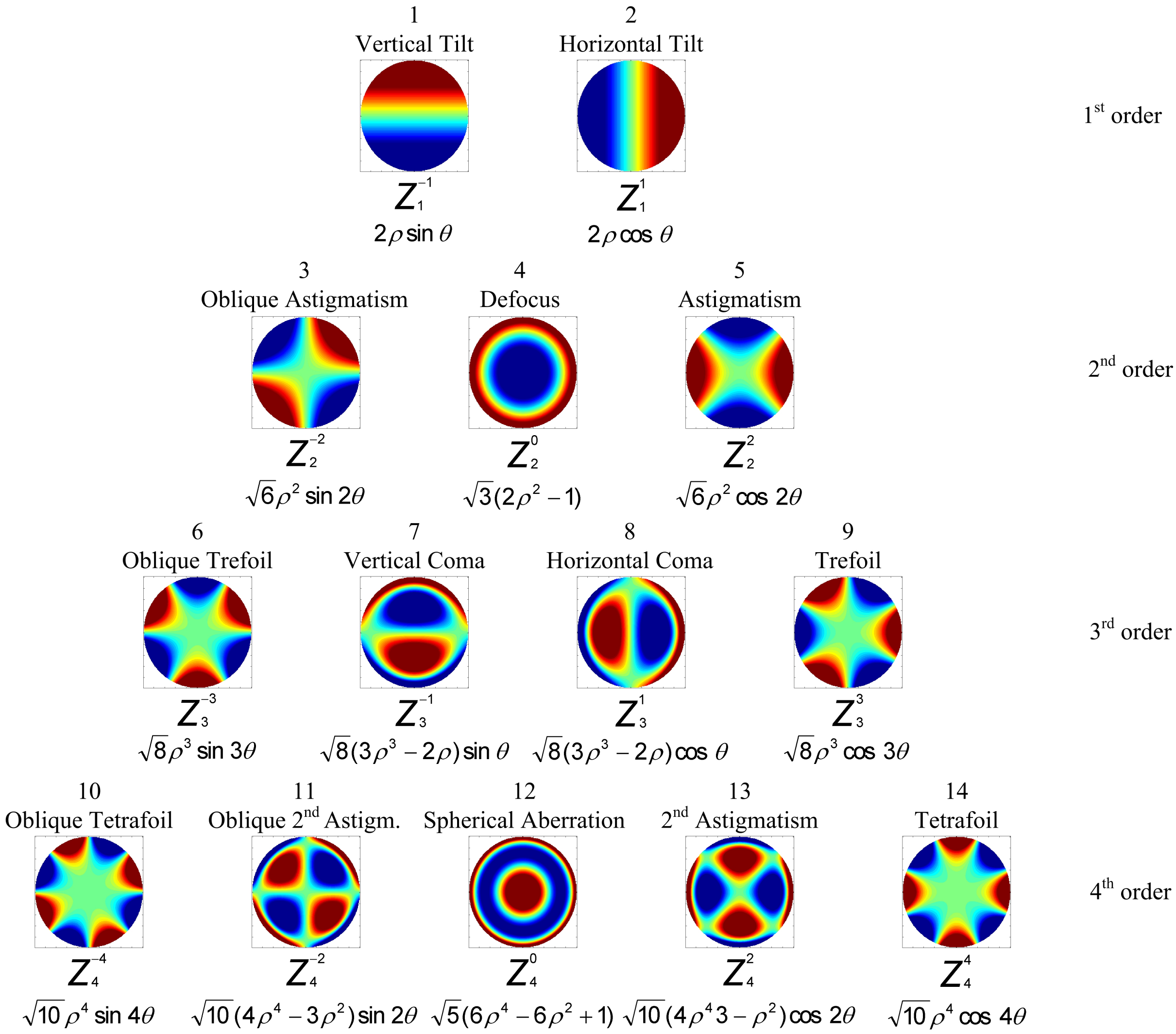

Figure 1.13 – Zernike aberrations up to the fourth order.

Lower and higher order aberrations are grouped as monochromatic aberrations. In addition to monochromatic aberrations, chromatic aberrations also affect vision, but cannot be described by Zernike expansions. Monochromatic aberrations are dependent on a specific wavelength of the spectrum of visible light. This means that with change of wavelength the impact of monochromatic aberration also changes. Aberrometry techniques measure the monochromatic aberrations only. Therefore it is important to recognise that chromatic aberrations contribute substantially to the image quality on the retina in contrast to monochromatic aberrations, when interpreting the results of aberrometry (Kruger *et al.*, 1995; Marcos, 2003).

It is very well known that the human eye is far from being a perfect optical system. Lower order aberrations such as defocus and astigmatism influence retinal image quality more than higher order aberrations. Lower order aberrations are easy to correct with spectacles or contact lenses. In general, aberrations increase with the size of the pupil (see Figure 1.4), with the impact of higher order aberrations on vision being more significant with large pupils (Meyer-Arendt, 1972; Charman, 1991; Marcos, 2003; Applegate *et al.*, 2007). Therefore, Liang and Williams (1997) suggested to correct aberrations up to the third order for small pupils (3.4 mm) and up to the eighth order for large pupils (7.3 mm). They compared levels of correction with an aberration free eye, where image quality is only restricted by diffraction. The results showed that correcting higher order aberrations higher than the eighth order could not improve the image quality significantly.

As mentioned before, Zernike coefficients are highly dependent on pupil size. In general the coefficients increase with increasing pupil size. Figure 1.14 shows a comparison of two pupil diameters (3.4 mm and 7.3 mm, respectively). This graph shows that aberrations increase with increasing pupil diameter. The increase of aberrations with increasing pupil size is caused by the violation of the Gaussian approximation due to rays that are further away from the optical axis.

For measuring aberrations it is necessary to note that the tear film and accommodation have an effect on the results of the measurement. Montés-Micó *et al.* (2004) showed by analysing corneal topography that the tear film is stable for only six seconds after a blink. It is important to acknowledge this finding, when performing aberrometry. Also, wavefront aberrations are influenced by the age of the subjects (Applegate *et al.*, 2007; Charman, 2005).

1.5.2 Myopia and higher order aberrations

Several authors tried to find correlations between ametropia and the amount of higher order aberrations. There has, until now, been reports showing that

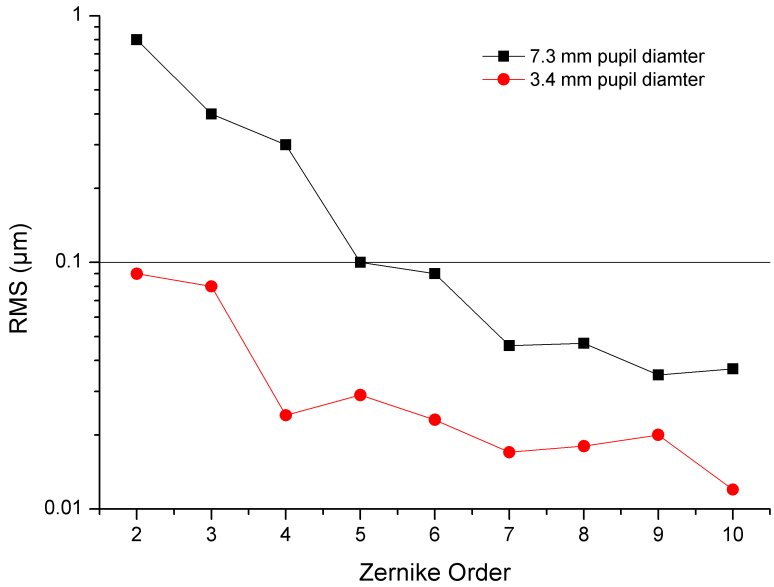

Figure 1.14 – Effect of pupil size on higher order aberrations. Greater pupils have a higher impact on the retinal image quality than small pupils do due to increased magnitude of higher order aberrations (partly redrawn from Liang and Williams, 1997).

myopes have larger higher order aberrations than emmetropes (see Charman, 2005 for review; Mathur *et al.*, 2009b).

The role of higher order aberrations on emmetropisation or myopisation remains unclear. Various studies imply different theories. Some studies negate an association between refractive error development and higher order aberrations (Porter *et al.*, 2001; Carkeet *et al.*, 2002), whereas other studies find a link between myopia and higher order aberrations (Collins *et al.*, 1995; He *et al.*, 2002; Paquin *et al.*, 2002; Llorente *et al.*, 2004). Other studies imply that blur caused by aberrations is not causal for refractive error development (Carkeet *et al.*, 2002; Charman, 2005).

1.5.3 Accommodation and higher order aberrations

Cheng *et al.* (2004) analysed the changes of aberrations arising with accommodation. A large variability between subjects was found for third and fourth order Zernike aberrations. Fifth and sixth order aberrations had the mean close to zero. The largest change with accommodation was observed in spherical aberration and Cheng *et al.* (2004) found it to be linear to the amplitude of accommodation.

He *et al.* (2005) also analysed aberration and accommodation in myopes and emmetropes. By comparing lens-induced and distance-induced accommodative responses they found that emmetropes are more sensitive to defocus in comparison to myopes, as accommodative lags in myopes were larger for lens-induced stimuli. Therefore myopic eyes have less ability to control the accommodation process, especially when higher amounts of aberration are present.

Plainis *et al.* (2005) and López-Gil *et al.* (2008) analysed especially spherical aberration during accommodation and found that spherical aberration usually moves towards more minus with accommodation.

1.6 Peripheral vision, peripheral refraction and peripheral aberrometry

1.6.1 Introduction

Due to the spread of cone receptors over the retina (see Figure 1.3) and a decrease in ganglion cell density, peripheral vision is poorer than central vision (Curcio *et al.*, 1990; Jonas *et al.*, 1992). In addition to the sampling density of retinal photoreceptors, the optical system in the periphery is reduced compared to the quality of the central optical system. However, peripheral aberrations are usually influenced by central aberrations (Rempt *et al.*, 1971; Navarro *et al.*, 1998; Grosvenor, 2002). Peripheral aberrations are dominated by coma (Guirao and Artal, 1999; Atchison and Scott, 2002).

Peripheral vision is important for various tasks. For example, it is important for detection in general (Atchison, 1987; Wang *et al.*, 1996), perception of peripheral motions (Johnson and Leibowitz, 1974), postural balance and mobility (Black and Wood, 2005) as well as driving (Wood *et al.*, 2009). It is possible to improve peripheral visual acuity considerably (Williams *et al.*, 1996; Wang *et al.*, 1997; Atchison, 2003; Gustafsson and Unsbo, 2003; Atchison *et al.*, 2006c; Lundström *et al.*, 2007). Although few studies suggest that an improvement of peripheral vision applies for contrast detection only (Thibos *et al.*, 1987; Wang *et al.*, 1996).

Peripheral refractive errors vary from the on-axis refractive error and change with eccentricity. The astigmatic refractive error increases with eccentricity especially in the horizontal meridian (Rempt *et al.*, 1971; Anderson *et al.*, 2001; Charman, 2005). Peripheral refraction along the horizontal meridian in emmetropic eyes becomes relatively myopic with increasing eccentricity in the periphery. This myopic shift decreases with myopia and becomes a hyperopic shift with -2.0 to -4.0 D of myopia. In the vertical meridian, myopes show a relative myopic shift (Atchison *et al.*, 2006c). A few studies showed an asymmetry for nasal and temporal peripheral refractions (Ferree *et al.*, 1932; Rempt *et al.*, 1971; Millodot, 1981; Atchison *et al.*, 2003). It seems to be that the angle α between optical axis and visual axis is the reason for this asymmetry (Lotmar and Lotmar, 1974)

With improving accuracy of central measurements of aberrations the interest in measuring peripheral aberrations has increased. Various studies have highlighted the problems occurring with peripheral aberrometry (Atchison *et al.*, 2007; Lundström and Unsbo, 2007; Lundström *et al.*, 2009a, see also chapter 3). Baskaran *et al.* (2010) showed that peripheral aberrometry is repeatable in emmetropes up to the third order of Zernike aberrations. Also spherical aberration was repeatable. These results were comparable to on-axis measurements.

Interest in peripheral refraction has increased, because it has been shown by animal studies that peripheral vision can have an influence on the axial eye growth (Troilo *et al.*, 1987; Smith *et al.*, 2005). Relatively new results of a study in Chinese children that used spectacle lenses that aim to reduce peripheral hyperopia indicated that this type of correction might reduce myopia progression (Sankaridurg *et al.*, 2010).

Peripheral refraction can be performed by different instruments. Lundström *et al.* (2005) compared subjective refraction, photorefraction with a Power Refractor, retinoscopy and wavefront aberrations with a Hartmann-Shack sensor for measurements along the horizontal meridian. Their results showed that the Hartmann-Shack sensor gave the most reliable results. Atchison (2003) came to similar conclusions. He compared the Hartmann-Shack technique with two open field autorefractors, namely Canon Autoref R1 and Shin-Nippon SRW-5000. The agreement between Hartmann-Shack sensor and Shin-Nippon SRW-5000 was better than between Hartmann-Shack sensor and Canon Autoref R1. Hartwig (2007) performed a comparison between retinoscopy, COAS aberrometer and Shin-Nippon NVision-K 5001. The COAS aberrometer uses the Hartmann-Shack principles and the Shin-Nippon NVision-K 5001 is the successor of the Shin-Nippon

SRW-5000 autorefractor. The study showed that the Shin-Nippon NVison-K 5001 gives the highest repeatability in this comparison. But it is important to keep in mind that results obtained by aberrometry can be influenced by several factors including the tear film (Applegate *et al.*, 2001). When performing measurements, these facts have to be taken into account while comparing the results.

In recent years peripheral refractions have been used to determine the eye shape according to the relative refraction in comparison to the fovea. Dunne (1995) did a validation study and questioned, if it is possible to derive ocular shape from peripheral refraction. A comparison of A-scan ultrasonography and peripheral refraction showed that both techniques correlate for measurements of field angles up to 40 degrees. It is accepted that peripheral refraction is a inexpensive way to determine ocular shape in comparison to A-scan ultrasonography and MRI (Berntsen *et al.*, 2008).

Several factors can affect peripheral refraction measurements. While performing peripheral refraction the question arises, if it makes a difference if the subject fixates the peripheral fixation target by head turn or by eye turn because there are different influences from the lids and the extraocular muscles (Seidemann *et al.*, 2002; Radhakrishnan and Charman, 2008). Seidemann *et al.* (2002) compared the two types of measurements of peripheral refraction. Using a double pass technique they measured a small group of three subjects comparing head turn and eye turn at 40 degrees. The mean results were 0.70 ± 0.36 D more myopia when measuring eye turn. Radhakrishnan and Charman (2008) compared peripheral refractions performed with head turn and eye turn using the Shin-Nippon SRW-5000 open field autorefractor on ten subjects. The measurements were taken consecutively in random order, head turn or eye turn, up to 30 degrees. The results separated for M, J_{180} and J_{45} showed no evidence that the type of measurement has an influence on the results.

To rule out that longer periods of oblique viewing change peripheral refraction results, Radhakrishnan and Charman (2008) performed measurements. Five subjects looked alternatively at a nasal or temporal fixation target 25 degrees away, respectively, from the central fixation target. While carrying out eye turns, the subjects fixated the target for 2.5 minutes before measurements were taken. Again, no differences were found. Due to this study and in contrast to some first observations it can be accepted that for measurements performed up to an eccentricity of 30 degrees and a fixation time of less than 2.5 minutes, it makes no difference if the subject turns the head or the eye (Radhakrishnan and Charman, 2008). These results are similar to a sub-study by Atchison *et al.* (2005b), in which they found only a difference of 0.17 D between the measurements, fixating a target at 35 degrees nasal and temporal eccentricity, respectively.

Atchison *et al.* (2005b) investigated the effect of age on peripheral refraction. They recruited two groups of subjects, one young group and one old group with a mean age of 24 and 59 years, respectively. They found a similar distribution of the refractive components M, J_{180} and J_{45} along the horizontal visual field in both groups. Furthermore they found a similar asymmetry between the nasal and temporal visual field in the young and old group and observed that the peripheral hyperopic defocus (M) increases with increasing myopia and that the peripheral astigmatism J_{180} decreases with increasing myopia. To access any trend of the peripheral refraction, Atchison *et al.* (2005b) compared their results with results on children (mean age: 10 years). This comparison lead to the suggestion that peripheral refraction in hyperopic children does not change with age.

As accommodation might change peripheral refractions Calver *et al.* (2007) compared peripheral refractions for distance and near vision and concluded that myopia development is not affected by peripheral influences during near vision. They measured peripheral refractions for distance vision with the subject's correction and without correction. For measuring peripheral refraction at near they used trial lenses to correct the subjects, not the subject's spectacles. It would be interesting to do these measurements again with subjects wearing their own correction for distance and near vision, because the correction could have an impact on the peripheral refraction due to peripheral errors induced by the surface curvature of the spectacle lenses, which are different in comparison to trial lenses.

For peripheral aberrometry it needs to be considered that Zernike aberrations are based on a unit circle. Due to oblique viewing for peripheral aberrometry this assumption is not met. When peripheral aberrometry is performed the pupil is not round but elliptical (Figure 1.15 and Figure 1.16 as well as appendix A).

Most studies on peripheral vision examine the horizontal meridian (Hoogerheide *et al.*, 1971; Dunne, 1995; Atchison and Scott, 2002; Seidemann *et al.*, 2002; Atchison, 2003, 2006a; Calver *et al.*, 2007; Radhakrishnan and Charman, 2008), even the distribution of rods and cones is mainly analysed

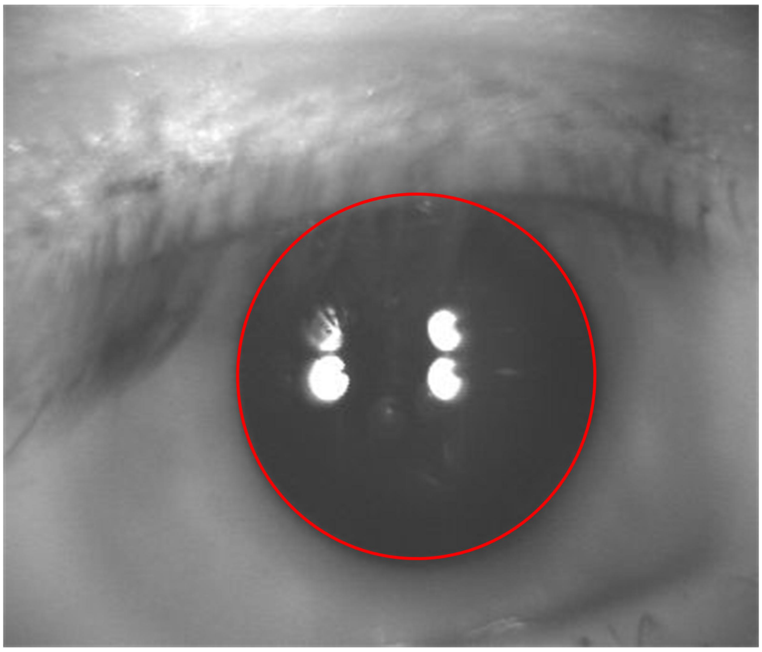

Figure 1.15 – Pupil for central aberrometry: the pupil size (red circle) is 5.0 mm wide and 5.1 mm high.

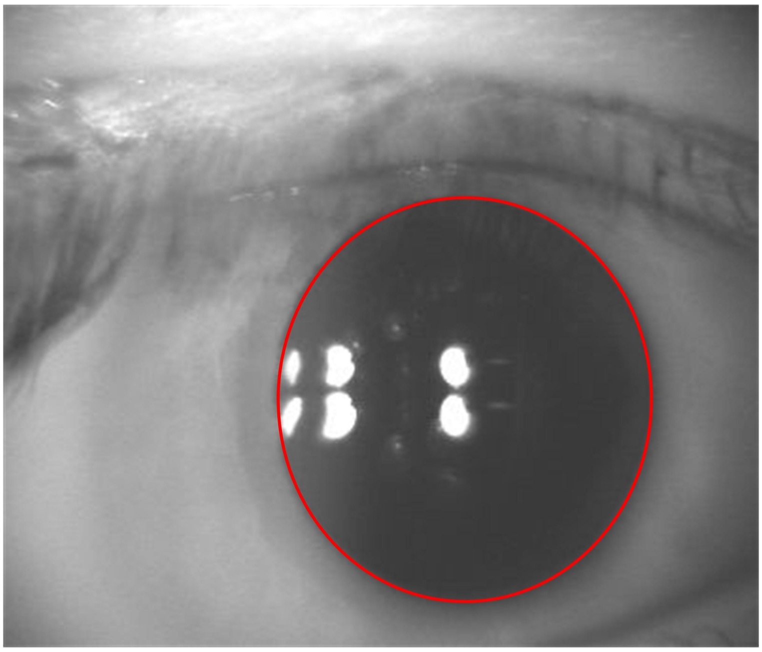

Figure 1.16 – Pupil for 20 degree eccentricity: the pupil size (red circle) is 5.25 mm wide and 5.65 mm high

for the horizontal meridian (Freeman and Hull, 2003 p. 517; Diepes, 2004 p. 61-62). Only a few studies have concentrated on the vertical meridian for refraction (Mutti *et al.*, 2000; Atchison *et al.*, 2006b) and photoreceptor distribution (Curcio *et al.*, 1990). For some aspects, as shown by the following example, it would be useful to examine the vertical meridian in detail. For example Zylbermann *et al.* (1993) found a high prevalence of myopia in Orthodox Jewish boy schools. The student's daily tasks at school is characterized by reading small printed texts, while rocking back and forth with the upper part of the body. This means that the eyes additionally need to move vertically to keep the fixation. Usually, while reading with a more or less stable upper part of the body, the eyes only move horizontally along the text. This leads to the next consideration: high myopia prevalence is also observed in countries, where a Chinese language is an official language, like China including Hong Kong, Taiwan and Singapore (Lin *et al.*, 1999; Saw, 2003; Lin *et al.*, 2004; Morgan and Rose, 2005; Rose *et al.*, 2008b; Wu *et al.*, 2010; see also Figure 1.1). In the past Chinese characters were only written vertically. Nowadays this attribute has changed and Chinese characters are widely written horizontally, but occasionally vertical, in newspapers for example.

It was observed that different brain areas are used in dependency, if Chinese or alphabetic characters are read (Liu and Perfetti, 2003). Another study showed that children that have problems reading texts which are written in English characters improve their skills when reading texts which are displayed by simple Chinese characters (Rozin *et al.*, 1971). The idea that alphabet characters are processed by the left hemisphere and Chinese characters by the right hemisphere is still argued (Tan *et al.*, 2000; Chen *et al.*, 2002). Nevertheless, there seems to be differences between the perception and processing of Chinese and alphabetic characters. These differences could influence the emmetropisation process. It is possible that the change between vertical and horizontal reading might influence emmetropisation.

Logan *et al.* (2005) found no difference between white and British Asian students in the prevalence of ametropia, when they were exposed to the same educational system in the U.K. However, this study accessed British Asians in general and not British Chinese students. Nevertheless, most Asian countries use different characters than alphabetic characters. If British Asian students study in the U.K., it can be implied that they predominantly use alphabetic characters. On the opposite side Kleinstein *et al.* (2003) found in a multicenter study in the USA that the prevalence of myopia changes among the ethnic groups. They found the prevalence of myopia as shown in Table 1.5. Even though all measurements took place in the USA, a significant difference was shown in children aged from 5 to 17 years.

Simensen and Thorud (1994) found a higher prevalence of myopia in textile workers who are responsible for quality control of textiles. It is not exactly

African American	Asian	Hispanic	White
6.6%	18.8%	13.2%	4.4%

Table 1.5 – Prevalence of myopia in different ethnic groups (Source: Kleinstein *et al.*, 2003)

described in their methods, but textile workers who control the textile usually sit in front of a panel of textile. While the textile is braid, it moves from the textile worker away and therefore the eyes follow a vertical movement again (see Goldschmidt, 2003 for illustration). Adams and McBrien (1992) found a high myopia prevalence in clinical microscopists. The way the microscopists usually used the microscope was not mentioned. In this context it also needs to be mentioned that the existence of lower field (upper retina) myopia in humans has been discussed for several years. Lower field myopia was first observed in animals and explained with the necessity to see the ground clearly to find forage and be aware of predators as well as alarm signals simultaneously (Fitzke *et al.*, 1985; Hodos and Erichsen, 1990; Schaeffel *et al.*, 1994; Henze *et al.*, 2004). Seidemann *et al.* (2002) first described lower field myopia in humans, as their results showed a significant trend of increasing myopia in the upper retina. The pooled change was -0.0169 $\pm$ 0.0085 D per angular degree and therefore roughly -0.17 D per 10 degree. A comparison to animal data is not possible, because the data from the animal studies is not given as refractive error in correspondence to the eccentricity (Fitzke *et al.*, 1985; Hodos and Erichsen, 1990). In addition, Henze *et al.* (2004) measured an increasing astigmatism in the lower visual field from the optical axis to the periphery in turtles but not in the upper visual field.

1.7 Posture

1.7.1 Posture and vision

Even though Zadnik *et al.* (1994) found a high dependency of genetics on myopisation, they concluded that a combination of genetic and environmental factors is responsible for myopia development. One environmental factor could be posture. Evidence comes from few studies (Adams and McBrien, 1992; Zylbermann *et al.*, 1993; Simensen and Thorud, 1994; McBrien and Adams, 1997) that describe high myopia levels in certain occupational groups with prolonged visual tasks indicating that certain postures due to these occupations might be linked with myopisation.

Zylbermann *et al.* (1993) compared refractive errors in boys and girls attending Orthodox and non-Orthodox Jewish schools. The characteristic of Orthodox schools is that boys sway, bending back and forward, for several hours while reading small printed texts. A significant increase in myopia development was found in the boys attending the Orthodox schools compared to a nominally genetically similar control group of boys attending non-Orthodox schools, or Jewish girls at either type of school. Adams and McBrien (1992) and McBrien and Adams (1997) analysed the refractive error in adult clinical microscopists and found, in comparison to the general population, a high prevalence of myopia (71%) and an increased prevalence of onset and progression of myopia after entry to the profession. Simensen and Thorud (1994) studied textile workers who were responsible for quality control of textiles. Although these workers inspected for weaving errors at the relatively long distance of approximately 60 cm while the textiles moved continuously past them, they all developed myopia, the level of myopia increasing with the number of years of work. Both the microscopists (Adams and McBrien, 1992) and textile workers (Simensen and Thorud, 1994) either did not have myopia before they started employment or had only a small amount of myopia. Alternatively it could be argued that the patterns of eye movements were different in the two groups and that, perhaps, forces on the eyeball brought about by the extraocular muscles and lids during the eye movements required to inspect the cloth led to greater myopia in the textile workers (Buehren *et al.*, 2003a, 2005; Collins *et al.*, 2006a,b; Radhakrishnan and Charman, 2007). Similarly, it might be that the forces exerted on the eyeballs during the reading tasks of the Orthodox Jewish boys were more important for myopia development than the actual dynamically-changing accommodative demands. Further evidence comes from a study by Lam *et al.* (2008). They analysed the change of steroacuity with different head tilts. In 63 subjects they showed that steroacuity decreases nearly linear with increasing head tilt.

Mutti *et al.* (2002) found by calculating the time spent for studying, playing video games and watching television that myopes spent most time for studying in comparison to hyperopes and emmetropes. Recent studies performed by Ip *et al.* (2008b) and Ip *et al.* (2008c) showed that environmental factors have an influence on myopia development. In contrast to Mutti *et al.* (2002) these studies were not able to find a significant link between myopia and the time spent for near tasks. Hence something different than time spent on nearwork might influence myopia progression which might be posture while reading or the way a book, newspaper etc., is presented to the eyes.

Zhu *et al.* (2003) found that short periods of interrupting a pattern reduced the myopic progression. Rucker and Kruger (2006) mentioned that the pattern of reading is important. These observations raise the question, if non-ocular components might influence emmetropisation. For some tasks, like tracing objects, it was found that the eye is highly connected to the hands to coordinate their movements. For other tasks, like drawing, the connection is less tight (Gowen and Miall, 2006). In contrast the eye growth is also well coordinated after optic nerve section (Troilo *et al.*, 1987; Wildsoet and Pettingrew, 1988). This example shows the complexity of interactions between eyes and other organs. So the non-optical and emmetropisation influencing component could be posture, which gives a feedback to the state of emmetropisation.

A more optical related topic under the context of posture is the way a book or newspaper is held. Reading might influence the perception and therefore submit different signals. Hence it might be a lack in studies that use a Badal optical system to prompt the eye to accommodate, as this excludes the question of posture (Rucker and Kruger, 2001).

It needs to be questioned, if the position of the head in reference to the fixated object or the alignment of the fixated object influences the emmetropisation process. If the head is tilted just a few degrees for example, a different distance of about 3.0 cm to the fixated object is easily reached. Depending on the reading distance, 3.0 cm can induce a difference in accommodation of nearly up to 1.0 D between both eyes and of course a change in vergence. The circumstances are similar, if a book, newspaper etc. is not held straight in front of the eyes. All these issues can be studied using an eye-tracker to observe the posture while performing different near tasks like reading and writing.

1.7.2 Head and eye movements

Eye movements are performed to acquire and improve visual information. A group of different types of eye movements are performed for different tasks (Leigh and Zee, 2006):

- *Saccades:* to bring an object of interest rapidly on retina.
- *Vergence:* required to foveate objects at various distances.

- *Vestibulo-ocular-reflex:* stabilises gaze and allows clear vision during head movements or when the whole visual field moves due to external factors (viewing out of a moving car or train for example).
- *Optokinetic nystagmus:* is driven by vestibulo-ocular reflex to assist keeping the retinal image still.
- *Pursuit:* tracking a moving object.
- *Fixation:* prevention of image fading and keeping a static fixation target on the retina.

Depending on the task eye movements are complemented by head movements. The main reason is the extension of eye movements. For all types of above described eye movements there is a sophisticated coordination between head and eye movements (see Proudlock and Gottlob, 2007, for review). It was found that eye and head movements are highly connected on one side, but at the same time very flexible to adapt to changing situations (Proudlock *et al.*, 2003). The development of eye and head movements in children last approximately until the age of nine years. During that time eye movements become more regular with increasing age (Gilbert, 1953). However, the coordination of eye and head movements is subject to changes with age. There is a tendency of increasing head movements with age (Proudlock *et al.*, 2004).

Eye and head movements can vary between individuals for different visual tasks. Possibly the type of eye movements and the coordination of eye and head movements, for example, differs. Certain conditions of eye and head movements parameters could be a precursor for myopisation. This assumption is emphasised by earlier findings, that showed posture might be associated with higher rates of myopia (Adams and McBrien, 1992; Zylbermann *et al.*, 1993; Simensen and Thorud, 1994; McBrien and Adams, 1997).

1.8 Rationale

Preliminary studies would be important for the validation of measurement techniques especially for peripheral aberrometry.

As outlined before there is some evidence that head posture and eye movements might have an influence on myopisation. Therefore, eye and head movement parameters will be compared systematically between myopes and non-myopes. These parameters will also be associated with refractive error progression.

To further address the question of the involvement of nearwork in myopisation, changes in ocular biometric parameters during accommodation will be analysed.

Summarising the literature peripheral refraction appears to be an important factor that might have the potential to control myopisation. Based on findings that are reported in the literature, the following studies were conducted to gain more knowledge in the area of myopia. The projects concentrated on peripheral vision, eye movements and head posture.

After preliminary studies in chapter 2, 3 and 4 that deal with the repeatability of peripheral aberrometry and the handling of elliptical pupils during peripheral aberrometry as well as ocular biometry chapter 5, 6 and 7 discuss the role of eye movements and head posture. Differences between myopes and non-myopes were analysed and eye and head parameters were associated with refractive error progression.

In chapter 8 biometric changes of ocular parameters during accommodation, in particular axial length, were compared between myopes and non-myopes. As peripheral vision seems to play an important role in myopisation acommodative responses to peripheral stimuli were compared between myopes and emmetropes (chapter 9). Chapter 10 and 11 report peripheral refraction and peripheral aberration data. These measurements were analysed in conjunction with myopia progression data.

To access the possible influence of higher order aberrations in myopisation in general, higher order aberrations in anisometropes were analysed and compared to aberrometry data in isometropes (chapter 12).

Chapter 2

Repeatability of higher order aberrations along the horizontal meridian and repeatability as an indicator for changes in ocular shape

2.1 Abstract

Purpose: It might be argued that a change in eyeball shape may be induced by extraocular muscle forces when fixating eccentrically. This would be reflected in the variability of the peripheral higher order aberrations. We have therefore studied the repeatability of peripheral higher order aberrations using an IRX-3 aberrometer

Methods: Peripheral aberrations were measured for 20 visually-normal subjects using the IRX-3 for central and eight peripheral gaze positions up to 20 degrees along the horizontal meridian. Five readings were taken at each gaze position and the coefficient of repeatability was calculated as a measure for repeatability.

Results: Coefficients of repeatability are presented for horizontal coma and spherical aberration. For both aberration coefficients the repeatability remains somewhat constant along the horizontal meridian. Repeated-measures analysis of variance for all higher order aberration coefficients up to the fourth order indicated no significant relationship with eccentricity.

Conclusions: As the repeatability of the IRX-3 is similar for central and peripheral measurments it appears to be a useful technique for peripheral aberrometry. This good repeatability also indicates that forces of the extraocular muscles are unlikely to influence the shape of the eyeball during a one-minute periode.

2.2 Introduction

The interest in measuring aberrations has increased recently with aberration data being incorporated in refractive surgery (Thibos, 2000) and contact lens correction (Lindskoog Pettersson *et al.*, 2010). Furthermore, the evidence that peripheral vision might have an impact on refractive error development in particular in myopia has sparked an interest in studying peripheral aberrations (Hoogerheide *et al.*, 1971; Smith and Hung, 1999; Mutti *et al.*, 2000; Wallman and Winawer, 2004; Charman, 2005; Smith *et al.*, 2010; for review, see Charman and Radhakrishnan, 2010; Holden *et al.*, 2010; Sankaridurg *et al.*, 2010).

The idea of peripheral aberrometry follows from the interest in peripheral refraction, which has been used extensively (see Fedtke *et al.*, 2009, for review on technical issues) and is regarded as a surrogate to describe retinal shape (see Dunne, 1995, for review). The interest in peripheral ocular aberrations has increased because it may help understand peripheral vision and its potential impact on emmetropisation. Peripheral vision is important for general detection (Atchison, 1987; Wang *et al.*, 1996), perception of peripheral motion (Johnson and Leibowitz, 1974), balance and mobility (Black and Wood, 2005) as well as driving (Wood *et al.*, 2009).

It has been speculated that peripheral aberrations may have an influence on refractive error development. Horizontal coma is of particular significance because it changes systematically with eccentricity and might therefore provide a signal for eye growth. Certainly, myopic eyes seem to be more hyperopic in terms of refractive error in the periphery than emmetropic eyes (Hoogerheide *et al.*, 1971; Mutti *et al.*, 2011, for instances). The idea that peripheral aberrations play a role in myopia is supported by the fact that orthokeratology appears to be capable of reducing the rate of myopia progression (Cho *et al.*, 2005; Santodomingo-Rubido *et al.*, 2010). Presumably it is no coincidence that horizontal coma changes its sign in the periphery when using orthokeratology lenses (Mathur and Atchison, 2009). Similar effects are seen after refractive surgery (Atchison, 2006a). The significance of the sign of horizontal coma is uncertain.

Hartwig *et al.* (2011c) showed that the sign of peripheral horizontal coma may be reversed from that expected according to geometrical optics in more than 30% of subjects who had no surgery or had not used orthokeratology lenses. These findings emphasise the importance of measuring and understanding peripheral aberrations. Alternatively, it might be argued that peripheral aberrations play no part in eye development; for example Mathur *et al.* (2009b) compared higher order aberrations between myopes and emmetropes in the peripheral visual field of young adults and could find only minimal differences.

Previous work suggested that forces related to the extraocular muscles could have an effect on the eyeball and therefore lead to myopisation (Radhakrishnan and Charman, 2007, 2008). This concept is supported by findings that the stiffness of the posterior sclera is only about 60% of that of the anterior sclera (Friberg and Lace, 1988), which highlights the susceptibility of the posterior pole to forces exerted by extraocular muscles. A low coefficient of repeatability for peripheral higher order aberrations would prove the concept that extraocular muscles have an effect and therefore change peripheral aberrations over time. Alternatively a high coefficient of repeatability would indicate that higher order aberrations do not change and therefore forces of extraocular muscles do not deform the eyeball. This is important for future concepts to avoid high rates of myopia progression especially in some Asian countries.

Measurement of aberrations is slightly more complex in the periphery. An example is the treatment of elliptical pupils (e.g. Lundström *et al.*, 2009a; Wei and Thibos, 2010). When measuring peripheral aberrations, the pupil appears increasingly elliptical with increasing eccentricity. Aberrations are usually described by Zernike polynomials, which are defined for a round unit-circle. This assumption is violated for peripheral aberrometry. Therefore, Navarro *et al.* (1998) and Atchison and Scott (2002) have suggested that the ellipse could be stretched along the minor axis to obtain a round pupil. Alternatively it is possible to analyse aberrations over a round pupil that can be fitted within the elliptical pupil over which the measurements are obtained (Lundström and Unsbo, 2007). It has been shown that, for up to 20 degrees eccentricity, a theoretical modification of the measured data is not essential (Hartwig *et al.*, 2011c) to obtain accurate peripheral aberration data in visually normal individuals.

At present, no commercial aberrometer is available specifically for measuring peripheral aberrations. Only the COAS HD (AMO Wavefront Sciences, Albuquerque, NM, USA) has a commercial add-on that can turn the COAS HD into an open-field aberrometer which could then be used for peripheral aberration measurement (Baskaran *et al.*, 2010). Most research on peripheral aberrations is conducted by changing the instrument setup and adapting the aberrometer for obtaining peripheral aberration data. Knowledge of repeatability of peripheral aberration measurements when the instrument is adapted for peripheral measurements will enable us to understand the limitations of such measurements.

The repeatability for central aberration measurements has been reported by various studies (Mirshahi *et al.*, 2003; Zadok *et al.*, 2005; Efron *et al.*, 2008; Miranda *et al.*, 2009a). For peripheral aberrometry, repeatability was shown in only one study so far using the COAS HD (Baskaran *et al.*, 2010). This study showed a good repeatability for the measurements taken with COAS HD when the data were averaged across the visual field. For the purpose of analysing the repeatability in the periphery, rather than analysing each Zernike coefficient for all eccentricities and therefore averaging the variance across the visual field, we analysed the repeatability for each eccentricity and each Zernike coefficient separately.

The purpose of the present study was to analyse the intra-session repeatability of higher order aberrations measured by the IRX-3 aberrometer in the horizontal peripheral visual field and use the coefficient of repeatability as an indicator for changes in peripheral aberrations that might be caused by forces of extraocular muscles, which is a novel area of myopia research.

2.3 Methods

Twenty subjects (12 male and 8 female) were recruited for the study. The age of the subjects ranged between 21 and 62 years (mean ± SD: 29.6 ± 10.7 years). All subjects were free of any ocular pathology and could achieve at least 6/6 visual acuity when corrected. Best-sphere corrections were in the range of -7.00 D to +0.50 D (mean ± SD: -2.03 ± 1.99 D). The group included 3 non-myopes (spherical equivalent power between +0.50D and -0.50 D) and 17 myopes (spherical equivalent power of less than -0.50 D). In all cases, astigmatism was <3.50 D. The research followed the tenets of the Declaration of Helsinki and the project protocol was approved by the Senate Committee on the Ethics of Research on Human Beings of the University of Manchester. All subjects gave their informed consent after being told the purpose of the experiment.

Ocular aberrations were measured using an IRX-3 Shack-Hartmann aberrometer (Imagine Eyes S.A.R.L., Orsay, France). This instrument is equipped with a 32×32 lens-let array. The light source emits 780 nm infrared radiation. No refractive corrections were worn during the measurements. Habitual contact lens wearers did not use their contact lenses from the evening before the measurement. Wavefront errors were recorded from the right eye, with the left eye occluded. No cycloplegia was used. All measurements were taken under dim lighting conditions. Ocular aberration data were analysed for 3.5 mm pupil diameter. Zernike coefficients of aberrations from the second to the fourth order were analysed.

The internal viewing target of the IRX-3 aberrometer is designed for central measurements. To obtain peripheral measurements along the horizontal visual field a modified target system was used. A beam splitter was inserted between the subjects eye and the aberrometer. The beam splitter allowed viewing peripheral targets while aberrometry readings could be taken as usual. A custom-made horizontal band with nine LEDs coloured red and green alternatively was used as fixation target. The distance between each LED was 60 mm. The target was placed 690 cm away from the subjects' eye. This made a field angle of 4.97 degrees for each target separation. Therefore measurements were taken at approximately 5, 10, 15 and 20 degrees in the nasal and temporal retina respectively. The sequence of gaze position was randomized and five readings were taken at each position sequentially. Five readings were taken to be able to show any possible changes over time. Subjects fixated at peripheral targets by eye turn. The patients head was stabilised in a head rest. In total 45 measurements were taken for each subject at nine gaze positions. For each participant the measurements took about 10 minutes.

2.3.1 Data analysis

All statistical analysis was performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). Analysed pupil diameter was 3.5 mm. If the pupil diameter was smaller than 3.5 mm, these readings were not used for further analysis. Due to this exclusion criterion 11% of the total of 900 measurements was not available for analysis. For statistical purpose these data were identified as missing data.

The coefficient of repeatability (COR) was calculated as following: Paired differences between the five repeats for each eccentricity were used to compute the average difference between any two measurements for each subject-eye. The COR was computed as 1.96 times the standard deviation of the difference between any two repeated measurements. Boxplots have been applied to present coefficient of repeatability data. The box of the boxplots mark the lower quartile, median and the upper quartile. The whiskers show the extent of the remaining data within 1.5 times of the interquartile range from the end of the box. Data beyond the whiskers are classified as outliers and marked by asterisks.

We present data for horizontal coma and spherical aberration only as these are the two higher order aberration coefficients with the highest magnitude (Porter *et al.*, 2001). The outcome for the remaining higher order aberration coefficients was similar to those of horizontal coma and spherical aberration. Especially horizontal coma changes markedly with eccentricity along the horizontal meridian (Hartwig *et al.*, 2011c).

Zernike coefficients are usually recalculated to correct for elliptical pupils using methods described by Atchison and Scott (2002) or Lundström and Unsbo (2007). However, as stated above, in a previous study we found that recalculation of eccentricities up to 20 degrees is not essential (Hartwig *et al.*, 2011c). In the present study, we did not analyse absolute peripheral aberrations, but just the repeatability for each eccentricity separately. Therefore in this case recalculation of elliptical pupils was not performed.

2.4 Results

Figure 2.1 shows the distribution of higher order aberrations in terms of higher order root mean square along the horizontal meridian of the retina.

Figure 2.2 presents the coefficient of repeatability for horizontal coma at all measured eccentricities in terms of box plots. There are only very few outliers, which are indicated by asterisks. There are more outliers in the nasal retina compared to temporal retina. The coefficient of repeatability does not change markedly with eccentricity. Regardless of whether the slope of horizontal coma is positive or negative (see Hartwig *et al.*, 2011c) the repeatability remains constant.

Figure 2.3 represents the coefficients of repeatability of spherical aberration.

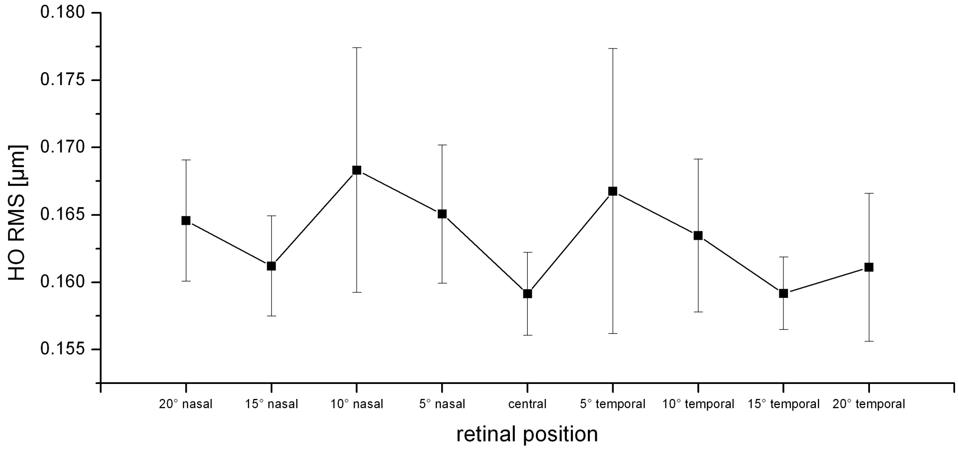

Figure 2.1 – Distribution of higher order root mean square (HO RMS) along the horizontal meridian. Error bars represent ± 1 standard deviation.

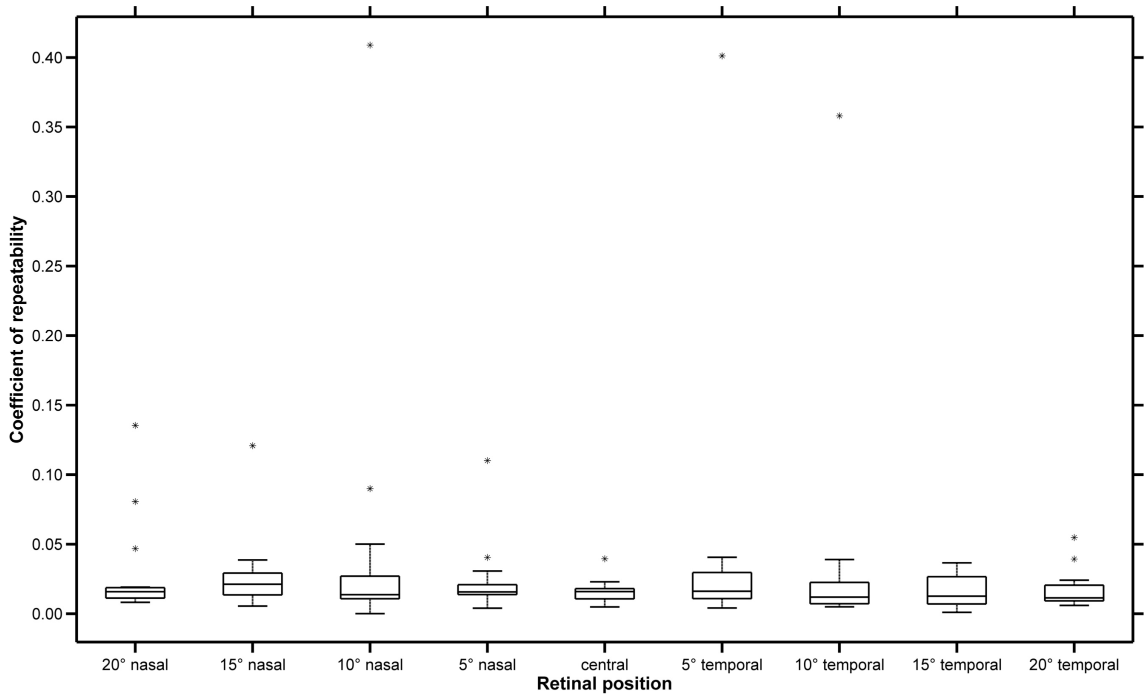

Figure 2.2 – Boxplots for coefficients of repeatability of horizontal coma. Asterisks indicate outliers.

Similarly as for horizontal coma (Figure 2.2) eccentricity does not have an effect on the coefficient of repeatability. However, other than for horizontal coma, for spherical aberration the number of outliers is similar for nasal and temporal retina.

Repeatability was also analysed by repeated measures analysis of variance. For this purpose for each aberration coefficient and each eccentricity repeated measures analysis of variance was applied for 81 situations. Due to multiple comparison Bonferroni correction was applied, which provides a significance

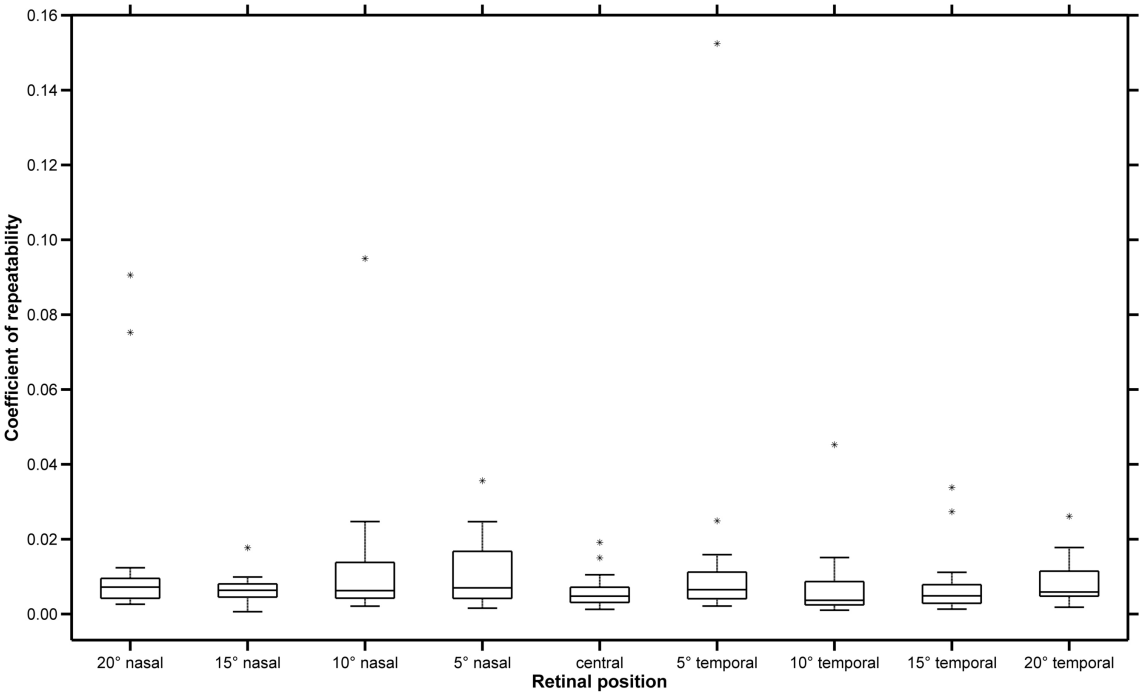

Figure 2.3 – Boxplots for coefficients of repeatability of spherical aberration. Asterisks indicate outliers.

level 0.00006. All data were not significant at this level. Also no significant combination was found at the weaker 0.05 level.

2.5 Discussion

In the present study we analysed higher order aberrations to find the intrasession repeatability of the IRX-3 for peripheral aberrometry. We feel that the repeatability of the IRX-3 is satisfactory for peripheral aberrometry as results for central and peripheral aberrometry are similar. Comparing our results for central data to other studies that also used the IRX-3 provides similar values. For peripheral aberrometry a comparison is complicated as only one study measured repeatability and used a different instrument. For instance, Miranda *et al.* (2009a) found a coefficient of repeatability of 0.030 for spherical aberration measured centrally. Our coefficient of repeatability for spherical aberration in the central retina is lower than the findings of Miranda *et al.* (2009a). Most of our coefficients of repeatability for spherical aberration in the periphery are close to that of Miranda *et al.* (2009a). Only one value is higher (5 degrees temporal). However, this is still in line with the coefficient of repeatability that Efron *et al.* (2008) found for central measurements (0.065). In general, for central aberrometry our coefficients of repeatability are lower than these found by Efron *et al.* (2008). The repeatability of peripheral measurements is within acceptable limits, as it is comparable to results for central aberrometry. However, for all comparisons with other studies it is important to consider that we calculated the coefficient of repeatability based on five measurements rather than two measurements to check for the influence of the extraocular muscles on the eyeball.

The findings are also in line with Baskaran *et al.* (2010) as they found the COAS HD to be repeatable for peripheral aberrometry for eccentricities up to 40 degrees. They measured higher order aberrations in young emmetropes only (mean age 23.9 ± 3.1 years). In the present study the mean age was slightly higher (29.6 ± 10.7 years) and we included emmetropes as well as myopes.

The higher order RMS data presented in Figure 2.1 appear to be different then expected. Higher order aberrations usually increase with increasing eccentricity (compare Mathur *et al.*, 2009b for instance). Here the data appears to be somewhat stable. This observation is possibly caused by variations in horizontal coma as reported earlier (Hartwig *et al.*, 2011c).

We did not correct our data for elliptical pupils for two reasons: first a recalculation would not affect repeatability and second we showed earlier that recalculation is not essential for eccentricities up to 20 degrees (Hartwig *et al.*, 2011c). Subjects performed eye-turns to fixate peripheral targets. We assumed that eye or head turns would not effect peripheral aberrometry as it was shown earlier that peripheral refraction does not change whether an eye or a head turn is performed (Radhakrishnan and Charman, 2008). Due to reduced stiffness of the posterior pole of the eye (Friberg and Lace, 1988; Radhakrishnan and Charman, 2007), it is possible that forces of the extraocular muscles slightly deform the posterior eyeball and therefore influence peripheral refractions or peripheral aberrations. This could have an impact on myopisation. As we showed good intrasession repeatability this hypothesis does not seem to be very likely.

Our data were repeatable for peripheral aberrometry even though we used an external fixation target. Subjects had to fixate the targets through a beam splitter, which is not easy. A low repeatability was therefore expected. However, the data shows that the new setup is a valid technique that allows relatively straightforward measurements of peripheral aberrations using a commercial aberrometer.

Mathur *et al.* (2009b) compared higher order aberrations in the peripheral field between young myopes and emmetropes. The differences were very marginal. Possibly it is necessary to improve the accuracy of peripheral aberrometry in order to detect any differences in peripheral aberrations between myopes and emmetropes.

In conclusion, we feel that the IRX-3 in conjunction with an external fixation target is a repeatable technique for peripheral aberrometry. The good repeatability also indicates that it is unlikely that forces of extraocular muscles have an effect on the eyeball as there does not seem to be significant changes in higher order aberrations during five readings. It remains unanswered, if changes during longer periods of eccentric fixation might occur.

Acknowledgment
The authors thank Jeremiah Kelly for his ideas on the data analysis.

2.6 Remarks

For chapter 2 the data were collected by me and I analysed the data. The first draft of the manuscripts was written by me.

It is intended to submit this manuscript soon.

Chapter 3

Peripheral aberrations measurements: elliptical pupil transformation and variations in horizontal coma across the visual field

3.1 Abstract

Purpose: The aim was to determine the critical eccentricity at which two methods of elaborating peripheral wavefront measurements are significantly different and to characterise horizontal coma in healthy young adults.

Methods: Peripheral aberrations were determined for 20 observers for central and eight peripheral gaze positions up to 20 degrees using an IRX-3 aberrometer. In one subject, additional measurements up to 40 degrees were obtained. Two definitions of stretching coefficients were compared. The raw empirical data were compared with theoretical modelling.

Results: For both 3.5 mm and 6.0 mm pupils, no significant differences were observed between recalculated and non-recalculated elliptical pupils for both methods ($p > 0.05$) up to 20 degrees eccentricity. For eccentricities greater than 20 degrees and up to 40 degrees, significant differences between circular and elliptical pupils at some eccentricities were apparent, which corresponded to theoretical models. Wide individual variations in horizontal coma across the peripheral field were observed.

Conclusions: The data suggest that for eyes with average levels of aberrations, the elliptical transformation is of no practical importance for eccentricities up to 20 degrees. In some cases the slope of horizontal coma was reversed compared with previous findings in normal eyes.

3.2 Introduction

Prevalence rates for myopia are increasing dramatically across the world, especially in some Asian countries (Saw *et al.*, 1996; Goldschmidt, 2003; Morgan and Rose, 2005). It has been suggested that peripheral vision might play a crucial role in refractive error development (Seidemann *et al.*, 2002; Stone and Flitcroft, 2004; Charman and Radhakrishnan, 2010). Smith *et al.* (2005) showed that ocular elongation in primates induced by pinhole apertures recovered even after the macula had been destroyed by laser photocoagulation. This indicates that visual information from the macular area is not essential for the regulation of eye growth.

Peripheral refraction is often used to study ocular shape (Atchison *et al.*, 2004, 2005a; Hartwig, 2007). By comparing results of peripheral refraction with A-scan ultrasonographic results, Dunne (1995) showed that peripheral refraction is a valid method for determining the retinal contour. As stated by Atchison *et al.* (2004), peripheral refraction can give a good insight into the development of refractive errors, especially myopia, and is easier to perform than other methods of assessing retinal contour. The importance of measurements of peripheral refraction on the development of ocular refractive error was reported as early as 1971 (Hoogerheide *et al.*, 1971). Several other studies have measured the peripheral refractive patterns in myopes and emmetropes (Rempt *et al.*, 1971; Atchison *et al.*, 2004, 2005a; Atchison, 2006a; Atchison *et al.*, 2006b; Hartwig, 2007). Most of these studies showed that, along the horizontal meridian, peripheral refraction in myopic eyes is hyperopic relative to the axial refractive error, indicating that the myopic eye has a prolate shape (Logan *et al.*, 1995; Atchison *et al.*, 2004; Logan *et al.*, 2004; Stone and Flitcroft, 2004; Singh *et al.*, 2006). This suggests that abnormal axial eye growth might be stimulated by the peripheral retinal image lying behind the retina.

More recently, higher-order ocular aberrations in the peripheral visual field have also been studied in an attempt to understand their relationship with eye growth (Atchison, 2006a; Atchison *et al.*, 2006a; Mathur and Atchison, 2009). As with refractive error, it is possible that peripheral aberrations provide a signal, which is linked in some way to the development of myopia (Charman, 2005; Atchison, 2006a; Mathur *et al.*, 2008). Coma is of particular interest because it varies systematically with eccentricity. Modelling (in the present study) using a simple relaxed Liou and Brennan eye (described by Atchison and Smith, 2000a, p. 256) shows that horizontal coma increases with increasing retinal eccentricity and some previous studies have presented empirical evidence to this effect (Navarro *et al.*, 1998; Atchison and Scott, 2002). Mathur *et al.* (2009b) noted that coma varied more rapidly with eccentricity in myopes compared with emmetropes, but overall found only small differences in peripheral aberrations between the two groups.

Measuring and describing peripheral aberrations is complicated by the fact that Zernike polynomials are defined for round pupils (Thibos *et al.*, 2002a; Atchison, 2004). A unit circle with orthogonal functions shapes the base of Zernike polynomials. To measure peripheral aberrations, it is necessary to measure through elliptical pupils, because the eye fixates on a peripheral target. Pupils appear to become more elliptical with increasing eccentricity. Some authors (Atchison and Scott, 2002; Lundström and Unsbo, 2007) have developed calculations to deal with the effect of elliptical pupils, for example, by expanding the minor elliptical radius of the elliptical pupil to the size of the major radius of the ellipse, which varies theoretically as the cosine of the rotation angle ϕ of the eye (Spring and Stiles, 1948; Jay, 1962; Atchison and Scott, 2002; Atchison *et al.*, 2003). Another approach based on the calculation of the short and long axes of the elliptical pupil recalculates the Zernike coefficients (Lundström and Unsbo, 2007). Lundström *et al.* (2009a) described three different mathematical approaches to deal with elliptical pupils during peripheral aberrometry.

To our knowledge, a comparison of aberrations from non-recalculated (circular) and recalculated elliptical pupils based on data obtained with a commercially available instrument has not been made. It is obvious that the correction for an elliptical pupil will be important for large but not small eccentricities, because with increasing eccentricities the pupil shape becomes increasingly non-circular. Here, we investigate the eccentricity at which the correction of Zernike coefficients becomes important for the average eye and what factors determine this limit. Hence, the main aim of the experiment was to establish the importance of transforming from elliptical to circular pupils in real eyes up to and including 20 degrees eccentricity.

A further aim of these experiments was to investigate the distribution of coma in our population because, as outlined more fully in the discussion, coma has a characteristic distribution across the visual field and therefore could convey information on defocus and its sign.

3.3 Methods

Twenty subjects (twelve men and eight women) were recruited in the present study. The age of the subjects ranged between 21 and 62 years (mean ± SD: 29.6 ± 10.7 years). All subjects were free of any ocular pathology and could achieve at least 6/6 visual acuity. Best-sphere corrections were in the range -7.00 D to +0.50 D (mean: -2.03 ± 1.99 D). The group included three non-myopes (spherical equivalent power between +0.50 D and -0.50 D) and 17 myopes (spherical equivalent power of less than -0.50 D). In all cases, astigmatism was 3.50 D or less. Some observers were regular contact lens wearers. The research followed the tenets of the Declaration of Helsinki and the project protocol was approved by the Senate Committee on the Ethics of Research on Human Beings of the University of Manchester. All subjects gave their informed consent after being told the purpose of the experiment.

Ocular aberrations and pupil diameters were measured with an IRX-3 Shack-Hartmann aberrometer. This instrument has a 32 × 32 lenslet array and uses 780 nm wavelength. No refractive corrections were worn during the measurements. Habitual contact lens wearers left out their contact lenses from the evening before the measurements. Wavefront errors were recorded from the right eye with the left eye being occluded. No cycloplegic drugs were used. All measurements were taken under dim lighting conditions. The ocular aberrations data were analysed for a 3.5 mm pupil diameter and a subset of the data ($n = 6$) was analysed for a 6.0 mm pupil diameter. The subjects of the subgroup were selected by the fact that their pupil diameters were larger or equal to 6.0 mm throughout the measurements. The mean age of the subgroup was 26.7 ± 1.5 years, ranging from 25 to 29 years. The average spherical equivalent of the subgroup was -2.60 ± 2.35 D.

The internal viewing target of the IRX-3 aberrometer is designed for central measurements. A modified target system was used to obtain peripheral measurements along the horizontal visual field. An additional beam splitter was inserted between the subjects eye and the aberrometer. The beam splitter allowed viewing of peripheral targets, while aberrometric readings could be taken as usual. A custom-made horizontal band with nine light emitting diodes (LEDs) coloured alternately red and green was used to present the fixation targets. The distance between each LED was 60 mm. The target was placed 690 mm away from the subjects' eye. This made a field angle of 4.97 degrees for each target separation. Therefore, measurements were taken at approximately 5, 10, 15 and 20 degrees in the nasal and temporal retina. The sequence of gaze position was randomised and five readings were taken at each position. In total, 45 measurements were taken for each subject. The measurements took approximately eight minutes.

In one subject (age: 28 years; spherical equivalent: 0.12 D), an additional series of measurements was obtained up to 40 degrees eccentricity, to compare the results of elliptical pupil transformation on eccentricities higher than 20 degrees with model eye data. In this case a pupil diameter of 4.5 mm was used.

3.3.1 Data analysis

All statistical analyses were performed using SPSS 16.0 (SPSS Inc, Chicago, IL, USA). Matlab code (Matlab R2008a; The MathWorks, Natick, MA, USA) was used for pupil size calculation and rescaling of the elliptical pupils (Lundström and Unsbo, 2007). Minimum pupil diameter was 3.5 mm.

3.3.2 Elliptical pupil transformation

The calculation of Zernike polynomials is referenced to a unit circle. Off-axis fixation causes the pupil and therefore, the resulting wavefront to appear elliptical as viewed by the aberrometer. Zernike coefficients were fitted by the software of the aberrometer using data from the most circular area of the pupil. These data are referred to as non-recalculated data. These coefficients were transformed by a Matlab script and referred to as recalculated data. The details of the mathematical transformations of the Zernike coefficients are fully described by Lundström and Unsbo (2007) where the Matlab code for performing the calculations is provided. The transformation was performed using a correcting factor (η_e) as follows:

$$\eta_e = \frac{r_{min}}{r_{max}} \tag{3.1}$$

where r_{min} is the minor radius of the elliptical pupil and r_{max} is the major radius of the elliptical pupil.

An alternative approach by Atchison and Scott (2002) and Atchison *et al.* (2007) is to use $cos\,\phi$, where ϕ is the angular rotation of the eye as a transformation factor. Spring and Stiles (1948) and Jay (1962) measured pupil size and shape when viewed eccentrically and showed that the ratio of the minor and major pupil radii when viewed obliquely is well estimated by $cos\,\phi$ for ϕ up to 40 degrees. In the present study both transformation factors (equation 3.1 and $cos\,\phi$) were compared using the Matlab script (Lundström and Unsbo, 2007).

Repeated measures analysis of variance was performed to compare non-recalculated and recalculated elliptical pupil measurements of aberrations for 3.5 mm pupils for each aberration mode. A pupil size of 3.5 mm is relatively close to the diffraction limit (Freeman and Hull, 2003, pp. 518-519), hence, data from a subgroup of six subjects who had a natural pupil diameter larger than 6.0 mm were also used to allow comparison between corrected and uncorrected data.

Zemax-EE software (Zemax Development Corporation, Bellevue, WA, USA) was used to calculate aberrations of schematic eyes. The relaxed Liou and Brennan and the Navarro model eyes were used (Atchison and Smith, 2000a, p. 256). Horizontal coma of the schematic eye was calculated for the horizontal eccentricities from central to 40 degrees in five-degree steps in nasal and temporal directions. The data were analysed for 3.5 mm and 6.0 mm pupils. Results were calculated for 555 nm, which lies at the middle of the visible spectrum. Modelling was performed into the eye and the entrance pupil was placed 3.042 mm into the eye.

All data are reported as mean and standard deviation unless otherwise stated. A p-value less than or equal to 0.05 was considered statistically significant. The Optical Society of America system is used to represent Zernike aberrations (Thibos *et al.*, 2002a; Atchison, 2004). RMS is the root mean square aberrations (calculated by equation 3.2):

$$RMS = \sqrt{\sum_{n,m}(c_n^m)^2} \tag{3.2}$$

where m is the angular frequency and n is the radial order.

To calculate the defocus M_e, which allows comparison of data irrespective of pupil size of the higher-order aberrations, the following equation was used (Thibos *et al.*, 2002b):

$$M_e = 4\sqrt{3}\frac{RMS}{r^2} \tag{3.3}$$

where r is the pupil radius.

3.4 Results

3.4.1 Elliptical pupil transformation

To asses the significance of correcting for elliptical pupils we compared the implementation of elliptical pupil factors calculated from equation 3.1 and the $cos\,\phi$ method used by Atchison and Scott (2002). This is important, because for the latter the correction factor is based only on the accuracy of the determination of eccentricity where there is minimal error, whereas for equation 3.1 the long and short axes of the elliptical pupil must be measured and this could introduce some measurement error. In particular, the fact that the entrance pupil of the eye rather than the real pupil is measured could induce measurement errors; however, it needs to be considered that $cos\,\phi$ is an assumption found by empirical data (Spring and Stiles, 1948; Jay, 1962).

To implement equation 3.1 (Lundström and Unsbo, 2007), images of the pupils were obtained for 10 subjects for each eccentricity up to 20 degrees and the radius of the major and minor axes measured. Five images were taken for each subject at each eccentricity and the radii were averaged to obtain a single value of r_{max} and r_{min} for each subject. These data were used to calculate the elliptical pupil factor η_e for each nasal and temporal retinal eccentricity. The data (solid symbols) with standard deviations are illustrated in Figure 3.1. The open symbols in Figure 3.1 illustrate values of $cos\,\phi$. Obviously, the latter shows no asymmetry between nasal and temporal retina. There is an indication that the measured values for r_{max} and r_{min} were different for temporal and nasal retina and that the errors for temporal retina were slightly larger than those for nasal retina. Asymmetries in pupil size caused by oblique viewing and resulting in an elliptical pupil have been reported previously (Spring and Stiles, 1948; Jay, 1962; Radhakrishnan and Charman, 2007). These might be linked to angle α (Rabbetts, 2007), which spans between the visual and optical axes. Its effects on the measurement of high-order aberrations are discussed by Charman and Atchison (2009).

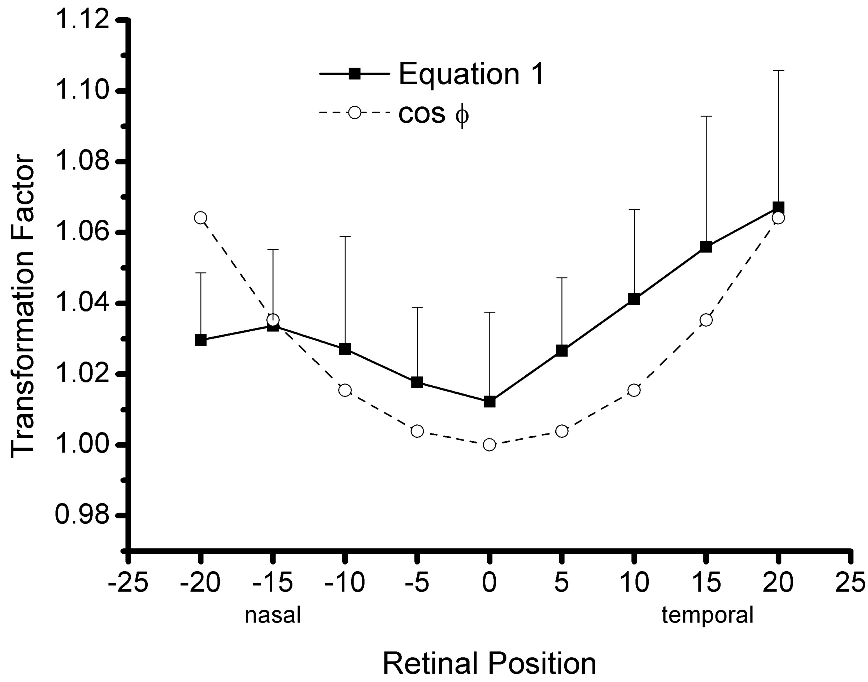

Figure 3.1 – Elliptical pupil transformation factor, calculated by equation 3.1 and calculated by $cos\,\phi$ for nasal and temporal retina separately. Error bars show +1 standard deviation.

Comparing Zernike coefficients for non-recalculated and recalculated elliptical pupils gave the following results. No significant differences were found ($p > 0.05$) for the comparison of Zernike coefficients of elliptical pupils when corrected by equation 3.1 or by $cos\,\phi$. An exception occurred for vertical coma at 3.5 mm pupil size ($p = 0.048$). The difference in vertical coma between recalculated and non-recalculated data for 3.5 mm pupils disappears for 6.0 mm pupils.

3.4.2 Horizontal coma

There are no differences between recalculated and non-recalculated pupils for all higher-order aberrations except vertical coma. To characterise the variation of horizontal coma in our group of observers we analysed the effects of elliptical correction on horizontal coma in particular. In Figure 3.2, we present horizontal coma measurements for 20 degrees nasal and temporal retinal positions at 5 degrees intervals comparing Zernike coefficients fitted to round pupils with those obtained following elliptical correction by equation 3.1. There appears to be more variability in the direction of the temporal retina than the nasal retina, as shown by Atchison and Scott (2002). For horizontal coma and other higher-order aberrations, it is likely that correcting for elliptical pupils is not important within 20 degrees eccentricity.

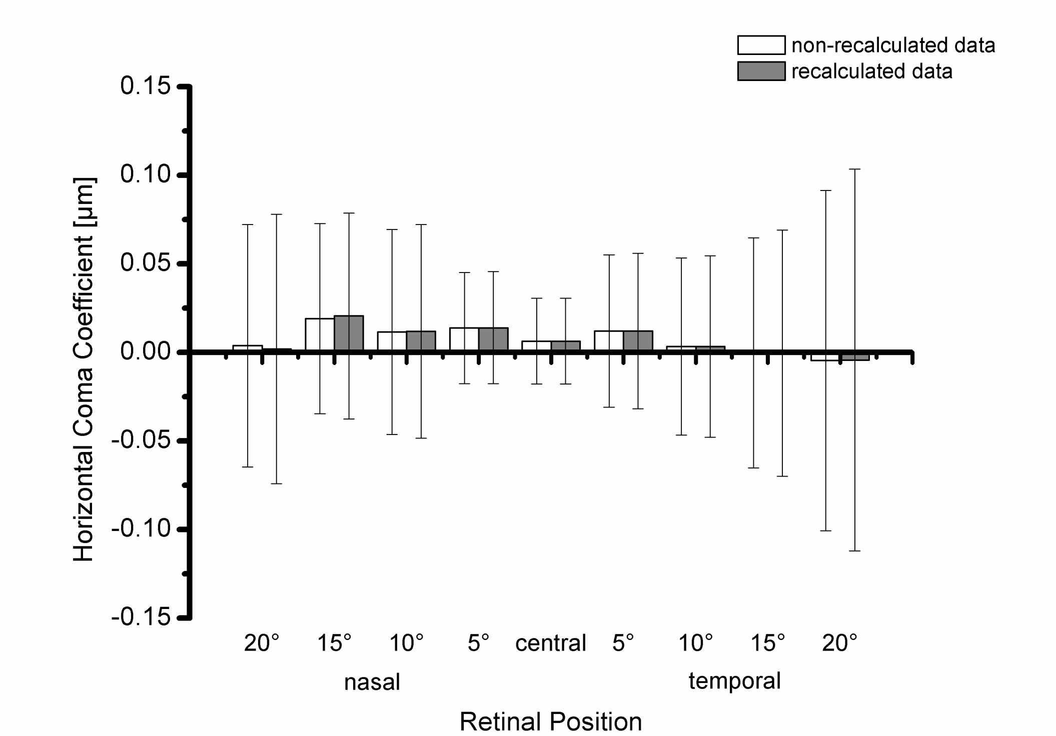

Figure 3.2 – Mean of 20 subjects to compare the difference between recalculated and non-recalculated elliptical pupils for horizontal coma and 3.5 mm pupils. Equation 3.1 was used to correct for elliptical pupils. Error bars show ± 1 standard deviation.

In Figure 3.3, this observation is reinforced for data over an extended range of eccentricities up to 40 degrees and comparing these measurements for the Liou and Brennan model eye. For elliptical recalculation $cos\,\phi$ was used. First, it is apparent that measurements of horizontal coma in observer AH match the calculated values using the Liou and Brennan model eye (Atchison and Smith, 2000a, p. 256) regardless of whether the data are corrected for the non-circular pupil. Second, both empirical and theoretical values show that the effects of correcting for the elliptical pupil are apparent only beyond 20 degrees eccentricity.

To allow comparison with data from other studies and the modelling, Figure 3.4 A shows data for the Liou and Brennan model eye (3.5 mm pupil and corneal asphericity, Q equal to -0.18) and for a single eye (DAA) from Atchison

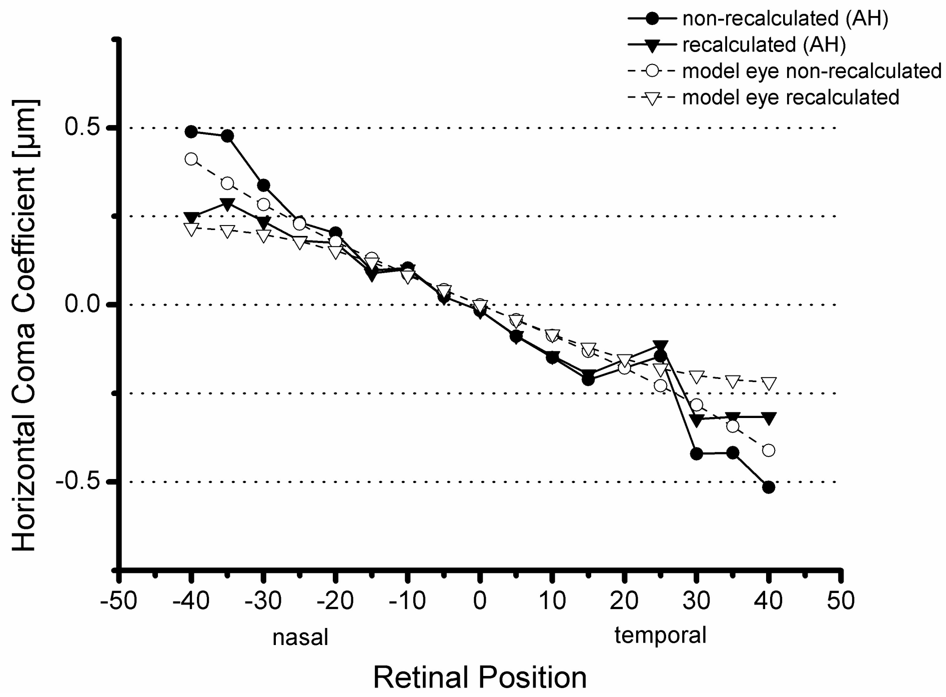

Figure 3.3 – Comparison of horizontal coma in one eye (subject AH) and the Liou and Brennan model eye for 4.5 mm pupils. Data is plotted with (recalculated) and without (non-recalculated) elliptical pupil correction. Standard deviations for measured values were less than 0.084.

(2006a). The filled triangles are the means and standard deviations for the present study and the filled squares are the data for the subset of eyes (n = 6) based on 6.0 mm pupils. Due to the wide individual variability, the 3.5 mm pupil values convey the impression that horizontal coma does not change markedly with eccentricity. Note that the model data and those from Atchison (2006a) fall well within one standard deviation of our measurements. The dip at 10 degrees nasal retina for 6.0 mm pupil data with the high standard deviation is possibly an artefact of the optic nerve head.

The distribution of the horizontal coma in right eyes in the present study was assessed by dividing it into groups B, C and D, as illustrated in Figures 3.4 B, 3.4 C and 3.4 D, respectively. In group B, the eyes fit the conventional picture of horizontal coma. To compare the data between groups, a linear fit over the 40 degrees field was performed and the slope of that fit was calculated. To rule out whether slopes are seriously affected by measurements in the 15 degrees nasal retina (position of the optic disc), data including the linear trend line for each individual were plotted and inspected. It was felt that the influence was minimal. Group B showed a slope of -0.003 μm/deg (being significantly different from zero, $p = 0.012$), which is consistent with previous findings for small pupils (Atchison, 2006a). Group C shows some variability, as seen by the large error bars, but on average there is no systematic change in horizontal coma with retinal position. Group D exhibits a quite different pattern with positive coma occurring in the temporal retina and negative coma in the nasal retina resulting in a slope of 0.003 μm/deg (being significantly different from zero, $p = 0.002$). The observation of reversed horizontal coma is independent of pupil size. Peripheral aberrometry has been repeated in three of these individuals to ensure that this observation was not an artefact. Comparing the first with the second observation for all nine gaze positions gave a standard deviation of less than 0.019 μm in all three subjects. Note that the pattern of 'reversed peripheral coma' has been reported previously in eyes that have either undergone refractive surgery (Atchison *et al.*, 2006a) or eyes that have been manipulated with orthokeratology (Mathur and Atchison, 2009).

It has been speculated (Atchison *et al.*, 2006a) that such reversal of horizontal coma might be associated with positive values of anterior corneal asphericity (referred to as Q, $Q = -e^2$; see Atchison and Smith 2000a, pp. 13-14 for further information). We tested this idea in Figure 3.5 by plotting horizontal coma for different asphericities using the Navarro model eye (Navarro *et al.*, 1985). As can be seen, if only the Q value varies then this has a marked effect on the pattern of horizontal coma. Increasing Q in a negative direction introduces higher negative slopes of horizontal coma. In the examples illustrated, typical slopes of around -0.003 μm/deg are associated with a Q value of around +0.26 using the parameters adopted here. To account for the reversed coma effect seen in our data (Figure 3.4 D) we would need a Q value of approximately +0.55, as depicted by the open circles in Figure 3.5. With increasing positive Q values of anterior corneal asphericity, spherical aberration becomes more positive (Calossi, 2007; Lim and Fam, 2009). Therefore, we correlated the slope of horizontal coma with central spherical aberration. The Pearson-correlation was not significant ($p = 0.466$); however, this correlation could be influenced by a compensation of spherical aberration by the crystalline lens.

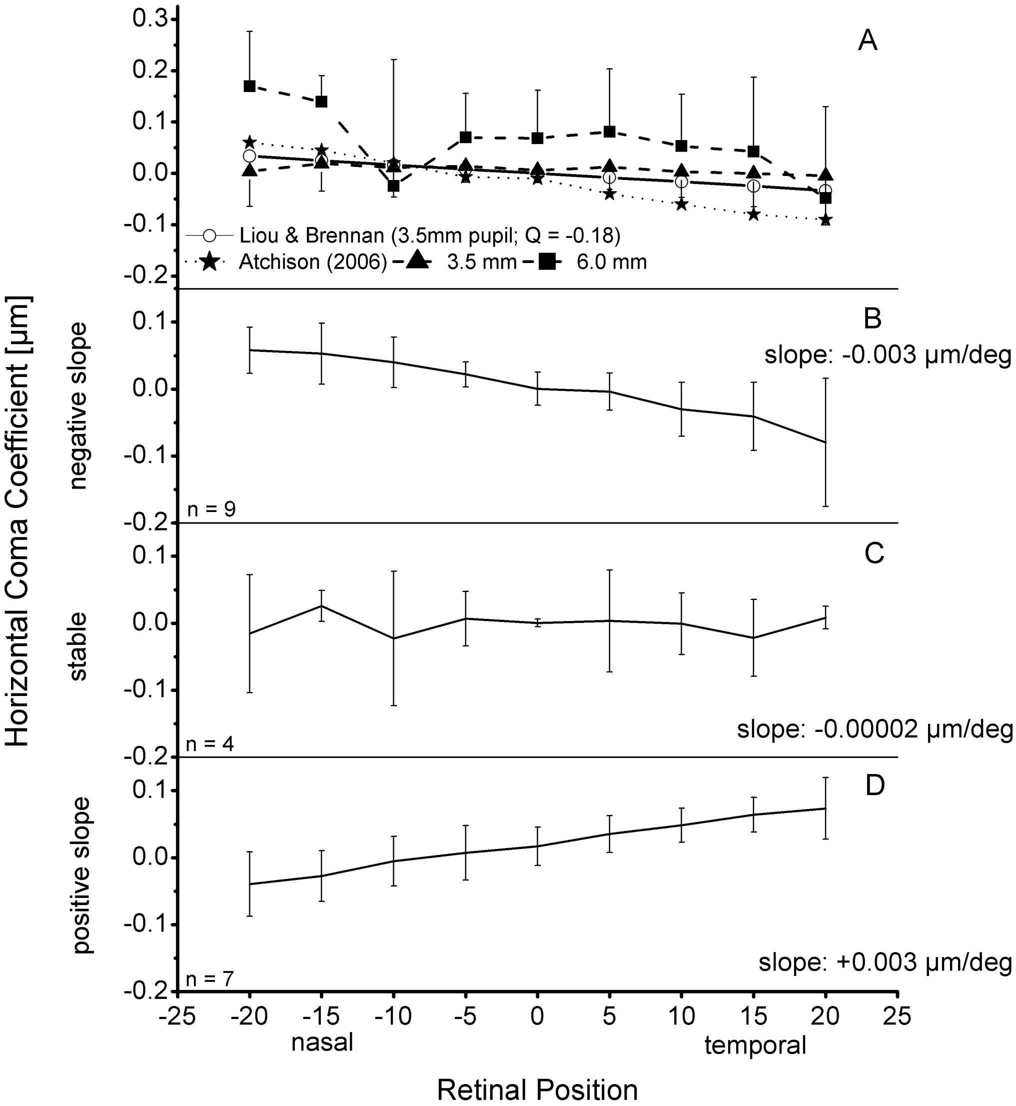

Figure 3.4 – A: Comparison between horizontal coma measured in 20 subjects (3.5 mm pupil) and calculated values for the Liou and Brennan model eye. Values from Atchison (2006a) subject DAA (6.0 mm pupil) are included. The error bars show the + 1 standard deviation for 20 subjects. B to D: Horizontal coma separated by the type of slope (positive, stable and negative) for 3.5 mm pupils without elliptical correction. Error bars show ± 1 standard deviation.

3.5 Discussion

When measuring peripheral aberrations, the pupil becomes increasingly elliptical as viewed by the optical system of the aberrometer. Recalculation for these effects is likely to be important only beyond 20 degrees. Substantial and repeatable interindividual differences in horizontal coma were found and these observations are discussed below.

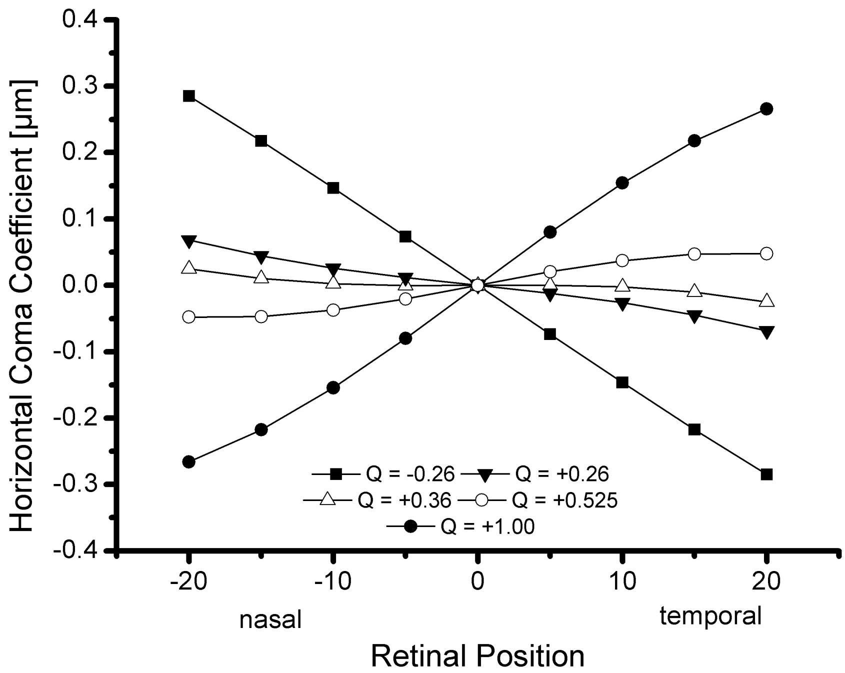

Figure 3.5 – Horizontal coma calculated for different anterior corneal asphericities using Navarro model eye (3.5 mm pupil).

3.5.1 Comparison to other studies

Repeatability for central measurements were reported by Efron *et al.* (2008) and Miranda *et al.* (2009a) using the IRX-3. As different pupil sizes were used in these studies, a direct comparison is not possible because of the change in Zernike aberration coefficients with pupil size. To overcome M_e caused by higher-order aberrations using equation 3.3 was calculated. M_e is given in dioptres and has the advantage that it is independent of pupil size. Table 3.1 gives an overview of the results of the central measurements in the present study compared with M_e measured by Miranda *et al.* (2009a) and Efron *et al.* (2008). The RMS standard deviation in the central retina in the present study is somewhat higher than the one obtained by Efron *et al.* (2008) and Miranda *et al.* (2009a). These differences might be caused by the different numbers of subjects and different numbers of repeats between the studies. As patients had to view the peripheral fixation targets obliquely in the present study, higher standard deviations could perhaps be a result of forces from extraocular muscles, lids or other structures, as reported in some individuals in a previous study (Radhakrishnan and Charman, 2007).

We used relatively small natural pupils (3.5 mm) for two reasons. First, we wanted the results to reflect normal everyday conditions. Second, it was

	Central retina		20 degrees nasal retina	
	Mean	**SD**	**Mean**	**SD**
Present study (3.5 mm pupil)				
RMS (μm)	0.094	0.134	0.128	0.126
M_e (D)	0.213	0.302	0.289	0.284
Miranda *et al.* (2009a) (4 mm pupil)				
RMS (μm)	0.125	0.023		
M_e (D)	0.217			
Paluru *et al.* (2003) (4 mm pupil)				
RMS (μm)	0.163	0.027		
M_e (D)	0.282			

Table 3.1 – Comparison of M_e in three different studies. All studies used IRX-3 to measure higher-order aberrations for central vision. As an example, RMS and M_e are also given for 20 degrees nasal retina measured in the present study. RMS = root mean square

important to avoid using cycloplegic or mydriatic agents because they are known to influence higher-order aberrations (Charman, 2004b).

3.5.2 Assessment of elliptical pupils

Although geometrically meaningful, if the elliptical pupils are recalculated, the measured ocular aberrations do not appear to differ significantly from the measurements that the aberrometer provides by analysing the most circular area of the pupil for eccentricities up to 20 degrees. It is likely that this observation holds only for normal levels of aberrations. The results for one subject (AH) suggest that the difference between the recalculated and non-recalculated elliptical pupils starts to increase from 20 degrees eccentricity onwards for temporal and nasal gaze positions, respectively (Figure 3.3). The pupil diameter, for which the aberrations were measured for this subject was 4.5 mm, whereas a 3.5 mm pupil diameter was used in the cohort of 20 subjects, implying that the gap between the two curves would be even smaller for the 3.5 mm data. According to the statistical analysis, there is a difference between recalculating and non-recalculating the elliptical pupil for vertical coma with the small but not the larger (6.0 mm) pupils. This seems unlikely and it is possible that the observation was a measurement artefact. Presumably the elliptical pupil correction is important if large pupils are used and if there are unusually high levels of aberrations such as in keratoconus or following refractive surgery.

In general, a recalculation of higher order aberrations measured at peripheral gaze positions can be ignored for eccentricities including and up to 20 degrees. This is especially true for horizontal coma. With a special aberrometer, which is made for peripheral aberrometry and is more accurate for peripheral aberrometry, it would make sense to perform a recalculation of the aberrations measured through elliptical pupils.

3.5.3 Horizontal coma

Despite its lack of rotational symmetry, the human eye usually exhibits a classical linear relationship between eccentricity and horizontal coma, C_3^1 in most subjects, as would be predicted from model eye calculations. For example, Atchison (2006a) reported an r^2 value of 0.98 for four normal eyes when plotting C_3^1 against eccentricity over an 80 degrees visual field, with slopes varying between -0.032 μm/deg and -0.021 μm/deg. These values were obtained for 6.0 mm pupils. For one observer, C_3^1 had a similar pattern with respect to eccentricity but the slope was reduced to around 0.0045 μm/deg, similar to the values obtained in the present study. In addition, horizontal coma varies systematically across the field (Atchison and Scott, 2002; Lundström *et al.*, 2009a; Mathur *et al.*, 2009b).

According to most studies (Atchison, 2006a; Atchison *et al.*, 2006a; Mathur *et al.*, 2008; Mathur and Atchison, 2009; Mathur *et al.*, 2009b), horizontal coma in right eyes is positive in the temporal visual field and negative in the nasal visual field, so that the rate of change with eccentricity is negative. Exceptions to this were described in Atchison (2006a), in which the slope of the horizontal coma was reversed in patients who had laser-assisted in situ keratomileusis (LASIK) refractive surgery. Similar observations were made in patients who use orthokeratology lenses when measurements are taken without the contact lenses (Mathur and Atchison, 2009). Here we report the same phenomenon, a reversal of the slope of horizontal coma but in normal eyes. The effect was seen in seven out of the 20 eyes tested (Figure 3.4 D). The measurements were repeated in three of the subjects and the same effect observed. As far as we know, reversed coma has not been measured before in normal eyes. There were no remarkable features, such as age, contact lens wearing, myopia or astigmatism that might distinguish the subjects who had reversed peripheral coma from the other participants. The slope of the reverse coma group (Figure 3.4 D) is much lower than that found in subjects with orthokeratology (Mathur and Atchison, 2009) or LASIK (Atchison, 2006a; Atchison *et al.*, 2006a). When comparing slopes between different studies, pupil size should also be taken into account. In the present study, even when accounting for pupil size, the slope is lower than that found in other studies (Atchison, 2006a; Mathur and Atchison, 2009; Mathur *et al.*, 2009b).

Atchison (2006a) suggested that the reversal of the slope of horizontal coma might be associated with corneal asphericity and showed how asphericity affects peripheral coma more than other factors, such as tilting or decentring the cornea. In the present study, we have conducted a similar exercise using the Navarro model eye and the data are illustrated in Figure 3.5. This confirms that asphericity has a profound effect on peripheral horizontal coma. For the conditions used, we found that the slope of the coma is reversed when Q is greater than +0.5 and this gives a rate of change with eccentricity similar to the mean of our observers, who exhibit reversed peripheral coma. The results also indicate that for horizontal coma slopes found in orthokeratology (Mathur and Atchison, 2009) and LASIK (Atchison, 2006a; Atchison *et al.*, 2006a) patients, asphericities considerably higher than +0.5 are likely to occur.

In conclusion, no difference was found between the data recalculated for the effect of the elliptical pupil and the raw data. The set-up used to measure peripheral aberrations is relatively inexpensive, technically straightforward and could be used under clinical conditions to study peripheral aberrations in a large population study. In approximately one-third of our observers, peripheral horizontal coma was reversed as a function of eccentricity compared with previous reports. Here we speculate that this might be attributable to corneal asphericity.

Acknowledgment
The authors thank Linda Lundström for providing the Matlab code for recalculating the Zernike aberrations and are grateful to David Atchison for his help with theoretical modelling and comments on a draft of the article.

3.6 Remarks

For chapter 3 the data were collected by me and I analysed the data. The first draft of the manuscripts was written by me and I dealt with reviewers' comments along with my supervisors.

This chapter has been published: Hartwig, A., I. J. Murray and H.

Radhakrishnan (2011). Peripheral aberration measurements: elliptical pupil transformation and variations in horizontal coma across the visual field. *Clin Exp Optom* **in press**.

Chapter 4

Correlations between refractive error and biometric parameters in human eyes using the LenStar 900

4.1 Abstract

Purpose: To investigate the relationship between refractive error and ocular biometry in healthy subjects using a new optical low coherence reflectometry device.

Methods: Biometric measurements were obtained with a LenStar LS 900 (Haag Streit, Switzerland) on one eye of 70 phakic subjects (mean ± SD age; 29 ± 9 years). Forty myopes and 30 non-myopes (best sphere range -9.63D to +0.63 D) were included. Outcome measures were compared for the two groups using one way between groups analysis of variance. These included; keratometry, central corneal thickness, iris width, anterior chamber depth, pupil diameter, lens thickness, axial length and retinal thickness. No mydriatic or cycloplegic agents were used.

Results: There were significant differences between groups for keratometry readings ($p = 0.021$ and $p = 0.038$ for steep and flat k readings respectively), anterior chamber depth ($p = 0.001$), lens thickness ($p = 0.026$) and axial length ($p < 0.001$). As expected significant correlations were found between spherical equivalent power and axial length (Pearson product-moment correlation $r = -0.75$, $p < 0.001$) and between spherical equivalent power and anterior chamber

depth (r =-0.29, p = 0.018). Anterior chamber depth and pupil diameter decreased with age (r = -0.429, p <0.001 and r = -0.386, p = 0.001 respectively) whereas lens thickness increased with age (r = 0.618, p <0.001).

Conclusions: Our data showed significant differences between myopes and non-myopes for the key biometric parameters assessed and provides information about the relationships between these biometric parameters and age. The results, coupled with a unique ability to image and analyse the ocular structures non-invasively make the LenStar a promising new instrument for ocular evaluation in research and clinical practice.

4.2 Introduction

The ability to obtain accurate measurement of the ocular dimensions is essential in many clinical and research applications. For example ocular biometry is used clinically in intraocular lens calculations prior to cataract and refractive surgery as well as in myopia studies to measure the structural and dimensional changes in the refractive components as myopia develops and progresses (Saw *et al.*, 2005a; Rabsilber *et al.*, 2010). Interferometry and ultrasound are established techniques for obtaining biometric data from the human eye in vivo. Interferometry has been shown to be more precise and more reliable than ultrasound (Drexler *et al.*, 1997, 1998a). Although ultrasound was traditionally regarded as the gold standard for axial length and other biometric measurements clinicians and researchers have recognised the need for higher resolution, non-contact biometry techniques.

Interferometry is the approach used in the IOLMaster device (Carl Zeiss AG, Jena, Germany) as well as in the relatively new LenStar LS 900 (Haag Streit AG, Koeniz, Switzerland) instrument. The Visante AS-OCT (Carl Zeiss Meditec, Dublin, CA, USA) uses low coherence interferometry to provide high resolution cross-sectional images of the anterior segment and can therefore be used for measuring anterior chamber dimensions, including corneal and crystalline lens thickness and anterior chamber depth (Dunne *et al.*, 2007).

The IOLMaster was the first commercially available instrument to use low coherence interferometry for the measurement of axial length. This non-contact instrument also provides data on corneal curvature, iris width and anterior chamber depth using imaging techniques. There is no facility to measure crystalline lens or retinal thickness. However, several studies have shown that the IOLMaster compares favourably to ultrasound in terms of its accuracy and repeatability (Meyer *et al.*, 2001; Rajan *et al.*, 2002; Lege and Haigis, 2004).

Previously it has been necessary to use more than one instrument to obtain data on central corneal thickness, anterior chamber depth, crystalline lens thickness, axial length and retinal thickness (Ojaimi *et al.*, 2005; Ip *et al.*, 2008a; Chen *et al.*, 2009; Xie *et al.*, 2009). The newer LenStar LS 900 measures all of these parameters. Additionally keratometry, pupil diameter and white-to-white horizontal visible iris diameter data are provided (Buckhurst *et al.*, 2009; Holzer *et al.*, 2009). The additional features make this a potentially useful clinical and research tool allowing the user to more easily explore the relationships between the key biometric parameters of the eye, which is particularly useful in monitoring myopia progression in children and adults.

A prototype of the LenStar instrument was found to give precise and repeatable measurements when used on healthy phakic subjects (Holzer *et al.*, 2009). This confirmed the findings of another research group who used the LenStar instrument on a group of older cataract patients (Buckhurst *et al.*, 2009). Rohrer *et al.* (2009) found that measurements obtained with a prototype of the LenStar 900 were in agreement with those obtained with an IOLMaster and pachymetry. Data were obtained from normals and patients with a range of conditions including cataract, aphakia, pseudophakia and following silicone oil treatment. Another study investigating the use of the LenStar in 38 healthy volunteers showed that although small but significant differences were found in measures obtained with the LenStar, Visante and IOLMaster, these did not result in clinically significant differences in intraocular lens power calculations (Cruysberg *et al.*, 2010). This study also showed that measurements with the LenStar were highly reproducible.

The primary aim of the present study was to use the commercially available LenStar LS 900 to explore possible differences in biometry between relatively young myopic and non-myopic eyes and to investigate the relationship between refractive error and aspects of ocular biometry.

4.3 Methods

4.3.1 Subjects

The research followed the tenets of the Declaration of Helsinki and the project protocol was approved by the Senate Committee on the Ethics of Research on Human Beings of the University of Manchester. All subjects gave their informed consent after being told the purpose of the experiment.

Seventy phakic subjects (28 male and 42 female) were recruited for the study. The age of the subjects ranged from 19 to 60 years (mean ± SD: 28.53 ± 8.97 years). All subjects were free from any ocular pathology and achieved at least 6/6 visual acuity with spectacle correction. Best-sphere corrections were in the range -9.63D to +0.63 D (mean ± SD: -1.96 ± 2.37 D). The group included 30 non-myopes (spherical power greater than -0.50 D) and 40 myopes (spherical power -0.50 D or less). In all cases, astigmatism was equal to or less than 2.00 DC. All measurements were performed under natural pupil conditions.

4.3.2 Optical low coherence reflectometry

The LenStar uses the effect of time domain interferometric or coherent superposition of light waves to measure ocular distances in the eye. It uses an 820 nm superluminescent diode with a Gaussian-shaped spectrum to provide a high axial resolution. The LenStar was focussed and aligned using the image of the eye on the computer monitor whilst the subject was asked to look at an internal fixation light. Subjects were asked to blink just prior to measurements being taken. The instrument takes 16 consecutive scans per measurement and 5 measurements were taken for each subject as recommended by the manufacturer. Each measurement took approximately 20 seconds and the LenStar software was used to calculate the mean of these five measurements automatically. The instrument uses low coherence reflectometry to provide data on central corneal thickness (CCT), anterior chamber depth (ACD, corneal endothelium to anterior lens surface), lens thickness (LT) and axial length (AL) automatically and retinal thickness (RT) is determined manually using a cursor. Central corneal topography is assessed by analysing the images of two rings of spots reflected from the pre-corneal tear film. Iris diameter and pupil diameter were measured using the instruments inbuilt edge detection software.

4.3.3 Data analysis

Data from the right eye only were included in the analyses to avoid the effects of inter-ocular correlation confounding the results. The results were entered into SPSS 16.0 (SPSS Inc., Chicago, IL, USA) for statistical analysis. Datasets for the two refractive error groups were compared using between groups analysis of variance. Pearson product-moment correlation coefficient was used to assess the relationship between spherical equivalent power, axial length, central corneal thickness, anterior chamber depth, lens thickness, retinal thickness, corneal radius, iris diameter, pupil diameter and age. A p-value of less than 0.05 was defined as being statistically significant.

4.4 Results

Measurements were obtained for all 70 eyes tested. The mean values, standard deviations (SD), measurement ranges and significances (p-values) are summarised in Table 4.1.

		Mean	**SD**	**Minimum**	**Maximum**	**p-value**
Steep corneal meridian, K_s [mm]	Myopic	7.69	0.30	7.20	8.33	0.021*
	Non-myopic	7.86	0.31	7.34	8.44	
Flat corneal meridian, K_f [mm]	Myopic	7.86	0.30	7.37	8.49	0.038*
	Non-myopic	8.01	0.30	7.44	8.49	
Corneal thickness [μm]	Myopic	542.57	40.95	486.00	660.00	0.942
	Non-myopic	543.30	41.00	451.00	636.00	
Horizontal visible iris diamter [mm]	Myopic	12.31	0.38	11.52	13.08	0.397
	Non-myopic	12.22	0.53	11.07	13.17	
Anterior chamber depth [mm]	Myopic	3.17	0.29	2.54	3.71	0.001*
	Non-Myopic	2.92	0.31	2.19	3.44	
Pupil diameter [mm]	Myopic	5.46	1.11	3.74	7.89	0.381
	Non-myopic	5.22	1.08	3.13	7.31	
Lens thickness [mm]	Myopic	3.65	0.27	3.26	4.40	0.026*
	Non-Myopic	3.80	0.26	3.29	4.45	
Axial length [mm]	Myopic	24.73	1.13	22.96	27.75	<0.001*
	Non-myopic	23.69	0.75	22.14	24.94	
Retinal thickness [μm]	Myopic	195.02	31.71	116.00	254.00	0.636
	Non-myopic	192.03	15.38	171.00	228.00	

Table 4.1 – Summary of the results obtained for the measured variables for the two groups. Data were compared using one way between groups analysis of variance and significant differences are denoted by an asterisk.

Figure 4.1 shows the correlations between the biometric parameters and the spherical equivalent refraction data that were found to be significant. As expected, significant correlations were found between spherical equivalent power and axial length (two-tailed Pearson product-moment correlation, r = -0.750, n = 64, p <0.001, Figure 4.1 A) and between spherical equivalent power and anterior chamber depth (Pearson product-moment correlation, r = -0.290, n = 66, p = 0.018, Figure 4.1 A). Significant correlations were also found between axial length and anterior chamber depth (Pearson product-moment correlation, r = 0.390, n = 68, p = 0.001, Figure 4.1 B) as well as axial length and lens thickness (Pearson product-moment correlation, r = -0.278, n = 68, p = 0.022, Figure 4.1 B). Corneal curvature correlated significantly with axial length (Pearson product-moment correlation, steep meridian: r = 0.344, n = 68, p = 0.004; flat meridian: r = 0.378, n = 68, p = 0.001, Figure 4.1 C). Axial length correlated significantly with horizontal visible iris diameter (Pearson product-moment correlation, r = 0.330, n = 68, p = 0.006, Figure 4.1 D). Highly significant correlations were also found between age and lens thickness (Pearson product-moment correlation, r = 0.618, n = 70, p <0.001, Figure 4.1 E), age and anterior chamber depth (Pearson product-moment correlation, r = -0.429, n = 70, p <0.001, Figure 4.1 E) and between age and pupil diameter (Pearson product-moment correlation, r = -0.386, n = 69, p = 0.001, Figure 4.1 F). Significant correlations between anterior chamber depth and lens thickness were also found (Pearson product-moment correlation, r = -0.679, n = 70, p <0.001).

4.5 Discussion

Obtaining accurate measures of axial length, anterior chamber depth and keratometry is essential in calculating IOL power in patients undergoing cataract surgery and in other keratorefractive procedures. Being able to acquire reliable measurements of the ocular dimensions is also important in research applications such as studies concerned with the development of refractive error, crystalline lens growth and presbyopia. The relatively new LenStar instrument has been shown to give measures of axial length, anterior chamber depth, keratometry and central corneal thickness that agree closely with those obtained from the IOLMaster and pachymetry in normal subjects and in patients with a range of ocular conditions (Buckhurst *et al.*, 2009; Holzer *et al.*, 2009; Cruysberg *et al.*, 2010). The aim of the present study was to use the LenStar instrument to investigate relationships between refractive error and its ocular covariates in relatively young healthy human subjects.

The mean corneal curvature values obtained for all subjects in the present

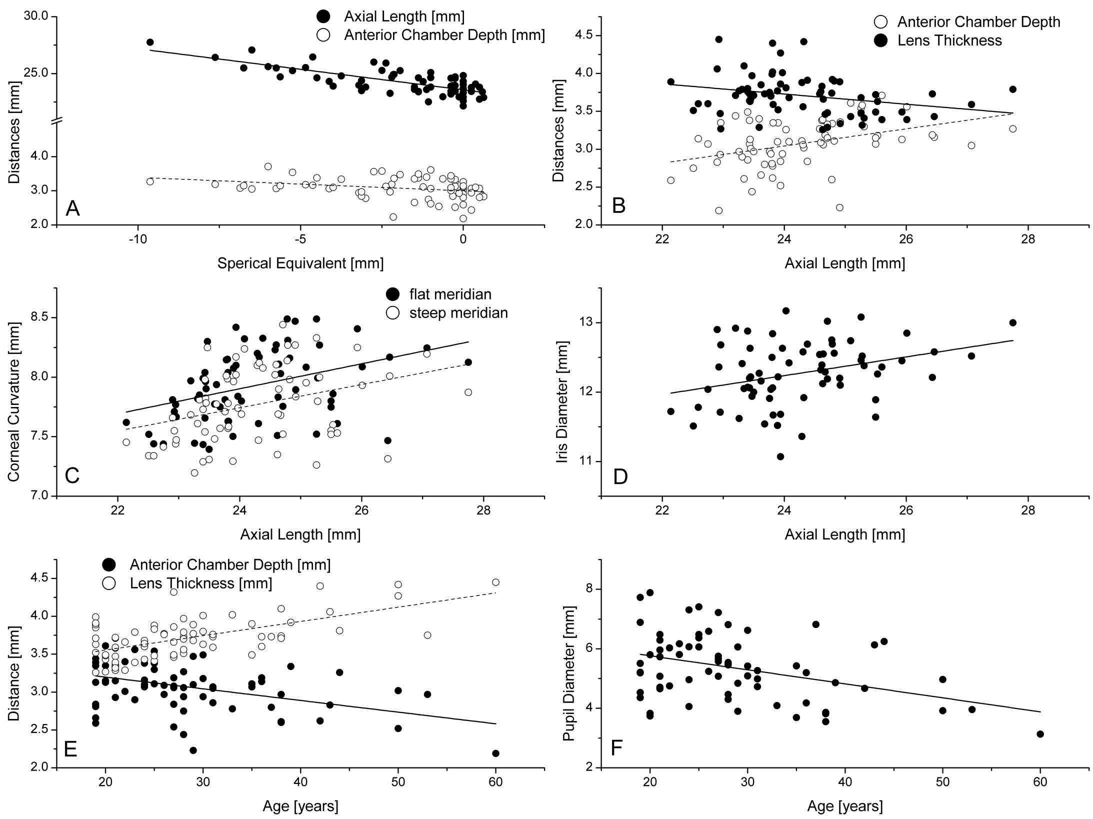

Figure 4.1 – Significant correlations found between the various study parameters. Note different scales on the axes. Solid trend lines relate to filled symbols and dashed trend lines relate to open symbols.

study (Table 4.1) are comparable to those obtained by other authors using the LenStar (Rohrer *et al.*, 2009; Cruysberg *et al.*, 2010; Rabsilber *et al.*, 2010). Cruysberg *et al.* (2010) found K_s and K_f to be 7.65 ± 0.20 mm and 7.80 ± 0.20 mm respectively when measured with the LenStar 900 in their study of 38 volunteers of a similar age to those in the present study. Rohrer *et al.* (2009) found the LenStar K_s and K_f values to be 7.53 ± 0.31 mm and 7.74 ± 0.27 mm respectively in their study of 80 subjects, age range 20-90 years. Rabsilber *et al.* (2010) used the LenStar to measure ocular biometry components in 100 cataract patients. In their study K_s and K_f averaged 7.61 ± 0.31 mm and 7.77 ± 0.30 mm respectively. Hoffer *et al.* (2010) measured a mean corneal radius of 7.77 ± 0.16 mm, which again is comparable with the afore-mentioned studies. In the present study there was a significant difference between the myopes and non-myopes in central corneal curvature, with the myopes having relatively steeper corneas. However, refractive error did not correlate significantly with corneal curvature. This is in agreement with Xie *et al.* (2009) but in contrast to Carney *et al.* (1997) who did find a significant correlation with corneal curvature (obtained using keratometry) and refractive error in their study. Thus the literature on the relationship between central corneal curvature and the development of refractive error is somewhat conflicting.

Central corneal thickness values obtained in the present study ranged from 451 to 660 μm. These values are in agreement with published literature values for central corneal thickness in healthy human eyes (Doughty and Zaman, 2000). Studies (see Doughty and Zaman, 2000, for review) using slit-lamp-based pachymetry have reported lower CCT values (530 $\pm$ 29 μm) compared to ultrasound-based studies (544 $\pm$ 34 μm). Doughty and Zaman (2000) suggest that the method of pachymetry used may reflect the type of subjects studied (nonsurgical vs. pre-surgical patients). A recent study using the LenStar to measure CCT on subjects of a similar age to those in the present study, found slightly lower average corneal thickness values than in the present study (533 vs. 543 μm respectively, Cruysberg *et al.*, 2010). However, the mean LenStar corneal thickness data from Tappeiner *et al.* (2009) is in agreement with the present study data.

The literature suggests (Chen *et al.*, 2009) that there seems to be little difference in central corneal thickness between myopes and other refractive groups. This appeared to be corroborated by our data (Table 4.1) and the absence of a significant correlation between corneal thickness and spherical equivalent refractive error.

The estimation of central anterior chamber depth is important in newer biometric formulas for IOL power calculations and for the implantation of phakic IOLs and accommodative IOLs. Also a shallow anterior chamber depth (ACD) has long been regarded as a risk factor for angle closure in most racial groups. A significant difference in anterior chamber depth between myopes and non-myopes as found by Xie *et al.* (2009) was confirmed in the present study. In contrast with Xie *et al.* (2009) a significant correlation was found in the present study between anterior chamber depth and spherical equivalent refractive error. Xie *et al.* (2009) suggested that the lack of correlation in their study may have reflected the fact that increasing ACD may only occur in the early stages of myopia development and that most of the myopes in their study had moderate or high myopia.

Although ultrasound biometry is often used for ACD measurement the IOLMaster has also been found to provide reliable and reproducible measurements (Vogel *et al.*, 2001). Meinhardt *et al.* (2006) showed that the values for ACD measured with non-contact vs. contact instruments can differ greatly. The mean ACD measurement obtained for all subjects in the present study (around 3.05 mm) was shallower than those obtained from Meinhardt *et al.* (2006) and shallower than the measures obtained with the anterior segment OCT (Visante; Lavanya *et al.*, 2007). The present measures were also shallower than the mean values obtained with the LenStar in a study by Cruysberg *et al.* (2010) and by Holzer *et al.* (2009), but they broadly correspond to the values of Tappeiner *et al.* (2009). Differences between methodologies and subjects will account for some of the observed differences between studies. Methods where accommodation is not controlled would be expected to result in an apparent reduction in anterior chamber depth. Anterior segment OCT (Visante) has previously been shown to give deeper anterior chamber measures than interferometric methods (Lavanya *et al.*, 2007).

In the present study the average white-to-white horizontal visible iris diameter distance was measured as 12.27 ± 0.45 mm, which is comparable to Cruysberg *et al.* (2010) and Buckhurst *et al.* (2009). There was no significant difference found between the myopes and non-myopes for white-to-white distance although the distance was found to correlate positively with axial length (Figure 4.1 D).

Cruysberg *et al.* (2010) found the average pupil diameter of their participants to be 5.53 ± 1.08 mm when measured with the LenStar 900. The pupil diameter data obtained in the present study were similar to that of Cruysberg *et al.* (2010) and greater than that of Buckhurst *et al.* (2009) who studied older subjects, which corresponds to the significant correlation found in our study between age and pupil diameter (Figure 4.1 D).

In vivo measures of lens thickness are important in various applications including studies of myopia progression and ocular accommodation. A variety of methods are available for lens thickness measurement, but A-scan ultrasonography is considered to be the gold standard method in both research and clinical practice. The Visante OCT has recently proved to be a valid and repeatable non-contact method for measuring lens thickness in cyclopleged eyes of young children, with measurements agreeing well with ultrasonography (Lehman *et al.*, 2009). The Visante has the advantage over ultrasound of not physically contacting the cornea, and therefore not requiring corneal anaesthesia and avoiding concerns about possible cross-infection between patients. Furthermore, precise positioning of the A-scan probe can prove difficult meaning that the technique may be unable to measure lens thickness changes less than 1.00 D (McDonald, 1986).

The advantage of the LenStar over some non-contact techniques such as Scheimpflug photography is that pupil dilation is not necessarily required to visualise the posterior surface of the lens. In the present study, measures of lens thickness were obtained without pupil dilation, for all eyes tested. However, anterior-segment OCT instruments are also capable of measuring the posterior crystalline lens surface without dilation. The range of values obtained in our study was comparable to published LenStar values for subjects of similar age (Cruysberg *et al.*, 2010). As expected, the present study values for lens thickness were, on average, lower than those obtained in previous studies of older patients awaiting cataract surgery (Buckhurst *et al.*, 2009; Tappeiner *et al.*, 2009).

There was a significant difference in lens thickness between the two refractive groups in the present study, with lens thickness being significantly higher in the non-myopic subjects. This is in contrast to Xie *et al.* (2009) who found no difference between lens thickness in the different refractive groups in their study. However, our results are in line with Zadnik *et al.* (1995) who found thinner lenses in myopic children compared to emmetropic children. Wong *et al.* (2010) analysed changes in lens thickness of Singaporean children with age and found a 'u' shaped change in lens thickness with age in most subjects. The thinnest lens was found for children with persistent myopia and only in persistent hyperopes did lens thickness remain unchanged. It is important to consider that differences in lens thickness between age-groups could be biased by a change in refractive index of the crystalline lens (Mutti *et al.*, 2005).

Despite a relatively young subject group, we found a significant correlation between age and lens thickness, supporting the theory of a growing and hardening crystalline lens with age (Charman, 2008; Shih *et al.*, 2009). Perhaps unsurprisingly a significant correlation was found between ACD and lens thickness with ACD decreasing as lens thickness increased.

Myopia progression is often measured by assessing the changes in vitreous chamber depth associated with the axial elongation (Carroll, 1981; Smith and Hung, 1999; Stone and Flitcroft, 2004; Atchison *et al.*, 2006c), therefore attention is often drawn to vitreous chamber depth in myopia research (Xie *et al.*, 2009). The LenStar 900 does not specify the vitreous chamber depth separately in the output given, although, vitreous chamber depth could be calculated based on the differences in other biometric measurements.

Eyes where axial elongation has outpaced changes in corneal curvature, are more likely to be myopic. Researchers have suggested that myopia results from a failure of corneal compensation for increasing axial length (Benjamin *et al.*, 1957). Thus axial length measures are essential in myopia research and non-invasive methods such as the LenStar are more suited to studies that include paediatric populations. The axial length values obtained in the present study were slightly greater than those in two recent LenStar studies containing myopic and non-myopic individuals (Holzer *et al.*, 2009; Cruysberg *et al.*, 2010).

The difference in axial length found for the myopic vs. the non-myopic group in the present study was expected, as myopia is mainly achieved by an increase in axial length (Gilmartin, 2004; Atchison *et al.*, 2006c; Mutti *et al.*, 2007). As expected, significant correlations were found between spherical equivalent power and axial length, as well as between spherical equivalent power and anterior chamber depth, the latter in agreement with Ojaimi *et al.* (2005). Axial length and anterior chamber depth measurements were also significantly correlated. The corneal curvature values were correlated with axial length, indicating that longer axial length and therefore higher levels of myopia are associated with steeper corneas.

The LenStar enables the measurement of the thickness of the retina at the fovea. There was no significant difference in foveal thickness found between myopes and non-myopes in the present study. However, Table 4.1 shows that the standard deviation of retinal thickness in the myopic group was larger than that in the non-myopic group. The LenStar at present does not automatically provide retinal thickness measurements and it has to be marked using a cursor after the measurements are taken by examining the peaks on an A-scan profile. Although it is possible that the interpretation of the peaks differed between the myopes and the non-myopes, this seems unlikely. Given that myopic eyes have longer axial lengths, the retinal thickness marked by the examiner could however have been subject to bias. Usually myopic eyes tend to have thinner retinae producing a tigroid appearance (Morita, 1995; Panozzo, 2004). Xie *et al.* (2009) suggest that during myopia development axial elongation of the eye can cause mechanical stretching of the posterior pole. They claim that this stretching is more likely to occur in the parafoveal area to preserve the function of the central retina.

In summary, the present study data show that the non-invasive LenStar instrument provides measurements that are broadly in agreement with published literature values for the ocular biometric parameters assessed. The study results provide information about the relationships between these biometric parameters and refractive error. These results, coupled with a unique ability to image and analyse the ocular structures make the LenStar a promising new instrument for ocular evaluation in clinical practice and in research applications.

Acknowledgment
The authors acknowledge the assisstance of Haag-Streit UK Ltd. who provided the LenStar for the duration of this work.

4.6 Remarks

For chapter 4 the data were collected by me and I analysed the data. The first draft of the manuscripts was written by me and I dealt with reviewers' comments along with my supervisors.

This chapter has been published: O'Donnell, C., A. Hartwig and H. Radhakrishnan (2011). Correlations between refractive error and biometric parameters in human eyes using the LenStar 900. *Cont Lens Anterior Eye* **34**(1): 26-31.

Chapter 5

Working distance and eye and head movements during near work in myopes and non-myopes

5.1 Abstract

Purpose: Reasons for the development and progression of myopia remain unclear. Some studies show a high prevalence of myopia in certain occupational groups. This might imply that certain head and eye movements lead to ocular elongation, perhaps as a result of forces from the extraocular muscles, lids or other structures. The present study aims to analyse head and eye movements in myopes and non-myopes for near-vision tasks.

Methods: The study analysed head and eye movements in a cohort of 14 myopic and 16 non-myopic young adults. Eye and head movements were monitored by an eye tracker and a motion sensor while the subjects performed three near tasks, which included reading on a screen, reading a book and writing. Horizontal eye and head movements were measured in terms of angular amplitudes. Vertical eye and head movements were analysed in terms of the range of the whole movement during the recording. Values were also assessed as a ratio based on the width of the printed text, which changed between participants due to individual working distances.

Results: Horizontal eye and head movements were significantly different among the three tasks ($p = 0.03$ and $p = 0.014$, for eye and head movements, respectively, repeated measures analysis of variance). Horizontal and vertical eye and head movements did not differ significantly between

myopes and non-myopes. As expected, eye movements preponderated over head movements for all tasks and in both meridians. A positive correlation was found between mean spherical equivalent and the working distance for reading a book (r = 0.41; p = 0.025).

Conclusions: The results show a similar pattern of eye movements in all participating subjects, although the amplitude of these movements varied considerably between the individuals. It is likely that some individuals when exposed to certain occupational tasks might show different eye and head movement patterns.

5.2 Introduction

The prevalence of myopia has been increasing worldwide over the past few decades. This has led to a sustained but so far only partially successful effort to find its causes. There is now general agreement that myopic development has a multifactorial aetiology, with both genetic (Hammond *et al.*, 2001; Lyhne *et al.*, 2001; Hammond *et al.*, 2004) and environmental (Mohan *et al.*, 1988; Saw, 2003; Mutti, 2010) factors playing important roles.

It has been suggested that genetic factors account for up to 80 % cent of the variation in refractive errors (Hammond *et al.*, 2001). The odds of children becoming myopic significantly increase with the number of their parents who are myopic (Zadnik, 1997; Pacella *et al.*, 1999; Morgan and Rose, 2005), however, genetic factors alone cannot account for the very rapid increase in the prevalence of myopia that has occurred over two generations, for example, in Taiwan (Lin *et al.*, 1999, 2004) and Hong Kong (Edwards and Lam, 2004). A role for other factors is supported by findings of rapid increases in myopic refractive error in other population groups (Young *et al.*, 1969; Richler and Bear, 1980; Lam *et al.*, 1994) or sub-groups (Adams and McBrien, 1992; Zylbermann *et al.*, 1993; Simensen and Thorud, 1994; McBrien and Adams, 1997).

For over a century, long periods of near work have been discussed as a risk factor for myopia development (Rosenfield and Gilmartin, 1998; Mutti *et al.*, 2002; Hazel *et al.*, 2003). More recently, Ip *et al.* (2008c) found that the intensity rather than the duration of near work is of greater importance. Interestingly, Jones *et al.* (2007b) showed that it might be the time spent outdoors that is associated with lower myopic prevalence, rather than the time spent for near work being associated with increased myopia: this finding has been supported by later studies (Rose *et al.*, 2008a; Dirani *et al.*, 2009). A role for near work in myopisation remains possible and it is important that all relevant factors be properly explored.

One possible link between near work and myopic development is the associated stress imposed on the globe by the lids and extraocular muscles. Von Graefe (1857) and Donders and Moore (1864) were early enthusiasts for this idea, suggesting that pressure from the medial recti during convergence was particularly important in causing axial extension of the globe. This was reviewed by Duke-Elder and Abrams (1970) and Goss and Rosenfield (1998). The concept has been discussed more recently by Greene (1980, 1991). In support, Ferree *et al.* (1932) and Seidemann *et al.* (2002) found that the pattern of peripheral refraction changed during relatively short-term (minutes) eye rotation (adduction, abduction), presumably as a result of changes in the shape of the globe, although others could not duplicate this result (Radhakrishnan and Charman, 2007; Mathur *et al.*, 2009c). Lid pressures allied to lateral scanning during relatively short periods of reading can undoubtedly affect the shape of the cornea (Bowman *et al.*, 1978; Buehren *et al.*, 2003a). Moreover, the stiffness of the posterior sclera is only approximately 60% of that of the anterior sclera (Friberg and Lace, 1988), so that the posterior of the eyeball might be more susceptible to exterior forces and hence deform more easily. Thus, the possibility that extraocular muscle forces might temporarily distort the eyeball and that, over time, such distortion might become permanent and lead to myopia, cannot be dismissed.

If these suggestions have any validity, then it is reasonable to ask why, when exposed to similar tasks and environments, some individuals become myopic and others do not. Either the globes of potential myopes are genetically more susceptible to external forces or at-risk individuals adopt postures and eye movement patterns, when performing near tasks, which differ from those of emmetropes and create more mechanical stress on the eye. For example, the use of systematically shorter working distances would not only demand greater accommodation but also greater convergence and, since the angular subtense of the work would be increased, greater head and eye movements to explore the working field.

In the present study, using an eye and motion tracker, we investigated postural head and eye movements while myopes and non-myopes performed the same binocular near tasks, to determine whether there were significant differences between the characteristics of myopes and non-myopes. The hypothesis was that myopes might use systematically shorter working distances and/or eye movements of larger amplitude. Posture was analysed in terms of working distances, amplitudes of horizontal eye and head movements and the range of vertical eye and head movements during reading on a screen, reading a book and writing.

5.3 Methods

5.3.1 Participants

Thirty subjects (18 men and 12 women) were recruited. The age of the subjects ranged between 18 and 45 years (mean and standard deviation: 27.5 ± 5.6 years; median: 28 years). All subjects were free of ocular pathology and could achieve a visual acuity of 6/5 or better. Spherical equivalent refraction was determined by autorefraction using the Canon R1 open-field autorefractor (Canon, Tokyo, Japan). Three readings were taken and the average was used for further analysis. Mean spherical equivalent corrections were in the range of -6.86 D to +1.50 D (-1.59 ± 1.50 D; median: -0.44 D). The group included 14 myopes (spherical equivalent power between -6.86 D and -0.60 D; mean: -3.60 ± 1.72 D; median: -3.25 D) and 16 non-myopes (spherical equivalent power between -0.50 D and +1.50 D; mean: 0.18 ± 0.50 D; median: 0.25 D). In all cases, astigmatism was less than 1.75 D. The mean age was 28.3 ± 4.1 years in the myopic group and 26.8 ± 6.6 years in the non-myopic group. In the myopic group there were nine men and five women and in the non-myopic group there were nine men and seven women. All ametropic participants, including the only hyperopic subject (+1.50 D), wore their habitual soft contact lens corrections for distance vision. None of the participants required a presbyopic correction. The study followed the tenets of the Declaration of Helsinki and written informed consent was obtained from all participants after the nature of the study and possible consequences of the study had been explained. The project protocol was approved by the Senate Committee on the Ethics of Research on Human Beings of the University of Manchester.

5.3.2 Eye and head tracking

An Eye Link II (SR Research Ltd, Mississauga, Canada) was used in conjunction with Motion Monitor software (Innovative Sports Training Inc, Chicago, IL, USA) and motion sensors (Polhemus, Colchester, USA) to monitor eye and head movements. Eye movements were recorded binocularly at 500 Hz in both the horizontal and vertical planes using two videobased cameras mounted on a helmet. The cameras were positioned in the extreme inferior peripheral field to avoid obstruction of the field view and were set for pupil-tracking mode. A Polhemus sensor was attached to the helmet to record three-dimensional head movements at 120 Hz. A calibration procedure involving fixating nine successive targets was necessary to convert the eye-position signals into a measure of eye angle, referenced to the centre of the head, in degrees. Head movements were recorded in three directions in terms of yaw, pitch and roll motions (see Proudlock and Gottlob (2007) for further information). The total weight of the helmet and associated head-mounted equipment was 420 g.

5.3.3 Procedure

Eye and head movements were measured while the participants performed three different near tasks. In Task 1, subjects were seated on an office chair and were asked to adjust their perpendicular horizontal distance from a vertical screen until they felt they could perform the task most comfortably. The chair height was kept at the same level of 50 cm for all participants. Task 1 involved reading part of a novel (Wuthering Heights) that was printed at 1.5 line spacing in 12-point font (Arial) and non-justified on an A4 page (210 x 297 mm); the text occupied an area of approximately 160 x 250 mm. The A4 sheet was attached to the screen and positioned centrally in front of the participant. The screen position was fixed and remained the same for all participants, although the chosen reading distance altered between participants. This set-up (Figure 5.1) was meant to simulate visual display screen/computer work.

For Task 2, the subjects were asked to hold in their hands at their normal, comfortable, reading distance a second piece of A4 paper with the continuation of the novel in the same 12-point font and line spacing, and read that text. During Tasks 1 and 2, subjects read the text aloud to make sure they were concentrating on the tasks.

In Task 3, the subjects were asked to write on a blank sheet of A4 paper a text that was dictated to them. The paper was placed on the flat horizontal surface of a desk in front of each seated subject. The subjects were encouraged to adjust the chair and adopt a comfortable working distance and posture while writing. Each task was performed for two minutes. The analysis

Figure 5.1 – Set-up for the reading screen task (Task 1).

presented in this study was based on only the first minute of the recordings, as preliminary analysis showed no significant difference between data sets from the first and second minutes of the eyemovement recordings, also indicating good repeatability. No chin rest or bite bar was used during the monitoring of head and eye movements, because the aim was to allow the participants to adopt their natural posture. In each task, the chosen working distance between the paper and the head was measured manually using a metre ruler.

Ametropic subjects were corrected with their habitually worn soft contact lenses because it was found that spectacles induced additional reflections that did not allow precise eye tracking.

5.3.4 Data analysis

Only data from right eyes were analysed. Five parameters were used for the analysis of each task: distance from task material, horizontal and vertical eye movements, and horizontal and vertical head movements. Horizontal movements, which were related to the length of each line of text or writing, were analysed in terms of amplitudes and vertical movements, which were related to the height of the A4 page, in terms of range. To quantify horizontal eye movements, a customised Matlab script (The Mathworks, Inc, Natick, MA, USA) was used that identified peaks in the movements, as shown in Figure

5.2. After identification, the difference between the peaks was calculated automatically and the mean of all differences was used for further analysis.

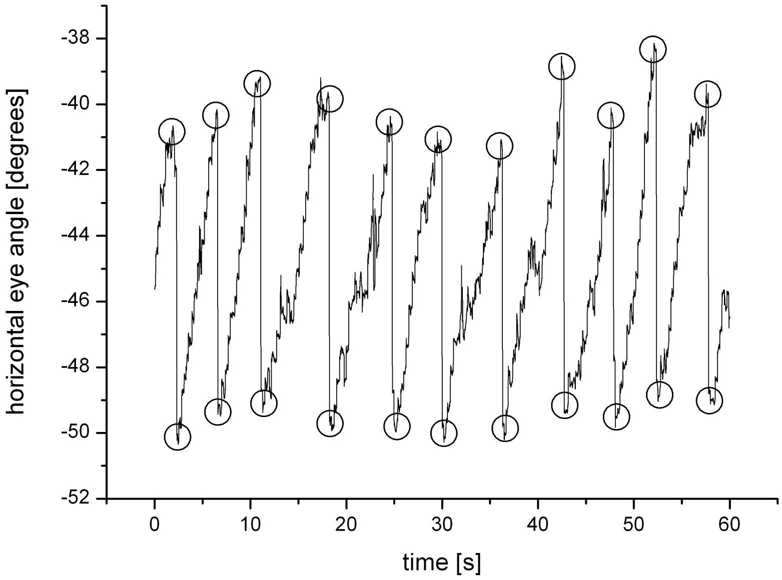

Figure 5.2 – Example of peak analysis in one patient (TP, right eye). Time is sampled at a rate of 500 Hz. Circles highlight peaks that were chosen by the Matlab script.

Amplitudes for head movements were calculated with reference to the time points from the eye-movement peaks. This allowed the values for head-movement range to become negative, indicating a head movement in the opposite direction to a simultaneous eye movement. Vertical eye and head movements were analysed by calculating the difference between the maximum and the minimum value within the time period of one minute.

Two approaches were used in further analyses to compare eye and head movements. In the first instance, absolute values were used. These results are dependent on the working distance, which changed between subjects; a longer working distance reduces task subtense and hence the amplitudes of eye or head movements required. To analyse the data without the influence of the working distance, eye and head movements were also analysed in terms of relative or normalised movements. To obtain this relative data, the absolute eye and head movements in terms of horizontal or vertical angles were divided by the angular subtense of the task at the individuals corresponding working distance.

All statistical analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). A mixed analysis of variance was used to identify interactions between different tasks and the refractive error groups. Furthermore, two-tailed Pearson correlations were applied for comparisons in reference to the refractive error and among the various movements.

Due to loss of pupil detection for tracking eye movements, it was not possible to obtain accurate eye tracker data for some subjects for some tasks. These data were excluded and therefore there are different numbers of subjects in some tasks.

5.4 Results

5.4.1 Working distance

The means of the working/reading distances used for each task by myopes and non-myopes are given in Table 5.1, which also includes working distances separated for men and women. Note the substantial standard deviations; the extreme values selected by different subjects in each task differed by a factor of nearly three. It is probable that the shorter working distances for women reflect their generally smaller stature but no data on height or arm length were recorded.

	Task 1 Reading screen	**Task 2 Reading book**	**Task 3 Handwriting**
Working distance myopes (mm), n = 14	615 ± 137	376 ± 64	394 ± 50
Working distance non-myopes (mm), n = 16	689 ± 102	414 ± 103	422 ± 62
Working distance males (mm), n = 18	693 ± 115	412 ± 82	401 ± 65
Working distance females (mm), n = 12	598 ± 118	373 ± 93	421 ± 46

Table 5.1 – Mean working distances (mm) and their standard deviations, separated for myopes and non-myopes as well as gender, when performing the three tasks.

A one-way, between-groups analysis of variance did not show a significant difference in mean working distances for reading (Tasks 1 and 2) or writing (Task 3) tasks between myopes and non-myopes (reading on screen: $F_{(1,28)} = 2.89$, $p = 0.10$; reading book: $F_{(1,28)} = 1.38$, $p = 0.25$; handwriting: $F_{(1,28)} = 1.84$, $p = 0.19$). A positive correlation between the distance for reading a book (Task 2) and refractive error (mean spherical equivalent) was found ($r = 0.41$, $n = 30$, $p = 0.025$), with myopes selecting shorter working distances (Figure 5.3). The correlations between refractive error (mean spherical equivalent) and reading distance for the reading screen task (Task 1) and the handwriting task (Task 3) were not significant (Task 1: r = 0.3, n = 30, p = 0.11; Task 3: r = 0.24, n = 30, p = 0.20). When calculating the correlations separately for men and women, only the correlation between refractive error and reading distance for Task 2 in men remained significant (r = 0.59, n = 18, p = 0.01). Remaining correlations between refractive error and working distances were not significant (men, Task 1: r = 0.35, n = 18, p = 0.16; men, Task 3: r = 0.37, n = 18, p = 0.13; women, Task 1: r = 0.41, n = 12, p = 0.19; women, Task 2: r = 0.22, n = 12, p = 0.49; women, Task 3: r = -0.12, n = 12, p = 0.71). All of these correlations are two-tailed Pearson product-moment correlations. In each refractive group, the working distance for Task 1 was significantly larger than for Tasks 2 and 3 (repeated measures analysis of variance: $F_{(2,58)} = 86.5$, $p < 0.001$; Bonferroni pairwise comparison between reading book and handwriting: p = 1.00, remaining combinations: $p < 0.001$). No significant correlations were found between the working distances and age.

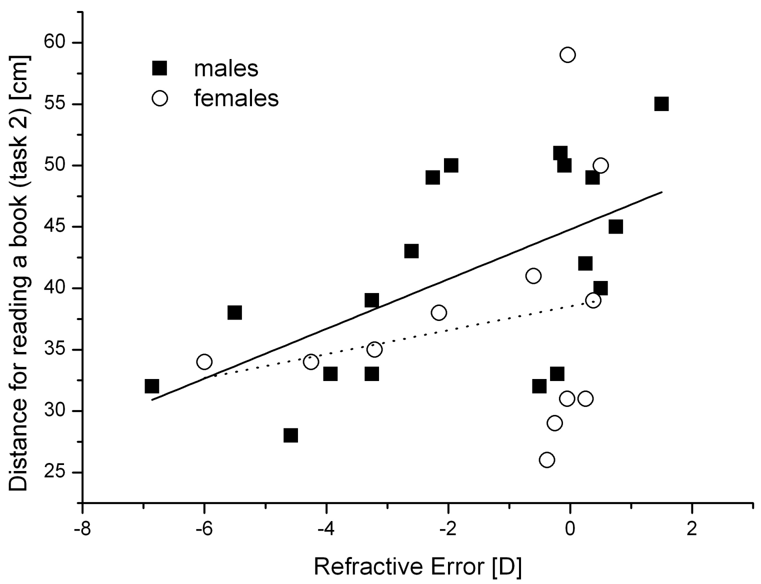

Figure 5.3 – Working distance for the reading book task (Task 2), as a function of refractive error for male and female subjects. The straight line fits are continuous line for males and broken line for females.

Table 5.2 shows the corresponding approximate mean horizontal and vertical extents of the printed text or written material in degrees of visual angle.

Task	1: Reading screen (degrees)		2: Reading book (degrees)		3: Handwriting (degrees)	
	Horizontal	**Vertical**	**Horizontal**	**Vertical**	**Horizontal**	**Vertical**
Myopes (n = 14)	16.4 ± 4.3	25.4 ± 6.7	26.2 ± 6.4	40.5 ± 9.7	28.1 ± 5.2	42.5 ± 7.1
Non-myopes (n = 16)	14.1 ± 2.9	22.0 ± 4.7	24.1 ± 6.3	37.5 ± 10.4	26.0 ± 7.6	39.5 ± 11.0

Table 5.2 – Mean chosen angular subtenses (degrees) and their standard deviations of printed or written material in the three tasks for all myopes and non-myopes. The subtenses for each subject and each task varied due to different working distances.

5.4.2 Absolute eye and head angles

In general, head movements were independent of eye movements (Figure 5.4 A); however, three subjects moved their head in a manner parallel to the eye movements (Figure 5.4 B).

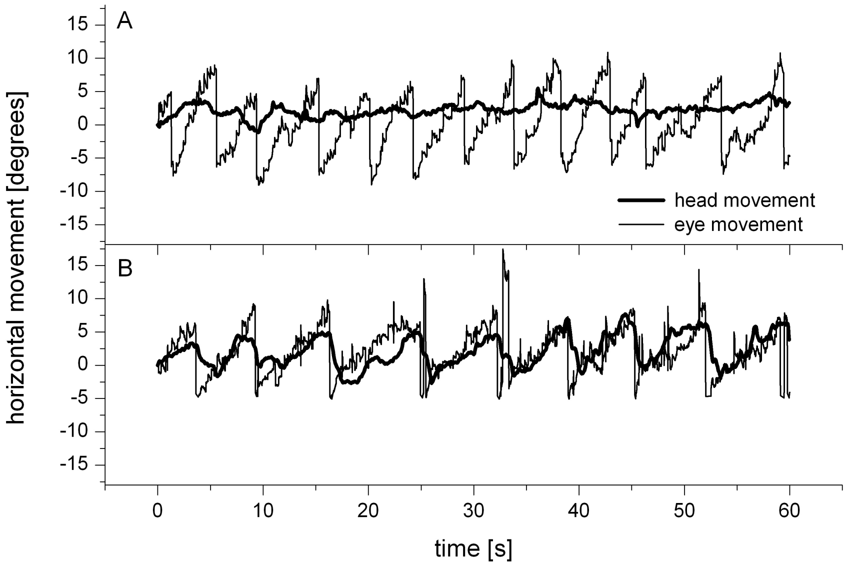

Figure 5.4 – Horizontal head and eye movements for two individual subjects (A and B) while performing the reading screen task (Task 1), showing different proportions of eye and head movements.

Figure 5.5 shows the values for absolute horizontal eye and head movements between the two refractive error groups for the three tasks separately. As expected, the horizontal movements were mainly achieved by eye movements. Negative head amplitudes indicate a head movement in the opposite direction to the eye movement.

A mixed model analysis of variance was used to explore differences of absolute eye and head movements (dependent variable) between the three tasks

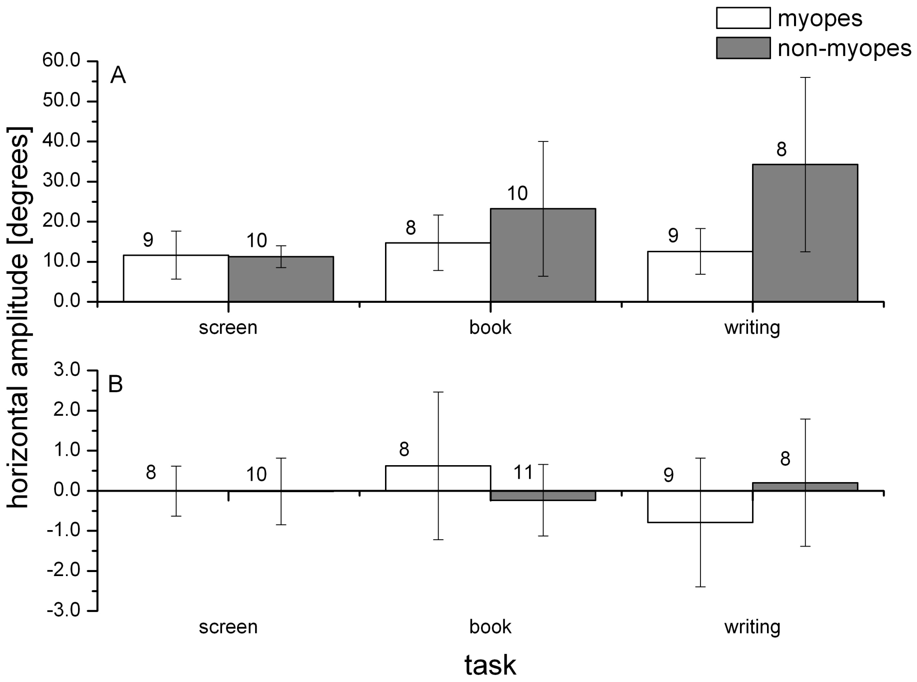

Figure 5.5 – Horizontal eye (A) and head (B) amplitudes in myopes and non-myopes for the three different tasks. Note the different scales on the y-axis for the two types of movement. Error bars show ± 1 standard deviation. Numbers on the bars represent the number of subjects included in the analysis.

in the two refractive error groups (independent variable). Horizontal eye and head amplitudes were significantly different among the three tasks ($F_{(2,26)} = 3.782$, $p = 0.03$ and $F_{(2,24)} = 7.914$, $p = 0.014$, for eye and head movements, respectively); however, the differences between myopes and non-myopes were not significant ($F_{(2,26)} = 2.787$, $p = 0.08$ and $F_{(2,24)} = 1.662$, $p = 0.222$, for eye and head movements, respectively).

In Figure 5.6, we present the data for the vertical range, indirectly indicating the speed of reading or writing, as all measurements were taken over a fixed time of one minute. Head movements were relatively more important in the vertical direction than in the horizontal direction. A mixed analysis of variance showed no significant differences in vertical movements among refractive error groups and tasks (among tasks $F_{(2,20)} = 2.651$, $p = 0.095$ and $F_{(2,50)} = 1.743$, $p = 0.$ 186, for eye and head movement, respectively; among tasks and refractive error groups $F_{(2,26)} = 0.154$, $p = 0.858$ and $F_{(2,50)} = 2.209$, $p = 0.136$, for eye and head movement, respectively).

The degree of refractive error, the horizontal amplitudes and vertical ranges of both the eye and head movements were compared in the whole study population using the Pearson correlation. No significant correlations were

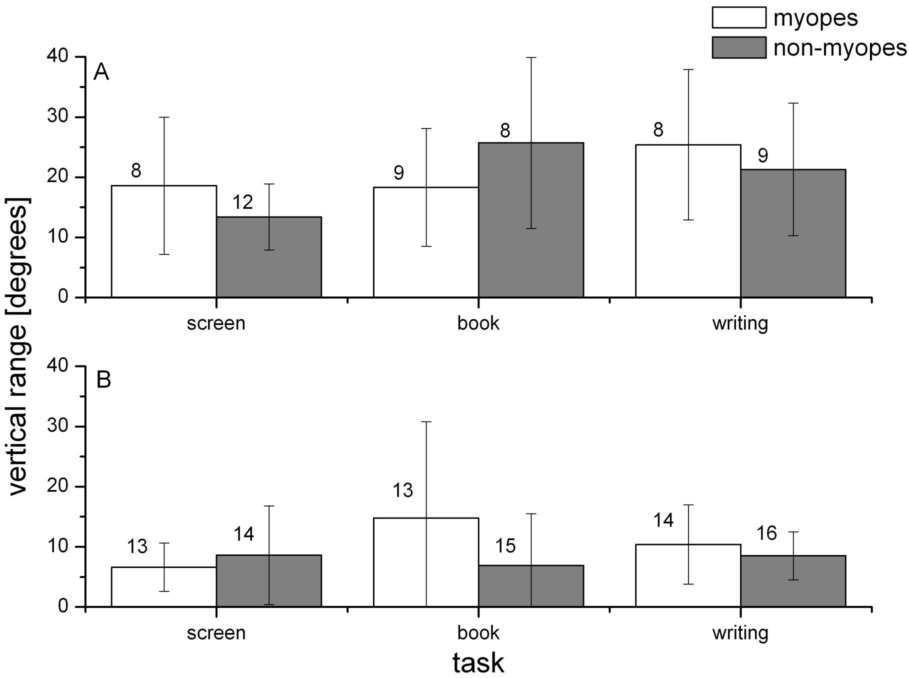

Figure 5.6 – Absolute vertical range in terms of angles in eye (A) and head (B) movements for three different tasks. Note different scales for the y-axis in each type of movement. Error bars show ± 1 standard deviation. Numbers on the bars represent the number of subjects included in the analysis.

found for horizontal (Task 1, reading screen: eye movements: r = -0.24, p = 0.32; head movements: r = -0.19, p = 0.45; Task 2, reading book: eye movements: 0.08, p = 0.75; head movements: r = -0.19, p = 0.45; Task 3, handwriting: eye movements: r = 0.39, p = 0.12; head movements: r = 0.27, p = 0.3) and vertical movements (Task 1, reading screen: eye movements: r = 0.26, p = 0.26; head: r = -0.05, p = 0.78; Task 2, reading book: eye movements: -0.37, p = 0.14; head movements: r = 0.27, p = 0.16; Task 3, handwriting: eye movements: r = -0.05, p = 0.86; head movements: r = 0.25, p = 0.19).

5.4.3 Analysis of data relative to working distance

As evident from the standard deviations in Table 5.1, the working distances varied markedly among individuals. As we wanted to examine natural postures for near tasks, we did not instruct the participants to sit at particular working distances; however, the working distance does have an impact on the amplitude of eye and head movements. For example, a longer distance would require smaller eye or head movements to overview the same text compared with those required at a closer distance. Therefore, analysis of the data was also performed when the data were normalised with reference to the angular dimensions of the area of printed text, which were dependent on the working distance. The relative amplitude of movements in terms of text subtense (both in terms of angles) is given for the three tasks for horizontal movements in Figure 5.7 and for vertical movements in Figure 5.8. Values below one indicate movements smaller than the angular extent of the text and values greater than one indicate movements larger than the text. All participants kept within the area of the printed text in horizontal and vertical directions, with the exception of the only hyperopic subject (mean spherical equivalent +1.50 D), who displayed a horizontal ratio of eye movements of 1.14 in the reading screen task and 1.09 in the handwriting task, indicating a horizontal movement wider than the printed text. This was felt to be unusual and therefore the eye and head movement recordings were repeated for this particular subject. Similar results were found and confirmed.

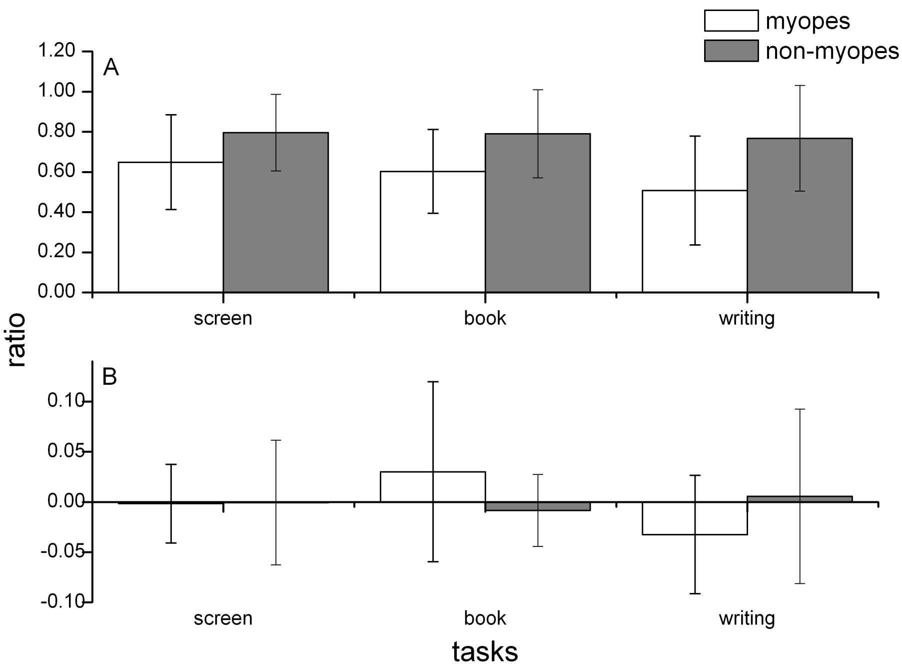

Figure 5.7 – Horizontal eye (A) and head (B) amplitudes relative to the horizontal angular extent of the text. Error bars show ± 1 standard deviation. Note difference in scales on the y-axis for the two types of movement. The number of subjects included in the analysis is the same as that given in Figure 5.4.

Horizontal scanning was achieved almost entirely by eye movements, whereas head movements played a greater role in the vertical direction. For both horizontal and vertical relative movements, a statistical comparison (mixed analysis of variance) revealed no significant differences between myopes

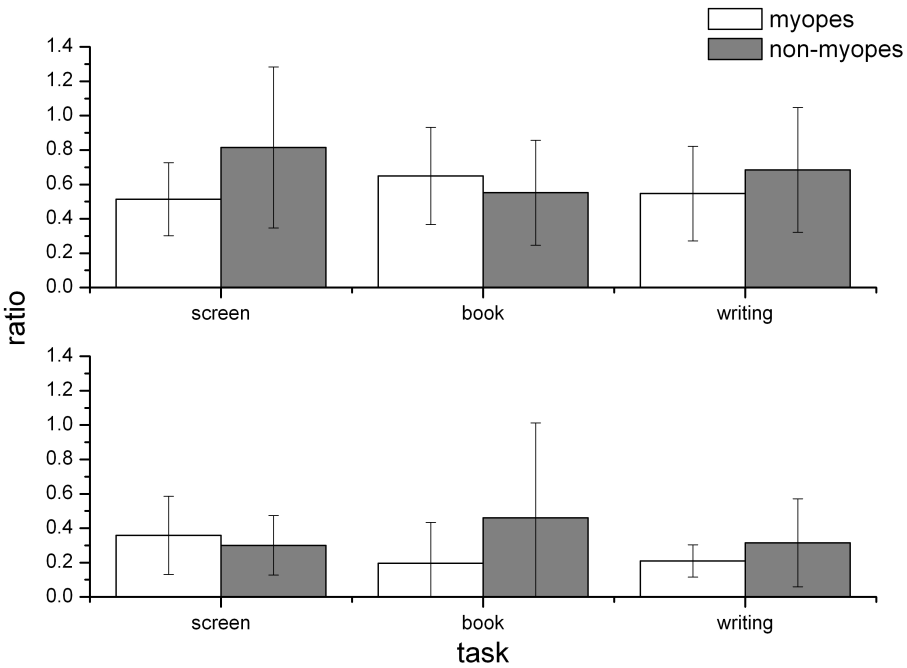

Figure 5.8 – Vertical eye (A) and head (B) ranges relative to the vertical extent of the text. Error bars show ± 1 standard deviation. Note difference in scales on the y-axis for the two types of movement. The number of subjects included in the analysis is the same as that given in Figure 5.5.

and non-myopes or among the three tasks.

No significant correlations (Pearson correlation) between spherical equivalent refractive error and relative horizontal (Task 1, reading screen: eye movements: r = 0.59, p = 0.81; head movements: r = -0.18, p = 0.47; Task 2, reading book: eye: 0.21, p = 0.4; head: r = -0.15, p = 0.54; Task 3, handwriting: eye movements: r = 0.36, p = 0.20; head movements: r = 0.34, p = 0.19) and vertical ranges (Task 1, reading screen: eye movements: r = 0.36, p = 0.11; head movements: r = 0.06, p = 0.76; Task 2, reading book: eye movements: -0.21, p = 0.41; head movements: r = 0.3, p = 0.13; Task 3, handwriting: eye movements: r = 0.01, p = 0.98; head movements: r = 0.34, p = 0.07) could be found for the whole study population.

5.5 Discussion

The results show a broadly similar pattern of eye and head movements in all the participants included in the study, irrespective of their refraction, although the amplitude of these movements varied considerably among individuals, due largely to their choice of different working distances. Eye movements were complemented by head movements in some individuals (Figure 5.4 B), thereby reducing the requirement for high amplitude eye movements for the reading and writing tasks; such individuals were found in both refractive groups. Head movements remained minimal in most other subjects (Figure 5.4 A). Previous research has shown that the propensity of individuals to move their heads during a task is specific for each person, with some individuals consistently demonstrating larger head movements than others (Fuller, 1992; Proudlock *et al.*, 2003; Proudlock and Gottlob, 2007).

All subjects tended to select a longer working distance when carrying out the simulated screen-based task (Task 1), rather than the hand-held, reading task (Task 2, Table 5.1). This difference is expected, because there is a general tendency to sit further away from a screen than the distance at which one would generally tend to hold paper to read or write. Working at a longer distance with the screen-based reading task has the advantage of reducing the overall subtense of the task and thus reducing the amplitude of the required eye movements while still leaving 12-point text legible. In contrast, the hand-held reading distance, like that for the writing task, depends partly on limb length rather than purely visual factors. The working distances given by Rah *et al.* (2001) for reading/studying (457 ± 178 mm) and computer/visual display unit (533 ± 152 mm) are comparable with the working distances measured in the present study (Table 5.1).

No statistically significant differences were found in mean working distances between the two refractive-error groups for each of the three tasks. There was a weak correlation between working distance and refractive error in the handheld reading task, with myopes tending to use shorter working distances. Further work is required to confirm this finding and to explore whether it is the cause or result of the development of myopia. The absence of any significant correlation between age and working distance suggests that, even for our oldest subjects (37 and 45 years), the results were not affected by the approach of presbyopia.

Eye and head movements are usually analysed when patients remain at a fixed distance from the task (Schaeffel *et al.*, 1999; Vasudevan and Ciuffreda, 2008; Sreenivasan *et al.*, 2009). The present study was carried out with the subjects doing near work at their habitual working distances. There was large variability among the individuals, making it likely that the relative analyses of eye and head movements are more sensitive than absolute data.

As expected, in the present study eye movements were always found to be larger than head movements. Proudlock and Gottlob (2007) state that typically the eyes overlook an area approximately 15 degrees in diameter without movements of the head. The head moves only in small intervals to bring the eyes back into the primary position (Oommen and Stahl, 2005). This is consistent with our results, especially for the reading screen task (Task 1), where the average horizontal text size was approximately 15 degrees (Table 2); the smallest range of horizontal head movements was found in this task (Figure 5.5 A). It is important to note that the head-mounted eye tracker could have an impact on the results, because wearing a 420 g helmet could reduce the amount of head movement. Although the movements might have been restricted compared with those made naturally during day-to-day activities, the presence of the head-mounted tracker is unlikely to have affected one refractive group more than the other.

The combined head and eye movements control the position of gaze adopted by the eyes; however, the mechanisms that control head and eye movements to obtain a particular gaze position remain unclear (Fuller, 1992; Oommen and Stahl, 2005; Proudlock and Gottlob, 2007). It has been suggested that the gaze position sustained by the eye is likely to be dependent on peripheral vision in addition to central visual quality (Oommen *et al.*, 2004; White *et al.*, 2008).

The absolute magnitudes of the horizontal eye movements varied among tasks, with writing (Task 3) tending to produce the largest amplitudes and reading on screen (Task 1), with its longer working distances, producing smaller amplitudes (Figure 5.5). Curiously, although the magnitude of eye movements changed with the task, the changes in head movements remained modest, which could be an effect of the helmet influencing the natural habits of head movements. This finding is consistent with previous results where participants were asked to read text on an A4 page (Proudlock *et al.*, 2003). This effect might be caused by prior knowledge of future gaze targets, because the text is visible in peripheral vision (Oommen *et al.*, 2004). The increase in the absolute amplitude of horizontal eye movements for the reading book and writing tasks (Tasks 2 and 3) was found to be linked to the angular subtense of each task. When the angular extent of the target was taken into account, the relative amplitude of the horizontal eye movements appeared to remain fairly constant across the three tasks (Figure 5.7 A).

Non-myopes showed slightly larger horizontal eye movements than myopes, even when the amplitudes were normalised in terms of the extent of the text or written material (Figure 5.7), although these differences were not statistically significant. Gaymard *et al.* (2000) found instantaneous increases in head movements when eye movements are restricted due to the onset of some diseases, indicating that the control of eye and head movements is rapidly interchangeable. Although our myopic subjects were corrected by soft contact lenses during the study, it is possible that some of them usually preferred to wear spectacles and that the restricted viewing range produced by their high-powered myopic spectacle lenses could have led to adaptational effects. Such adaptation would tend to reduce eye movements and increase head movements in these myopic individuals (Guillon *et al.*, 2000; Han *et al.*, 2003; Chu *et al.*, 2009). The adaptation is likely to be influenced by both peripheral refraction and the quality of vision in the periphery produced by the spectacle lenses worn by the patient. In turn, this adaptation can control the quality of peripheral vision and reduce the stress of the extraocular muscles on the globe during eye movements, perhaps reducing the stimulus for eye growth (Radhakrishnan and Charman, 2007). Spectacle lenses, which maintain peripheral visual quality, might reduce the adaptation in myopes (Tabernero *et al.*, 2009). Another factor is that in myopes contact lens wear stimulates greater accommodation and vergence during near work compared with spectacle wear.

Our subjects comprised university students and staff who were well accustomed to the everyday tasks of reading texts on computer screens or standard size pages of relatively modest angular subtense. Refraction-dependent differences might have been found with other, more challenging, visual tasks. One weakness of the study is that each of our tasks lasted only a short time. It remains possible that differences in behaviour with the refractive group might emerge if observations were to be continued over the much longer periods of near work that are involved in a normal working day.

5.6 Conclusion

The results of this study failed to demonstrate any major differences between head posture and eye movements of adult, university-based myopes and non-myopes when carrying out short periods of simulated everyday near work, and hence fail to support the hypothesis that such differences could be relevant to the development of myopia. It remains possible that even though the movements were similar, a weaker sclera in individuals at risk of developing myopia might result in the same forces from the extraocular muscles causing a greater change in the shape of the eyeball.

5.7 Remarks

For chapter 5 the data were collected by me and I analysed the data. The first draft of the manuscripts was written by me and I dealt with reviewers' comments along with my supervisors.

This chapter has been published: Hartwig, A., E. Gowen, W. N. Charman and H. Radhakrishnan (2011). Working distance and eye and head movements during near work in myopes and non-myopes. *Clin Exp Optom* **in press**.

Chapter 6

Binocular saccades in myopes and emmetropes

6.1 Abstract

Purpose: The present study aims compare saccadic eye movements between myopes and emmetropes as there is some evidence in the literature that eye movements could have an influence on refractive error development. Additionally, saccadic eye movement parameters were related to subjective refraction data and axial length measurements.

Methods: Horizontal eye movements of 28 participants (14 myopes and 14 emmetropes) were recorded using a head-mounted eye-tracker. To reduce the influence of head movements a chin rest was used. Fixation stimuli were presented on a computer monitor. Participants alternated their fixation between the two stimuli that were 20 degrees apart from each other immediately after they were aware that the target had changed.

Results: Durations of saccades, amplitudes, velocities and number of overshoots, undershoots and exact fixations were analysed. For all analysed parameters no significant differences were found between myopes and emmetropes. When analysing the whole study population none of the saccadic eye movement parameters were correlated with axial length or refractive error. When analysing myopes only there is a significant correlation between refractive error / axial length and peak velocity.

Conclusions: As saccadic eye movements appear to be similar in myopes and emmetropes there is no evidence that saccadic eye movements are involved in myopia development.

6.2 Introduction

The origins of the increase in the prevalence of myopia in many parts of the world remain elusive. While near work and peripheral refraction have been suggested as possible factors, it has, as yet, proved difficult to demonstrate this convincingly. This allows for the possibility that additional factors may influence myopia development and progression.

One factor that could contribute to refractive change is eye movement. The work of Adams and McBrien (1992), as well as that of Simensen and Thorud (1994), implied that myopia progression is not necessarily caused by accommodative demands and that some aspect of eye movements might be responsible for myopia development. Adams and McBrien (1992) studied a group of microscopists and Simensen and Thorud (1994) analysed myopia development and progression in textile workers. The microscopists (Adams and McBrien, 1992) looked at images that were placed nominally at infinity and the textile workers (Simensen and Thorud, 1994) inspected cloth for weaving errors at a distance of approximately 50 cm (see Goldschmidt, 2003 for illustration). These studies showed that, despite low accommodative demands, microscopists and textile workers tended to develop myopia and to progress at a rate higher than that usually reported in the literature (Saw *et al.*, 2002b for review; Jacobsen *et al.*, 2008; Walline *et al.*, 2008). These examples suggest that special types of posture or eye movements could contribute to myopisation. Eye movements during reading combined with lid pressure have been shown to cause corneal distortion, which could lead to myopisation (Zadnik *et al.*, 1999; Buehren *et al.*, 2005; Collins *et al.*, 2006a,b), although limited experimental studies by our group have so far failed to find any major differences in eye movements and posture in emmetropes and myopes when carrying out specific tasks (Hartwig *et al.*, 2011a,b).

We note that any study comparing existing myopes with emmetropes cannot differentiate between whether any differences in eye movement (or any other characteristic) are the cause of the myopia or are simply its effect. It might be, for example, that once the myopia had developed, the longer and weightier eyeball, associated perhaps with subtle differences in the attachment of the extraocular muscles or greater lid pressures, affected eye movements, possibly slowing them slightly. Nevertheless, demonstration of differences in the patterns of eye movements between different refractive groups would at least form a suggestive first step towards exploring the significance of such effects in relation to refractive development.

One earlier study (Müller *et al.*, 2003) has compared the saccadic eye movements of a group of myopes with those of emmetropes. The authors found differences which they felt were primarily associated with the wear of different types of correction by the myopes. Peak saccadic velocity was determined for amplitudes 7.5, 15, 22.5 and 30 degrees using electro-oculography electrodes. The myopic subjects were corrected by glasses or contact lenses. Their strongest finding was that myopes with higher prescriptions (myopia >6D) appeared to have slower peak saccadic velocities than emmetropes, particularly when corrected with contact lenses (Figure 6.1): myopes with corrections of less than 6 D did not differ from emmetropes. From the optical point of view, the result with high myopes is surprising, in that spectacle magnification considerations would lead to the expectation that spectacle-corrected myopes would have to make a smaller saccade and hence that their peak eye velocity would be lower than contact-lens corrected myopes, whose spectacle magnification effects are much smaller.

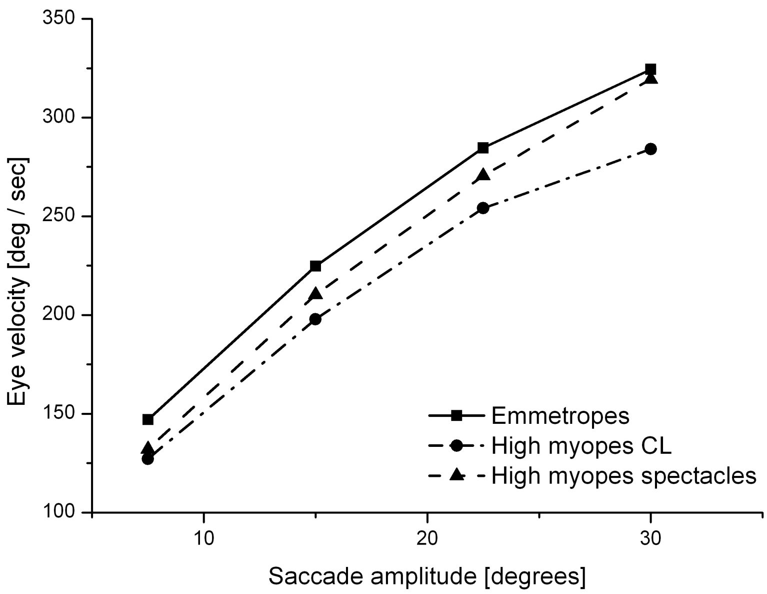

Figure 6.1 – Peak saccade velocity in emmetropes and myopes with refractions greater than 6 D corrected with either contact lenses (CL) or spectacles. (Data plotted from Table V of Müller *et al.*, 2003)

In the light of these suggestive but slightly perplexing results, which do not appear to have been followed up, the present study aimed to re-examine the characteristics of saccadic eye movements in myopes and emmetropes. In particular, we wished to determine whether saccadic performance depended systematically on the degree of myopia or axial length. We therefore included measurements of axial eye length and subjective refraction.

6.3 Methods

6.3.1 Participants

Twenty-eight (15 male and 13 female) participants were recruited. The age of the subjects ranged between 19 and 39 years (mean ± SD: 27.0 ± 4.7 years). All subjects were free of any ocular pathology and could achieve a visual acuity of 6/6 or better when corrected. Best-sphere corrections were in the range of -7.13 D to +0.50 D (mean: -1.55 ± 2.11 D). The group included 14 myopes (spherical equivalent power between -7.13 D and -0.88 D; mean: -3.10 ± 1.99 D) and 14 emmetropes (spherical equivalent power between -0.50 D and +0.50 D; mean: 0.01 ± 0.38 D). In all cases, astigmatism was less than 1.50 D. The mean age of the myopes and emmetropes was 27.6 ± 5.1 and 26.5 ± 4.33 years respectively. Myopic subjects were corrected with habitually worn soft-contact lenses, because spectacles induced additional reflections that did not allow precise eye tracking. The study followed the tenets of the Declaration of Helsinki and written informed consent was obtained from all participants after the nature of the study and possible consequences of the study had been explained. The project protocol was approved by the Senate Committee on the Ethics of Research on Human Beings of the University of Manchester.

6.3.2 Stimuli and procedure

Eye movements were recorded while the participants alternated their binocular fixation between two crosses that were horizontally separated by 20 degrees and vertically on the same level. Head movements were stabilised using a chinrest. The crosses subtended 0.02 degrees horizontally and vertically and were shown alternately for two seconds each on a monitor at a distance of 55 cm from the corneal plane of the subject. Participants were instructed to refixate immediately they were aware that the target had changed, so that the horizontal eye movement record approximated to a square wave of a four second-period and a ten degree amplitude. Each target was presented eight times, which resulted in 15 eye movements between the two targets.

Note from Figure 6.2 that the nature of the eye turn made in each fixation differed between the two eyes, and that it depended slightly upon the pupillary distance (PD). With a PD of 65 mm the left eye had a left turn $\theta_1 = 6.5$ degrees when fixating target A and a right turn $\theta_2 = 12.9$ degrees when fixating target B. The eye therefore had to turn through 19.4 degrees, when altering between the two targets. Since the range of PDs in our subjects was such that differences in the necessary rotation angles were minor, we did not correct for this effect but assumed in the calibration process that 20 degrees of eye rotation was required for each fixational movement.

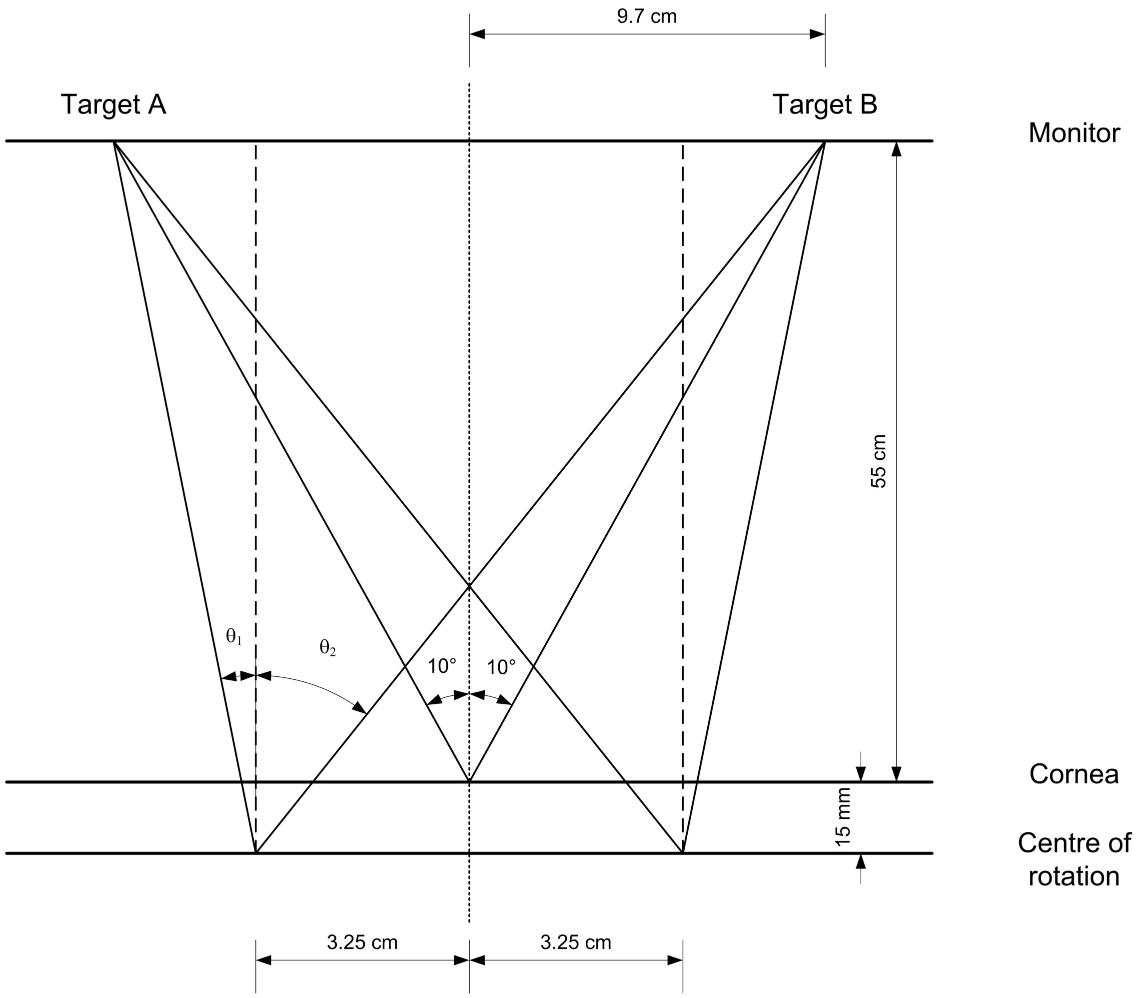

Figure 6.2 – Angle of required eye turn θ for two targets (A and B), which are 20 degrees apart from each other. Here the PD is 6.5 cm.

An Eye Link II (SR Research Ltd., Mississauga, Canada) was used in conjunction with Motion Monitor software (Innovative Sports Training Inc., Chicago, USA) to monitor the saccades. Eye movements were recorded binocularly at 500 Hz in horizontal and vertical planes using two video-based cameras mounted on a helmet. The total weight of the helmet and associated head-mounted equipment was 420 g. The cameras were set for pupil tracking mode. The datasets were calibrated using a Matlab script. After the subjects had been familiarised with the task, two complete datasets of movements were recorded, the first set being used for calibration, the second for analysis. Checks showed no significant differences between the calibrations produced by the two datasets.

A LenStar LS 900 (Haag Streit, Koeniz, Switzerland) was used to measure the axial length of the right eye. The device has been found to be repeatable and valid (Buckhurst *et al.*, 2009; Cruysberg *et al.*, 2010; Holzer *et al.*, 2009; Rohrer *et al.*, 2009; O'Donnell *et al.*, 2011). Five readings were taken for each participant and the internal software calculated the mean of five readings automatically. This mean was used for further analysis.

To determine the refractive error, a subjective refraction was performed on all subjects to an accuracy of ±0.25 DS and ±0.25 DC. The cylindrical component was found, if existent, using a cross-cylinder. To refine the spherical component at the end of the routine the duochrome test was used. For further analysis, the sphero-cylindrical result was converted into a spherical equivalent.

6.3.3 Data analysis

Figure 6.3 represents a typical eye movement recording. For some fixational movements there is undershooting or overshooting of the primary saccade, which is then followed by a small corrective movement. In the right-eye case illustrated, undershoots are more common during abduction (rightward fixation change) than adduction (leftward eye movement).

Only the horizontal data from right eyes were analysed. A customised Matlab code (The Mathworks Inc., Natick, MA, USA) was used to calculate the following parameters for each participant:

(i) Mean durations of rightward, leftward and all main saccades

(ii) Mean amplitudes of rightward, leftward and all main saccades

(iii) Mean peak velocities of rightward, leftward and all main saccades

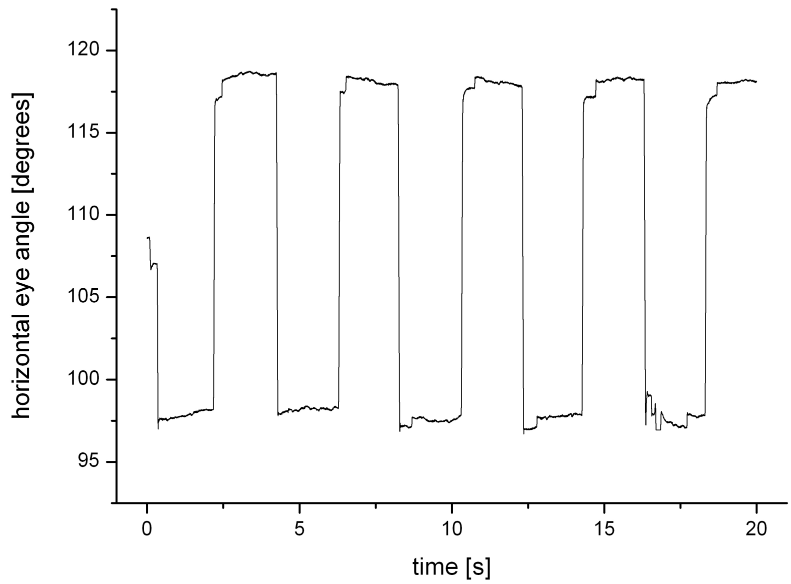

Figure 6.3 – Example of horizontal right eye angle data of one subject (AHT). The lower parts of the trace correspond to leftward fixation (adduction), the upper parts to rightward fixation (abduction). The angular scale is relative only.

(iv) Numbers of undershoots, overshoots and exact fixations of main saccades as a fraction of the total number of saccades

The starting point of the main saccade was taken as the instant at which the eye movement started, the end point as the instant when either a secondary eye movement with markedly different temporal characteristic commenced (i.e. a corrective movement) or exact fixation was directly established at the end of the main saccade.

All statistical analysis was performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). Between groups analysis of variance was used to compare differences between myopes and emmetropes. Differences in saccades to the right and left fixation target were analysed using repeated-measures analysis of variance. Mixed analysis of variance was used to check for interactions between repeats and refractive error groups. Two-tailed Pearson correlations were applied for comparisons in reference to refractive error and axial length.

6.4 Results

6.4.1 Characteristics of main saccades

As can be seen from Table 6.1, any differences between the two refractive groups were minor and failed to reach statistical significance, particularly when multiple testing was taken into account.

Characteristics	**Emmetropes**	**Myopes**	**Probability**
Rightward abduction duration (seconds)	0.096 ± 0.038	0.119 ± 0.031	p = 0.09
Leftward adduction duration (seconds)	0.106 ± 0.050	0.097 ± 0.040	p = 0.61
All durations (seconds)	0.095 ± 0.037	0.102 ± 0.034	p = 0.61
Rightward amplitude (degrees)	18.7 ± 1.9	19.9 ± 1.1	p = 0.07
Leftward amplitude (degrees)	18.6 ± 2.3	19.7 ± 1.2	p = 0.14
All amplitudes (degrees)	18.7 ± 2.5	19.7 ± 1.3	p = 0.21
Rightward peak velocity (deg/sec)	470 ± 72	452 ± 69	p = 0.50
Leftward peak velocity (deg/sec)	468 ± 64	451 ± 51	p = 0.48
All peak velocities (deg/sec)	473 ± 69	452 ± 45	p = 0.34

Table 6.1 – Main characteristics of saccades given as mean ± standard deviation separated for myopes and emmetropes. The column probability is for the comparison between myopes and emmetropes.

As can be seen from Table 6.1, the duration for the main saccades was 0.095 ± 0.037 seconds in emmetropes and 0.102 ± 0.034 seconds in myopes. No statistical significant difference was found between the two refractive error groups (all durations: $F_{(1,25)} = 0.26$, $p = 0.61$).

The myopic group had slightly higher mean amplitudes (all amplitudes: 19.7 ± 1.3 degrees, corresponding to a gain of 0.98 ± 0.06) of horizontal main saccades than emmetropes (all amplitudes: 18.7 ± 2.5 degrees, gain 0.94 ± 0.13). However, the difference in amplitude was not statistically significant (between groups analysis of variance, all amplitudes: $F_{(1,26)} = 1.6$, $p = 0.21$). In the whole study population the amplitude was significantly less than 20 degrees (one sample t-test, $p < 0.05$), the difference being accounted for by the small corrective undershoots and overshoots.

The peak velocity while changing fixation between the two fixation targets was similar in myopes (452 ± 45 deg/sec) and emmetropes (473 ± 69 deg/sec). The statistical comparison between myopes and emmetropes was not significant (between groups analysis of variance: $F_{(1,26)} = 0.94$, $p = 0.34$).

For the three parameters (peak velocity, amplitude and duration of saccades) no significant differences were found between abduction and adduction movement when using a mixed analysis of variance, where right- and leftwards movements were the dependent variable and the two refractive error groups were the independent variable (duration: $F_{(1,25)} = 2.18$, $p = 0.15$; amplitude: $F_{(1,25)} = 0.02$, $p = 0.89$; peak velocity: $F_{(1,25)} = 0.03$, $p = 0.87$).

6.4.2 Proportions of corrective movements

Counts of the numbers of undershoots and overshoots suggested that emmetropes had more undershoots than myopes, as would be expected on the basis of their lower main saccade amplitudes (Table 6.2). However, no statistically-significant differences were found between myopes and emmetropes for any of the categories in Table 6.2 (between groups analysis of variance, $p > 0.05$).

	Emmetropes	**Myopes**	**Probability**
Undershoots left	0.69 ± 0.23	0.49 ± 0.28	p = 0.06
Overshoots left	0.09 ± 0.11	0.18 ± 0.25	p = 0.27
Exact fixation left	0.22 ± 0.18	0.33 ± 0.24	p = 0.18
Undershoots right	0.60 ± 0.26	0.53 ± 0.35	p = 0.53
Overshoots right	0.11 ± 0.13	0.06 ± 0.12	p = 0.34
Exact fixation right	0.29 ± 0.25	0.41 ± 0.31	p = 0.28

Table 6.2 – Ratios presented as mean ± standard deviation for undershooting, overshooting and exact fixation separated for the left and right fixation target.

When emmetropes and myopes were analysed together, correlations between refractive error or axial length and saccadic parameters such as duration, amplitude and maximum velocity were not significant ($p > 0.05$). Analysing myopes and emmetropes separately gave no significant correlations for emmetropes but the correlations of peak velocity in myopes with refractive error and axial length were marginally significant at the $p = 0.05$ level (Pearson product moment correlation: axial length: $r = 0.55$, $p = 0.04$; refractive error: $r = -0.65$, $p = 0.01$; Figure 6.4). The correlations for duration and amplitude separated for myopes and emmetropes were non-significant ($p > 0.05$).

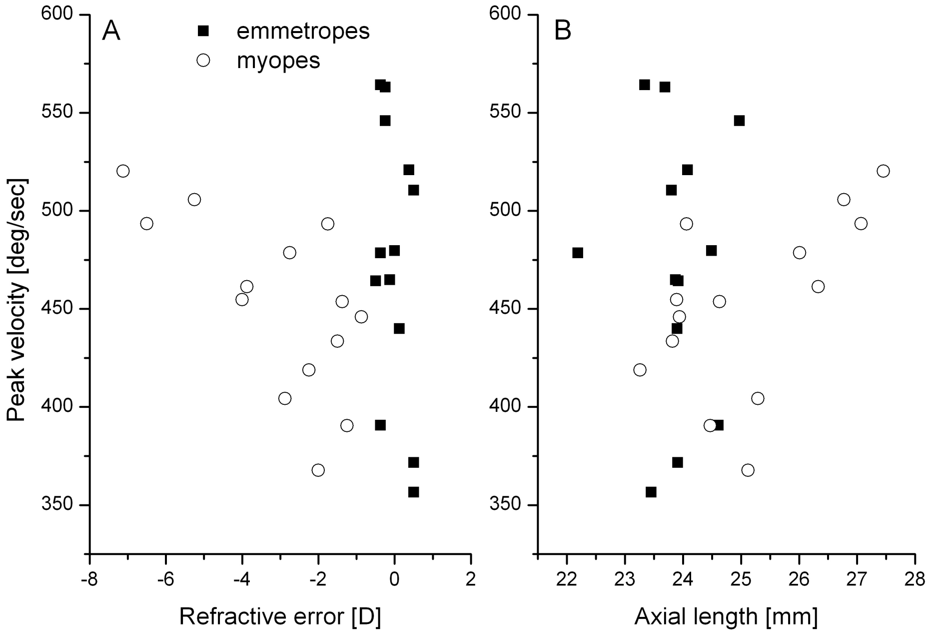

Figure 6.4 – Saccadic peak velocity versus refractive error (A) and versus axial length (B).

6.5 Discussion

The present study evaluated differences in saccadic eye movements between groups of myopes and emmetropes using a predictive saccade paradigm. When analysing the whole study population no significant differences were found between the two refractive groups, nor were any of the saccadic parameters correlated with axial length, which ranged quite widely, from 22.2 to 27.5 mm, or mean spherical refractive error (range -7.13 D to +0.50 D). Thus the results offered no support for the hypothesis that the generally greater length of the myopic eye or any other difference affected saccadic velocities or, indirectly, that saccadic differences might be involved in myopisation. There is only little evidence that peak velocity is associate with axial length and refractive error in myopes.

The data, obtained for 20 degrees saccades, do not directly support the results of Müller *et al.* (2003), who suggested that contact lens corrected myopes had saccades of significantly lower peak velocity than emmetropes for a saccade amplitude of 22.5 degrees (Students t-test on their data, p = 0.024 for all myopes; not significant for myopes <6 D; p = 0.001 for myopes >6 D). We note, however, that Müller and his colleagues took p = 0.05 as their level of significance, in spite of multiple testing (36 comparisons). Thus it would appear that it is likely that their result was only significant for the higher myopes. Our subjects included only 5 myopes with corrections >6 D, so it may be that there are differences for very high levels of myopia which we could not detect through a lack of suitable subjects. We note, however, that the peak velocities recorded by Müller *et al.* (2003) using their electro-oculagraphy technique were substantially lower than ours at around (280 deg/sec for a 22.5 degrees saccade compared with our value of about 460 deg/sec for a 20 degrees saccade) so that some doubts remain about the validity of their findings.

In general the characteristics of the saccades listed in Table 6.1 are similar to those found elsewhere in the literature for saccades of similar amplitude. We found a greater prevalence of hypometria (undershooting) than hypermetria (overshooting) (Weber and Daroff, 1971; Collewijn *et al.*, 1988). The mean undershoot of about 0.8 degrees is similar to that found by Collewijn *et al.* (1988) and Bötzel *et al.* (1993) under similar experimental conditions. Henson (1978) reasoned that undershooting keeps the visual target at the same side of the fovea, which might lead to more precision and less latency for the corrective saccade. The peak velocities found in the present study (about 460 deg/sec) are slightly faster than earlier findings for 20 degrees saccades. For example Boghen *et al.* (1974) found a peak velocity of 375 deg/sec and Baloh *et al.* (1975) found a peak velocity of 420 deg/sec, although Bahill *et al.* (1981) found a much quicker peak velocity of 657 deg/sec.

Overall, based on short term observations the present study does not support the hypothesis that the characteristics of saccades between two fixed points are markedly different in existing myopes as compared to emmetropes, at least for the range of myopia and axial lengths studied. This makes it unlikely that saccadic velocity, as such, could play any role in myopisation. It still remains possible that the mixture of head movements, saccades and other eye movements used when carrying out a more complex visual task by emmetropes who were at risk of developing myopia might differ from those of those emmetropes whose refractions remained stable. However, we have, as yet, found it difficult to demonstrate differences in head and eye movements between emmetropes and existing myopes when carrying out simple reading and writing tasks (Hartwig *et al.*, 2011a,b).

The present investigation studied regular binocular saccades between targets separated by 20 degrees, placed symmetrically about the midline. It might be that differences in saccadic characteristics could have emerged had a different experimental paradigm been used, involving for example the need for non-predictable saccades of different amplitudes at varied intervals of time, between targets which were not necessarily symmetrically placed about the midline. It may be too that if the saccadic task was continued over longer periods of time, as in real-life situations, greater differences might emerge. Saccadic characteristics might be similar but perhaps the myopic or potentially myopic eyeball is more susceptible to the external stresses associated with eye movement, thus causing small changes in axial length and refraction after lengthy sequences of movement. Such possibilities deserve further investigation.

To summarise, our present results show that saccadic eye movements of the same amplitude are similar in emmetropes and existing myopes and hence offer no support for the hypothesis that differences in saccadic characteristics are implicated in myopisation.

Acknowledgment
The authors acknowledge the assisstance of Haag-Streit UK Ltd. who provided the LenStar for the duration of this work.

6.6 Remarks

For chapter 6 the data were collected by me and I analysed the data. The first draft of the manuscripts was written by me.

It is intended to submit this manuscript soon.

Chapter 7

Analysis of head position for near tasks in myopes and emmetropes as a factor in myopia

7.1 Abstract

Purpose: The aim of the study was to compare head posture in young, adult emmetropes and corrected myopes during a reading task.

Methods: Thirty-two (32) myopes (mean spherical equivalent: -3.46 ± 2.35 D) and 22 emmetropes (mean spherical equivalent: -0.03 ± 0.36 D) participated in the study. Of the myopes, 16 were progressing (rate of progression $\geqslant$ 0.5 D over the previous 2 years), 12 were stable (changes of -0.25 D or less over 2 years) and four could not be classified. Seated subjects were asked to read a text binocularly in their habitual posture. To measure head posture, two simultaneous images were recorded from different directions. In a separate study with the same subjects and conditions, a motion monitor was used to track head posture for one minute. The habitual reading distance was measured in both studies, together with the stereoscopic acuity and fixation disparity for each subject.

Results: The results of the photographic study showed no significant differences in head posture or reading distance between the myopic and emmetropic groups ($p > 0.05$) but there was some evidence that downward pitch angles were greater in progressing myopes than in non-progressing

myopes (p = 0.03). No correlations were observed between the binocular parameters and head posture. Reading distances were systematically shorter with the helmet-mounted eye tracker and it was concluded that posture was affected by the weight of the equipment. With this reservation, it appeared that the rate of change of downward pitch angle over the one-minute recording session increased with the subject's rate of myopia progression (correlation between myopia progression and slope of pitch: r = -0.69, p = 0.001), implying a greater reliance on head movements when reading down a page.

Conclusions: Overall, while no differences in mean head posture were found between myopes and emmetropes, there was some evidence that head posture and movement during reading may differ in progressing myopes.

7.2 Introduction

In recent decades the prevalence of myopia has increased markedly, particularly in some Asian countries (e.g. Saw, 2003; Morgan and Rose, 2005). Genetic factors cannot be responsible for such a rapid change, so that factors such as visual experience, lifestyle and diet after birth must be involved (Mutti, 2010). If the main cause or causes of myopization could be identified, some form of intervention to reduce the extent of the myopic shift might be possible. However, in spite of a broad range of human and animal studies, the nature of the presumed myopization processes remains controversial.

One possible factor emphasised by early workers was posture. For example, Donders (1864, p. 419) remarks *"A stooping position was also mentioned as a promoting cause of myopia . . . "* and he recommends (p. 429) *". . . in writing to use a high and sloping desk. To the last I attach much importance. Rectilinear drawing on a horizontal surface is highly injurious to myopes."* Posture is rarely mentioned by more recent researchers, although Mohan *et al.* (1988) and Marumoto *et al.* (1999) found that head posture was one factor which correlated with myopia and Charman (2004a) suggested that the conflicting accommodation demands arising with pronounced head turn at near might cause myopic shifts. Duke-Elder and Abrams (1970) and Curtin (1985) briefly review relevant earlier work.

In spite of the current relative unpopularity of the hypothesis that posture plays a role in myopization, a few studies (Zylbermann *et al.*, 1993; Simensen and Thorud, 1994; McBrien and Adams, 1997; Collins *et al.*, 2006a) provide evidence that it might be at least a contributory factor. Each of these earlier studies shows that there is a high prevalence of myopia in an occupational group carrying out a near-vision task with particular postural requirements. Additionally, several published abstracts explore possible links between working distances and ametropia (Haro *et al.*, 2000; Drobe *et al.*, 2007, 2008).

Zylbermann *et al.* (1993) found that the prevalence of myopia in male students from Orthodox Jewish schools was significantly higher than in girls or male students from non-Orthodox Jewish schools. The Orthodox schools were characterised by a special procedure of reading, where boys swayed, bending back and forward for up to 16 hours a day while reading texts with small print. Simensen and Thorud (1994) looked at textile workers who were responsible for locating and repairing flaws in a moving belt of fabric as it moved steadily past the work station. The plane of the fabric was at about 45 degrees to the horizontal, with the fabric moving in the vertical direction: the workers leant forwards to carry out their task (see Goldschmidt, 2003 for illustration). Simensen and Thorud (1994) found a correlation between axial myopia development and the number of years of work in this occupation. Interestingly, accommodative demands were modest (around 2 D or less) suggesting the possibility that high levels of accommodation are not required for task-related myopization (e.g. Rosenfield and Gilmartin, 1998; O'Leary and Allen, 2001; Walker and Mutti, 2002; He *et al.*, 2005; Radhakrishnan *et al.*, 2007; Charman and Radhakrishnan, 2009). In a group of clinical microscopists, Adams and McBrien (1992) and McBrien and Adams (1997) found a high myopia prevalence of 71%. Additionally, in comparison to the general population, the microscopists showed an increased incidence and progression of myopia after they started work. The microscopists were described as using high and low-magnification binocular microscopes for at least 20 hours a week: such microscopes typically have eyepiece tubes inclined at angles between 20 degrees and 45 degrees to the horizontal plane, so that the microscopists were presumably seated at laboratory benches and were leaning forward to carry out their work. The effect of accommodation was probably minimal, because the image through the microscopes was nominally placed at infinity (although see Hennessy (1975), Richards (1976), and Wesner and Miller (1986), who show that microscopists may prefer to adjust the focus to a slightly myopic value matching their individual instrument myopia). Proximal accommodation might also have had an influence (Heath, 1956; Charman, 2008). Collins *et al.* (2006a) have recently suggested, on the basis of practical studies, that corneal distortions associated with eyelid pressure during visual microscopy and other near tasks cause a degradation of retinal image quality which leads to the myopization observed by McBrien and Adams (1997), the exact effects being dependent on the palpebral aperture and the pattern of eye movements associated with the near task, these being linked in part to posture.

Overall, these studies may suggest that task-related postures adopted by the individuals as described in the preceding paragraphs might have an impact on myopia development and progression. We note that it has alternatively been suggested that the increased prevalence of myopia in these occupational groups is due to their increased hours of near-work. However, several studies have failed to demonstrate any significant relationship between near-work hours and myopia development (Mutti *et al.*, 2002; Saw *et al.*, 2006; Ip *et al.*, 2008c). Thus, given that the accommodation demand with some of the tasks is low, it remains plausible that it is the posture used for the task, rather than the task duration or accommodation required, that leads to myopia development in these occupational groups.

To our knowledge, little previous work has been carried out on head posture and its correlation with refractive error. Mohan *et al.* (1988) looked at head positions when reading, in a study analysing environmental factors that could influence myopization. They analysed head posture only in terms of the angle the head was bent forward for a maximum reading distance of 50 cm and found that the forward (downward) head bend, or pitch angle, of myopes without a family history of myopia was significantly greater than that of myopes with a family history of myopia or non-myopes with or without a family history of myopia. Marumoto *et al.* (1999) claimed that young teenage myopes used both shorter working distances and greater head tilts than age-matched emmetropes performing the same table-top writing task, although it does not appear that they actually refracted their subjects, who wore no optical correction when carrying out the task. Additional evidence for the possible influence of head posture on myopization comes from an animal study, showing that particular postural positions could cause experimental myopia in rabbits (Mohan *et al.*, 1977).

The aim of the present study was to compare in more detail head postures for a near-vision reading task in myopes and emmetropes, the main hypothesis under test being that myopes might adopt a posture with greater forward head tilt. To monitor head posture, two alternative methods were used: photography from two angles and a head-mounted eye-tracker that also recorded head position data. Head-posture data were compared with data for refractive error, state of binocular vision and rate of progression in the myopes.

7.3 Methods

The study followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants after the nature of the study and possible consequences had been explained. The project protocol was approved by the Senate Committee on the Ethics of Research on Human Beings of the University of Manchester.

Fifty-four subjects (20 male and 34 female) were recruited. The age of the subjects ranged between 19 and 38 years. All subjects were free of any ocular pathology and could achieve a visual acuity of 6/6 partially (i.e. 6/6-2) or better when corrected.

Subjective refraction was performed to an accuracy of ±0.25 DS and ±0.25 DC to obtain maximum plus giving best visual acuity. The cylindrical component, if existent, was found using a cross-cylinder. To refine the spherical component at the end of the routine, the duochrome test was used. For further analysis the spherocylindrical results were converted into mean spherical equivalents. Fixation disparity was measured using the Mallet test for distance and for near vision. To measure quality of binocular vision, a TNO test for stereopsis was utilised.

Spherical equivalent was in the range of -9.63 D to +0.50 D (mean: -2.06 ± 2.48 D; median -1.38 D). The group included 32 myopes (mean spherical equivalent correction between -9.63 D and -0.63 D; mean: -3.46 ± 2.35 D; median -2.63 D) and 22 emmetropes (mean spherical equivalent correction between -0.50 D and +0.50 D; mean: -0.03 ± 0.36 D, median -0.19 D). The mean ages of the myopic and emmetropic groups were 25.3 ± 5.5 years and 24.5 ± 4.5 years respectively. In all cases, astigmatism was equal to or less than 1.50 DC. The gender distribution was as follows: in the myopic group there were eleven males and 21 females; in the emmetropic group there were nine males and 13 females. For some analyses myopes were grouped as progressing and non-progressing myopes. Therefore myopes were asked by how much their myopia progressed during the last two years. Myopes were classified as "progressing" when their myopia had increased by 0.50 D or more during the last two years. The myopic group contained 16 (57%) progressing myopes and twelve (43%) non-progressing myopes. The myopia progression ranged from 0.50 D to 2.50 D during the last two years. Four myopes had their correction for less than two years and therefore were not considered for comparisons between progressing and non-progressing myopes. The age of the progressing myopes ranged from 19 to 36 (mean: 24.9 ± 5.6; median 22.5 years). The non-progressing myopes were between 19 and 38 years old (mean: 27.5 ± 5.1; median 28 years). The refractive error (mean spherical equivalent) of the progressing myopes was between -9.63 and -1.38 D (mean: -4.02 ± 2.22 D; median -3.63 D). In the non-progressing group the refractive error (mean spherical equivalent) ranged between -7.63 and -1.38 D (mean: -3.56 ± 2.45 D; median -2.63 D).

Two web cameras taking simultaneous photographs were used to monitor head position. One picture was taken from the side to record pitch and the second picture gave a frontal view to record roll (Figure 7.1). To aid accurate analysis of the pictures, high-contrast linear targets were attached to the subjects forehead and to the subjects temple, a grid placed behind the participants being used as reference. The targets were aligned with the background when patients were in primary gaze position. The head angles were measured using the Angle tool of Image J 1.41o software (National Institutes of Health, USA).

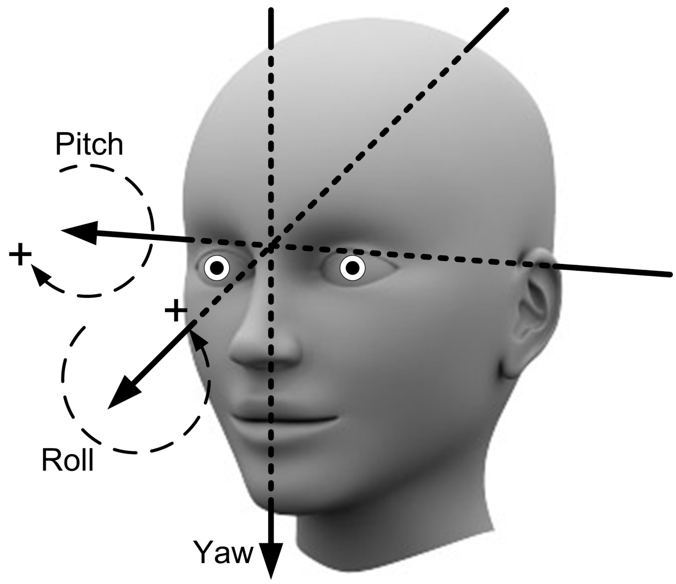

Figure 7.1 – Axes of recordings and sign convention shown by dashed lines: Yaw motions around the z (vertical) axis, pitch motion around the horizontal x axis and roll motion around the horizontal y axis.

Data on head positions were also acquired with an Eye Link II eye-tracker (SR Research Ltd., Mississauga, Canada), used in conjunction with Motion

Monitor software (Innovative Sports Training Inc., Chicago, USA) and motion sensors (Polhemus, Colchester, USA). Participants wore a helmet that contained the Polhemus sensor. The total weight of the helmet and head-mounted equipment was 420 g. The Polhemus sensor recorded three-dimensional head movements at 120 Hz. The Polhemus receiver was placed on a table at approximately 60 cm in front of the subject and where possible metal objects in the near environment were removed to minimise interference. Head movements were recorded in terms of yaw, pitch and roll motions (Figure 7.1) for 1 minute. As the Polhemus sensors were linked to the eye-tracker, which was the main instrument, we will refer to eye-tracker data, even though eye movements were not recorded.

Image and eye-tracker data were obtained separately in two experiments. However, the procedure and subjects for each experiment were identical. The order in which the two measurement techniques were used on individual subjects was quasi-random. Participants sat on an office chair (chair height and position were not adjustable) and, after positioning themselves comfortably, were asked to read aloud a hand-held text (a part of the novel 'The Railway Children' printed on a portrait A4 page, Arial 12 pt, 1.5 lines spacing) while their head posture was recorded. In both situations (image and eye tracker) subjects were asked to maintain their habitual reading position: the chosen reading distance between corneal vertex and the hand-held text was measured manually using a meter-ruler. Myopic subjects wore their normal spectacle or contact lens correction for the photos. For the eyetracker recording, participants inserted their habitually-worn contact lenses.

7.3.1 Data analysis

Head-position data from the photographs and eye-tracker were analysed in terms of roll and pitch angles (Figure 7.1). Yaw values were not analysed in the present study, since some subjects turned their heads regularly to follow the lines of text, rather than using eye movements, so that it was not possible to define a meaningful single yaw angle. The eye-tracker recorded head-position data for one minute. Rather than averaging the angles over the full minute of recording to obtain representative values for the roll and pitch angles, each angle was taken as its mean value averaged over one second, beginning five seconds after the recording started. In the photographic method, the two images were also recorded about five seconds after the participants started to read the text, so that the time at which the estimates of typical roll and pitch angles were made, with respect to the start of the reading session, was similar in both experiments. At the five-second point most subjects were still reading the first or second line of the text at the top of the A4 page.

It was observed from the eye-tracker recordings that whereas roll angles were small and relatively stable throughout the recording session, some subjects gradually changed their pitch angles as they read down successive lines of the page of text, i.e. they used head as well as eye movements. Figure 7.2 shows an example of this behaviour: note the periodic irregularities as successive lines were read. The slope of the linear regression fit to pitch angle against time over the one minute recording period was used to characterise this progressive change in pitch angle.

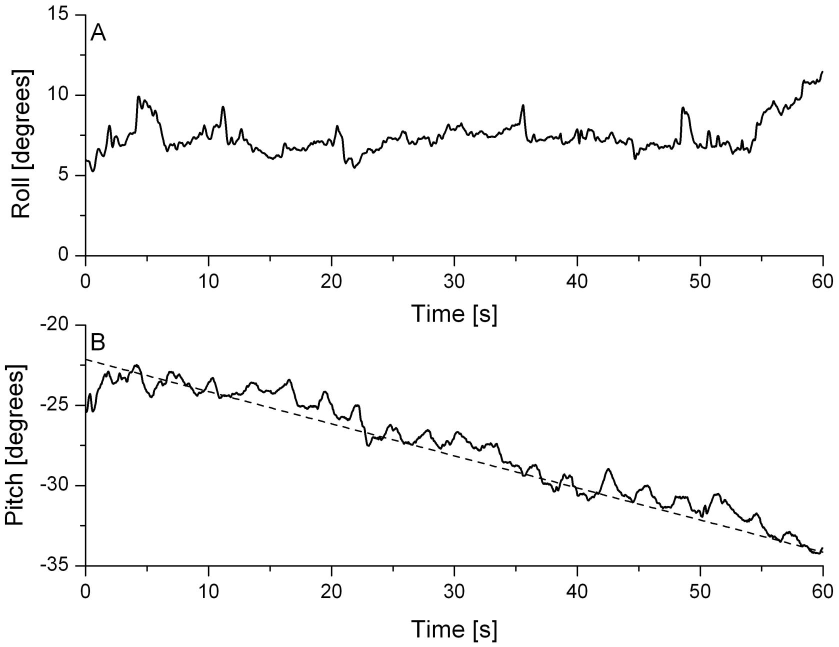

Figure 7.2 – Roll (A) and pitch (B) angle as a function of time as measured by the eye tracker over the one-minute recording period, for a single subject reading text aloud. Note the difference in the vertical scales of the two traces. The downward pitch angle increases as the subject reads down the page, implying that she is using head as well as eye movements in this direction (the total vertical subtense of the A4 page was about 35 degrees). The quasi-periodic small changes in pitch angle occur as the subject reads successive lines. Roll angles are small and roughly constant. The dashed line represents the linear fit for pitch.

Statistical analysis was performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). One-way between groups analysis of variance was used to assess differences between refractive error groups. Repeated measures analysis of variance was used to compare results from the eye-tracker with results from the photos. Furthermore, two-tailed Pearson correlations were applied.

7.4 Results

7.4.1 Comparison between the two recording methods

Before the full analysis of the head-posture results in relation to the refractive and binocular vision characteristics of the subjects, a comparison was made between the posture results obtained by the two recording methods (photos and eye tracker). This was because some subjects had complained of the weight of the helmet carrying the eye tracker and we feared that this might distort the associated data.

The reading distance provided a simple starting point to compare the two methods. The mean reading distances whilst the photos were taken were 46.8 ± 8.8 cm in emmetropes and 46.3 ± 7.7 cm in myopes. The mean reading distances measured during eye-tracker recordings were shorter, at 38.9 ± 8.3 cm in emmetropes and 38.8 ± 7.9 cm in myopes. There were no significant differences between the results for the myopes and emmetropes when measured by each of the individual methods (One-way between groups analysis of variance: eye tracker: $F_{(1,48)} = 0.01$, $p = 1.0$; photos: $F_{(1,51)} = 0.04$, $p = 0.84$ respectively). However, repeated measures analysis of variance showed that the reading distances as measured by the two techniques were significantly different ($F_{(1,48)} = 39$, $p = 0.001$). Nevertheless, the two reading distances for individual members of the whole study population from photos and eye-tracker were significantly correlated (two-tailed Pearson product-moment correlation, $r = 0.35$, $n = 49$, $p = 0.01$), as shown in Figure 7.3. Note, however, that the slope of the regression-line fit is less than unity and that the intercept differs substantially from zero, indicating a real difference rather than a simple scaling effect. In almost all subjects, the reading distance recorded during the photographic sessions exceeds that found when subjects wore the eye-tracker.

Since the two types of recording were not made simultaneously with each subject, we cannot discount the possibility that subjects simply adopted different reading postures in different sessions. However, as the order in which the recordings were made was quasi-random, we do not believe that true postural change can account for the systematic differences observed. Instead, we attribute these discrepancies to the weight of the helmet during the

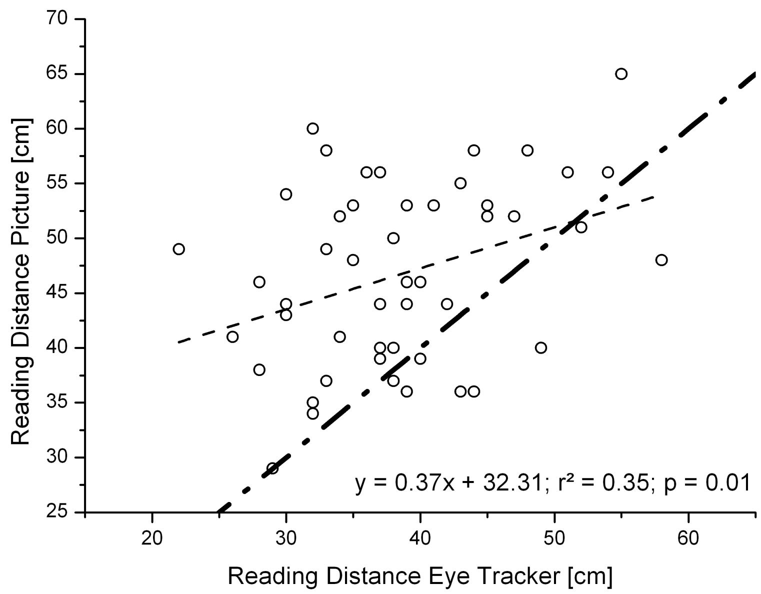

Figure 7.3 – Correlation between reading distance measured while the picture was taken and the eye tracker recordings. Dashed line represents linear fit. The heavy dot-dash line shows the ideal 1:1 relationship.

eye-tracker recordings, which tended to make subjects adopt shorter working distances. Larger pitch angles were also found with the eye-tracker. Under these circumstances we have confined the main analysis to the photographic recordings since posture in this case should be more natural.

7.4.2 Reading distance

As noted above, the mean reading distances for the emmetropes and myopes as measured photographically were 46.8 ± 8.8 cm (n = 22) and 46.3 ± 7.7 cm (n = 32) respectively. These distances did not differ significantly (p = 0.84). There were no significant correlations between reading distance and refractive error (p = 0.53) or the rate of myopia progression (p = 0.87). The age range of the patients was from 19 to 38 years. Thus the wide range of ages in the study could potentially lead to differences in working distance adopted by the individuals. However, no significant correlations were found between age and working distance for either photographic (p = 0.81) or eye-tracker (p = 0.20) measurements.

7.4.3 Pitch and roll angles

Mean pitch and roll angles after five seconds of reading, derived from the pictures and separated for myopes and emmetropes, are presented in Table 7.1. Mean pitch angles were higher than the roll angles, which were always small in magnitude. The mean of roll angle, while small, differed significantly from zero at the $p = 0.05$ level in emmetropes ($p = 0.03$), but not in myopes ($p = 0.95$). For both pitch and roll angles, no significant differences were found between myopes and emmetropes (One-way between groups analysis of variance: roll angle: $F_{(1,49)} = 2.82$, $p = 0.10$; pitch angle: $F_{(1,50)} = 1.87$, $p = 0.18$).

	Myopes	**Emmetropes**
Pitch [degrees]	-17.7 ± 6.3	-15.0 ± 7.8
Roll [degrees]	-0.03 ± 2.8	1.2 ± 2.4

Table 7.1 – Pitch and roll angle in myopes (n = 32) and emmetropes (n = 22) after five seconds of reading, as derived from photos. Values represent mean ± standard deviation.

There were no significant correlations between individual head angles and refractive error.

When the myopes were separated into progressing and non-progressing groups, the mean pitch angles derived from photos were -18.9 ± 6.0 degrees (progressing myopes, n = 16) and -13.3 ± 4.0 degrees (non-progressing myopes, n = 12). The difference in pitch between the two groups was just statistically-significant (One-way between groups analysis of variance: $F_{(1,24)} = 161$, $p = 0.03$) indicating that progressing myopes bend their head forward more than non-progressing myopes.

Figure 7.4 shows the relationship between individual pitch angles and myopia progression rates, together with the associated regression line fit. There is a weak trend towards more negative pitch angles (stronger forward bending) with higher myopia progression rates but the correlation is not significant ($p = 0.23$).

Pitch angle and reading distance were not significantly correlated when analysing the whole study population (two-tailed Product moment correlation, $r = -0.25$, $n = 51$, $p = 0.07$). When analysing emmetropes and myopes separately, pitch angle and reading distance correlated significantly in emmetropes (two-tailed Product moment correlation, $r = -0.49$, $n = 21$, p

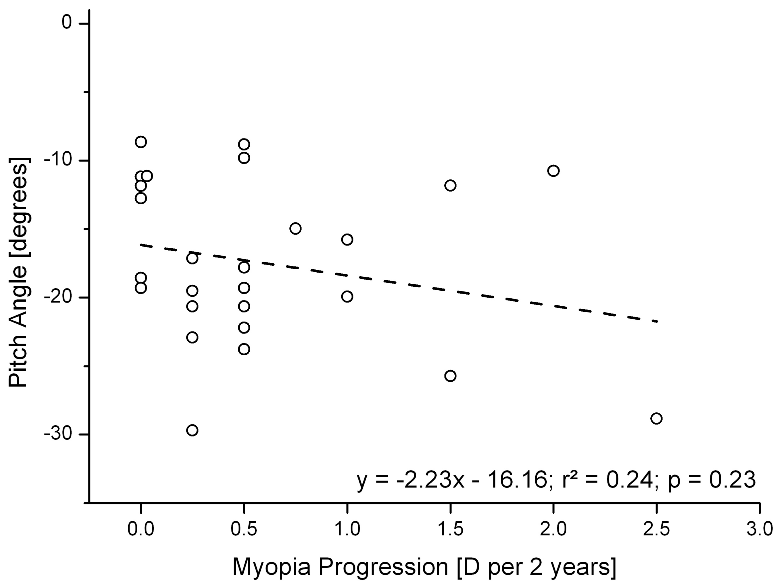

Figure 7.4 – Pitch angle as a function of myopia progression rate. The dashed line represents the linear fit. The correlation is not significant. Two data points are missing due to the poor quality of the photos. One data point for 0 D progression has been displaced slightly to avoid overlapping (photographic data).

= 0.03), but not in myopes (two-tailed Product moment correlation, r = -0.03, n = 30, p = 0.89).

7.4.4 Relation of reading distance, pitch and roll to binocular variables

No significant relationships were found between either fixation disparity (at distance or near) or TNO results and any of the posture parameters, either for all subjects or for the individual refractive groups. In detail the results of the two-tailed Product moment correlations applied for the whole study population were as follows: Pitch and horizontal fixation disparity at distance: r = -0.13, n = 52, p = 0.35; pitch and horizontal fixation disparity at near: r = 0.05, n = 52, p = 0.71; roll and horizontal fixation disparity at distance: r = -0.21, n = 51, p = 0.14; roll and horizontal fixation disparity at near: r = 0.17, n = 51, p = 0.23; reading distance and horizontal fixation disparity at distance: r = 0.28, n = 53, p = 0.84; reading distance and horizontal fixation disparity at near: r = 0.32, n = 53, p = 0.82. For the TNO test the non-significant results were as follows: Pitch and TNO: r = 0.20, n = 49, p = 0.16; roll and TNO: r = 0.14, n = 48, p = 0.34; reading distance and TNO: r = 0.03, n = 50, p = 0.84. Correlations between postural parameters and vertical fixation disparity were not analysed, because only two subjects showed values other than zero.

7.4.5 Dynamic measurements with the eye tracker

As noted earlier, we conclude that the eye tracker data were influenced by the weight of the helmet worn and that they cannot be directly compared with the photographic data. Nevertheless, in principle such data have the major advantage that they are dynamic and allow changes over time to be followed (Figure 7.2). It was of interest that the rate of change of pitch angle (degrees per seconds) over one minute of the recording session showed a highly significant correlation between myopia progression and slope of pitch motion (Figure 7.5, two-tailed Product moment correlation, r = -0.69, n = 20, p = 0.001) indicating a greater progressive forward bending (increasing pitch angle) in more rapidly progressing myopes when reading. We assume that this indicated greater reliance on head, rather than eye, movements to move fixation down the page of text. However, when the data for the two subjects with the highest progression rates (2.50 D per two years and 2.00 D per two years) were removed, the correlations between myopia progression and reading distance, as well as myopia progression and slope of pitch motion, were not significant.

7.5 Discussion

In the present study we aimed to analyse individual differences in head position and orientation while a near task was performed, based on the hypothesis that the head posture of myopes might differ in some way from that of emmetropes. However, no significant differences between working distances, as derived from photos of adult myopes and emmetropes could be found, in agreement with previous studies (Drobe *et al.*, 2006, 2007): the magnitude of the working distance was similar to those found in earlier work (e.g. Drobe *et al.*, 2006, 2007; Hill *et al.*, 2005, 2006). Similarly there were no significant differences between the head postures of the two refractive groups. Head roll angles were always small and showed no obvious dependence on refractive state or progression. We note that Hill *et al.* (2005, 2006) have shown that head posture

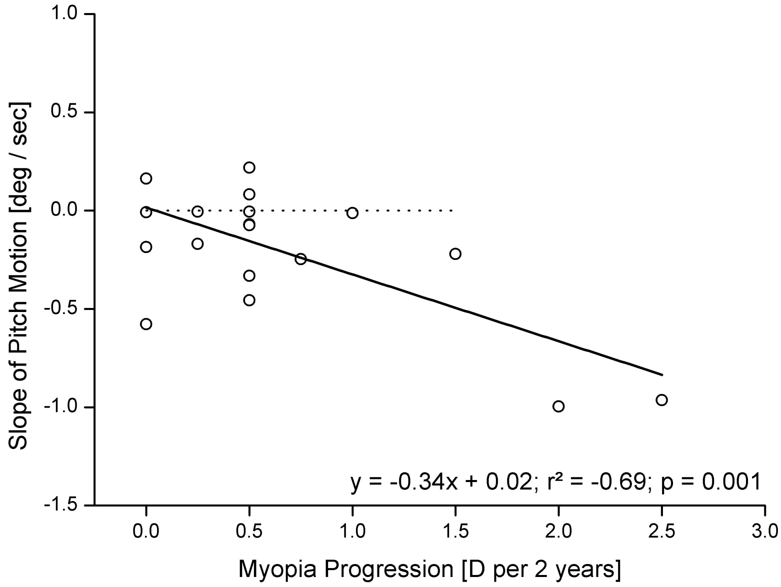

Figure 7.5 – Correlation between myopia progression and the slope of pitch motion during eye tracker recordings. The solid line represents linear fit for all subjects. The dashed line represents the linear fit, when two subjects with high progression rates were removed. The reduced number of data points is due to the fact that eye-tracker data was missing in some individuals.

varies substantially with the exact nature of any reading task, so that our mean values of pitch and roll were specific to the task and condition used. Binocular performance in terms of fixation disparity or stereopsis appeared to have no effect on head posture.

Only the pitch angles of progressing myopes and non-progressing myopes showed a difference, of marginal statistical significance, pitch angles being greater for those with rapid progression. From the eye tracker data, it also appeared (Figure 7.5) that rapidly progressing myopes made relatively greater use of head movements when scanning text and thus tended to change their pitch angles more rapidly while reading than myopes with low progression rates. However, as discussed earlier, this finding should be treated with caution as the eye-tracker data may be contaminated by the effect of helmet wear, and errors in self-reported myopia progression rates.

At first sight, our results do not agree with the findings of Marumoto *et al.* (1999) who claim that, during a desk-top writing task, “myopes” had a mean working distance of 15 cm and large head and body tilts, while “emmetropes” had a mean working distance of 30 cm and smaller head and body tilts (see their Figure 4). However, these authors give no details of the actual refractive status of their subjects and no subject appears to have worn a refractive correction during the task. As far as can be judged, subjects were classified as "myopic" purely on the basis of their uncorrected vision. Thus Marumoto *et al.'s* results cannot be compared with those, like ours, which are found with corrected subjects.

Overall we suggest that the data from the present study, at best, only hint that posture might play some role in myopia development, rather than confirming the hypothesis. Any change of the head (roll or pitch) angle might reflect a compensatory response to eye movements. The influence of the extraocular muscles on the eye ball could induce myopization. Friberg and Lace (1988) showed that the posterior pole of the sclera is only about 60% as stiff as the anterior sclera, so that the posterior of the eyeball may be more susceptible to exterior forces and hence may deform more easily. The possibility that extraocular muscle forces might temporarily distort the eyeball and that, over time, such distortion might lead to myopia, cannot be lightly dismissed. Additionally, as noted by Collins *et al.* (2006a), lid pressures during task-related eye movements may also distort the cornea.

We acknowledge a number of weaknesses in this study. Perhaps the most serious was that the reading period was relatively brief (only one minute), so that subjects might not have fully settled into their typical reading posture, moreover head posture was recorded at only one point in time. A longer reading period with head positions sampled at several points in time might have given more realistic estimates of typical head posture. Moreover it might have been better to record head position when subjects were reading the centre of the page of text rather than the top line or two. Another limitation was that, in the absence of clinical records, we were forced to rely on self-reported myopia progression rates although these should have been reliable since the subjects were optometry students. Six out of 54 participants wore glasses during the photographic sessions and contact lenses during the tracker recordings. This could have induced minor differences in posture, as accommodation and convergence demands differ with the type of correction.

Our subjects (mean age 24.9 years) were adults, whereas most myopia development usually occurs at a younger age (Jones-Jordan *et al.*, 2010; Low *et al.*, 2010) and it is possible that it is at this stage that any crucial postural differences are most prominent. Whereas Haro *et al.* (2000) found that working distances in children varied with their ametropia (although this was not confirmed by Drobe *et al.* (2008)), Drobe *et al.* (2006, 2007) found that such distances were independent of ametropia in pre-presbyopic adults. Drobe (2010) showed by analysing 169 Singaporean children aged between 6 and 14 years (87% were of Chinese ethnicity) that 67% only moved their eyes when they read, keeping their head almost stationary. As the youngest participant in the present study was 19 years old, it is possible that an adaptation during childhood takes place and has an impact on later myopia progression.

In conclusion this exploratory study provided some suggestive, but not compelling, evidence for an association between head position and myopia development. More useful information might be obtained by using tasks of longer duration and a lightweight motion tracker to study head motions dynamically, rather than using the camera technique to obtain head postures at a single point in time. Reduction in the weight and intrusiveness of any head-mounted eye-tracker equipment is required to ensure that the data obtained accurately depicts normal postures.

7.6 Remarks

For chapter 7 the data were collected by me and I analysed the data. The first draft of the manuscripts was written by me and I dealt with reviewers' comments along with my supervisors.

This chapter has been published: Hartwig, A., E. Gowen, W. Neil Charman and H. Radhakrishnan (2011). Analysis of head position used by myopes and emmetropes when performing a near-vision reading task. *Vision Res* **51**(14): 1712-1717.

Chapter 8

Changes in ocular biometry with accommodation in myopes and non-myopes

8.1 Abstract

Purpose: It is well known that some of the biometric parameters of the eye change with accommodation. Furthermore, near-work seems to have some impact on myopisation, suggesting the possibility that biometric parameters change differently in myopes and non-myopes. We therefore compared key biometric parameters during distance and near vision in myopes and non-myopes.

Methods: Biometry and autorefraction were performed for 12 myopes (mean SD: -4.3 $\pm$ 2.8 D) and 12 non-myopes (mean $\pm$ SD: +0.1 $\pm$ 0.5 D) who viewed either a distance (3 m) or a near (0.33 m) target. A Haag-Streit LenStar LS 900 was used for biometry and a Shin-Nippon SRW-5000 for the assessment of the accommodation response. Parameters measured were central corneal thickness, anterior chamber depth, lens thickness, retinal thickness, axial length, corneal curvature, pupil diameter, iris diameter and accommodation response.

Results: Of the biometric parameters measured, only axial length differed significantly between the myopes and non-myopes, in both the non-accommodated and accommodated conditions. Accommodation responses in the two groups showed no significant differences. As expected, in both groups anterior chamber depth and pupil diameter were significantly larger,

and lens thickness was significantly smaller, in the non-accommodated versus the accommodated state. The changes in parameters with accommodation were similar in both refractive groups. No significant changes with accommodation were found in axial length.

Conclusions: As expected, axial length differed significantly between myopes and non-myopes. However, the changes in biometric parameter values occurring as a result of modest amounts of accommodation (2.67 D stimulus change) were very similar in the two refractive groups, so that there was no support for the suggestion that the myopic eye undergoes systematically greater changes, particularly in axial length, during acccommodation. However, further work is desirable to explore the effects of different accommodation levels and observation periods on these biometric changes.

8.2 Introduction

Accommodation enables the distance-corrected eye to see clearly at different distances by changing the optical power of the lens. To achieve an increase in refractive power for near vision, the central thickness of the crystalline lens increases and the equivalent refractive index and surface powers of the crystalline lens change (see, e.g., review by Charman, 2008). Changes in the thickness of the lens or, more strictly, the position of its anterior pole, alter the anterior chamber depth (Garner and Yap, 1997; Jones *et al.*, 2007a; Nurispahic *et al.*, 2008; Read *et al.*, 2010).

Even though the physical changes during accommodation are well understood, there is still uncertainty about how the accommodative response is driven. However, it is possible that there are some parallels between the pathways of accommodation and the pathways of emmetropisation (Mutti *et al.*, 2009). If so, this would be interesting for various reasons. Firstly, it has been speculated that myopia development is associated with long periods of near work (Young *et al.*, 1969; McBrien and Millodot, 1986; Adams and McBrien, 1992; Zylbermann *et al.*, 1993; Simensen and Thorud, 1994; Mutti *et al.*, 2002; Hazel *et al.*, 2003). Secondly, the prevalence of myopia is increasing dramatically, especially in some Asian countries and in urban environments (Goldschmidt, 2003; Saw, 2003; Lin *et al.*, 2004; Ip *et al.*, 2008b), for reasons that are still unclear. An improved understanding of any links between accommodation and refractive error might lead to better strategies for the control of myopia development.

Some differences are known to occur between myopes and non-myopes in how the biometric parameters change during accommodation. Pandian *et al.* (2006) found that myopes responded more slowly than emmetropes and hyperopes, when facility of accommodation was tested with a semi-automated lens flipper for distance vision, but they could not show this difference for near vision (see also O'Leary and Allen, 2001). Culhane and Winn (1999) found slower accommodation responses in myopes after sustained near-vision tasks. Bolz *et al.* (2007) compared anterior chamber depth and lens thickness between myopes and emmetropes during accommodation. They found differences between myopes and emmetropes at 1.0 and 2.0 D accommodative stimuli, but not for higher stimuli (3.0, 4.0 and 5.0 D).

Using the IOL Master Mallen *et al.* (2006) measured axial length for various accommodative stimuli and found that axial length increases, by a few microns, with accommodation, even for short near-vision periods (20 seconds). Similarly Drexler *et al.* (1998b) measured axial length using a custom partial coherence interferometer and also observed an increase in axial length during accommodation. However, Drexler *et al.* (1998b) found that axial elongation was greater in emmetropes whereas Mallen *et al.* (2006) found it to be greater in myopes. Axial length elongation during accommodation might possibly be linked to myopia development (Drexler *et al.*, 1998b; Read *et al.*, 2010; Woodman *et al.*, 2010), as temporary elongation during accommodation could lead to a permanent elongation and therefore lead to myopia. Greater elongation in myopes would support the concept that the myopic sclera is weaker than that of the emmetrope.

One problem with interferometric measurements is that the actual measurement is of optical path rather than distance. Hence, the results depend upon assumptions about the refractive indices of the different media which cannot take full account of the still-unknown changes of the index gradients of the lens during accommodation (Atchison and Smith, 2004).

A recent review from Mutti (2010) points out the importance of simultaneously measuring all the biometric parameters, as looking at selected parameters in isolation does not allow the interactions between all the key parameters involved in the accommodative response to be explored. The only study so far to attempt this is that of Read *et al.* (2010), who measured most biometric parameters simultaneously using the LenStar LS 900 and, like Drexler *et al.* (1998b) and Mallen *et al.* (2006), found a small change in axial length with accommodation. Interestingly, they found that the change was the same in myopes and emmetropes. Read *et al.* (2010) did not measure the accommodative response, but instead used the accommodative stimulus in their analysis. This has the limitation that apparent differences in parameter change between refractive groups or individuals might arise simply because their accommodation response changes differed. Some previous studies have shown significant differences in accommodative response between myopes and emmetropes (Gwiazda *et al.*, 1993), especially when progressing myopes are included (Abbott *et al.*, 1998). Other studies show that myopes have lower accommodative responses, but that the differences are not statistically significant (Allen and O'Leary, 2006; Radhakrishnan *et al.*, 2007).

The aim of the present study was to follow up the Read *et al.* (2010) study and compare possible changes in key biometric parameters during distance and near vision in a group of myopes and a group of non-myopes, as well as to investigate the corresponding accommodation responses. Thus the intention was to compare the parameter changes in terms of accommodation response, rather than stimulus as was done in the earlier studies (Drexler *et al.*, 1998b; Mallen *et al.*, 2006; Read *et al.*, 2010). The LenStar LS 900 instrument was used to obtain the biometric measurements. It records most major ocular biometric parameters (axial length, central corneal thickness, anterior chamber depth, lens thickness, retinal thickness, pupil diameter, visible iris diameter and k-readings) in one measurement. However, it does not measure lens surface curvature.

8.3 Methods

Twenty-four subjects (8 male and 16 female) were recruited. The age of the subjects ranged between 19 and 43 years (mean ± SD: 26.4 ± 6.0 years). All subjects were free from any ocular pathology and achieved a visual acuity of 6/6 or better when corrected. Corrections based on the spherical equivalent were in the range of -9.2 D to +0.9 D (mean spherical equivalent ± SD: -2.1 ± 2.9 D). The group included twelve non-myopes (mean spherical equivalent between +0.9 D and -0.5 D; mean ± SD: +0.1 ± 0.5 D; age ± SD: 26.1 ± 6.7 years) and twelve myopes (mean spherical equivalent of less than -0.50 D; mean ± SD: -4.3 ± 2.8 D; age ± SD: 26.8 ± 5.5 years). In all cases, astigmatism was equal to or less than 1.5 D. The study followed the tenets of the Declaration of Helsinki and written informed consent was obtained from all participants after the nature of the study and possible consequences of the study had been explained. The project protocol was approved by the Senate Committee on the Ethics of Research on Human Beings of the University of Manchester.

The LenStar LS 900 (Haag Streit AG, Koeniz, Switzerland) was used to obtain biometry data for distance and near vision. The LenStar uses time-domain interferometry to measure ocular distances in the eye, and employs a 820 nm superluminescent diode with a Gaussian-shaped spectrum to provide high axial resolution. The relatively new LenStar LS 900 has been compared with the IOL Master for axial length, anterior chamber depth and keratometry measurements and has been shown to be reliable (Buckhurst *et al.*, 2009; Holzer *et al.*, 2009; Rohrer *et al.*, 2009; Cruysberg *et al.*, 2010; O'Donnell *et al.*, 2011).

As the instrument is designed for distance measurements (using an internal fixation target), an additional beamsplitter was added in front of the device to enable measurements at near. The beamsplitter allowed the instrument to take measurements in the usual way while the subject concentrated on fixation targets that were placed at two different distances. One target for distance vision was placed at 3 m and a second target for near vision was placed 0.33 m in front of the subjects eye, providing an accommodation stimulus change of 2.67 D. For convenience, we call the distant target 'unaccommodated' even though it provided a weak accommodative stimulus (0.33 D). High-contrast Snellen E's were used as fixation targets. The height of the distant target was 30 mm and that of the near target was 15 mm. Both fixation targets were aligned with the red diode that constituted the internal fixation target of the LenStar, so that the diode appeared to be superimposed on the middle of the central bar of the E. For the measurement, the LenStar was focused and aligned using the image of the eye on the computer monitor whilst the subject was asked to look at the distant or near target. Subjects were asked to blink just prior to measurements being taken, in order to reduce the influence of tear-film thinning on the measured optical path length. The instrument takes 16 consecutive scans per measurement and five measurements were taken for each participant, as recommended by the manufacturer. The LenStar software calculates the mean of these five measurements automatically. Data on central corneal thickness, anterior chamber depth (corneal endothelium to anterior lens surface), lens thickness, axial length and corneal curvature are provided. Corneal radii are given for the steep and flat meridians, together with their orientations (axis). Retinal thickness was determined manually by one of the authors (AH), using a cursor that was placed at the peaks of the A-scan LenStar record corresponding to reflections from the anterior and posterior surfaces of the retina. Iris diameter and pupil diameter were measured using the instruments inbuilt edge-detection software. The changes in biometric parameters (lens thickness, anterior chamber depth, axial length, etc.) that occur during accommodation were calculated in Excel (Microsoft, Redmond, WA, USA).

To ensure that the beamsplitter did not affect the measurements, readings of a model eye were taken with and without the beamsplitter in place. The model eye consisted only of the anterior lens and an air chamber, so that in this case the LenStar measured only the lens thickness and the axial length. The lens thickness of the model eye without the beamsplitter measured 4.15 $\pm$ 0.01 mm and the axial length measured 23.79 $\pm$ 0.01 mm. When the beamsplitter was in place, lens thickness measured 4.15 $\pm$ 0.01 mm and axial length measured 23.79 $\pm$ 0.01 mm. Using a paired-sample t-test no significant differences were found for lens thickness ($p = 1.0$) and for axial length ($p = 1.0$). This indicated that the beamsplitter did not influence the measurements significantly.

To measure each subjects accommodative response, a Shin Nippon SRW-5000 (Ajinomoto Trading Inc., Tokyo, Japan) open-field autorefractor was used. Three readings were taken at each accommodative stimulus level. Based on the spherical equivalent for each reading, an average of the three readings was calculated. The response was taken as the mean spherical equivalent with sign reversed. As in the biometry, the distance target was placed at 3 m and the near-vision target was placed at 0.33 m. The target characteristics were identical to those used in the biometry.

In all cases only the right eye was examined and the left eye was occluded using an eye patch. Myopes always wore their habitual soft contact lens corrections to allow them to see the fixation targets clearly. The Shin Nippon SRW-5000 has been shown to be a reliable instrument (Mallen *et al.*, 2001) and contact lenses do not appear to affect refractive error measurements taken with an autorefractor (Strang *et al.*, 1997). The contact lenses would, however, be expected to affect the values of corneal thickness, corneal curvature and axial length obtained with the LenStar, although not the magnitude of any changes occurring with accommodation.

8.3.1 Data analysis

The LenStar is designed for distance vision measurements only. Therefore the software assumes an average refractive index of the eye which is appropriate to the unaccommodated state (Read *et al.*, 2010). As the effective refractive index of the crystalline lens changes with accommodation, an error for measurements of the accommodated eyes occurs. Atchison and Smith (2004) proposed a method to correct for this error when using the Zeiss IOL Master. For each participant the optical path length (OPL) of the accommodated lens (formula 8.1) and thereafter the error (E) occurring due to the change in refractive index during accommodation (formula 8.2) were calculated. Both equations are essentially those are given by Atchison and Smith (2004) but formula 8.1 has been altered slightly to improve the correction for the changes in effective refractive index of the crystalline lens (Atchison and Charman, 2011).

$$OPL_L = 1.406t - \frac{0.00125155(t-Z_0)^3}{3} + \frac{0.0009371125(t-Z_0)^5}{5} - \frac{0.00125155(Z_0)^3}{3} + \frac{0.0009371125(Z_0)^5}{5} \quad (8.1)$$

$$E = \frac{OPL_L}{n_L} - (L_L + \Delta L_L) \quad (8.2)$$

In formula 8.1, t is the lens thickness measured in the accommodated eye. Z_0 represents the distance from the front surface vertex of the lens to the nucleus of the lens with highest refractive index. Z_0 was set to 2.0 mm, as assumed by **?**. In formula 8.2, n_L is the average refractive index of the gradient index lens and equals 1.39929. L_L is the measured length of the unaccommodated lens and ΔL_L is the change in lens length on accommodation. The measured axial length values are referred to as 'uncorrected' axial lengths and the corrected axial length values using the method described above are referred to as 'corrected' axial lengths.

It is possible that movements of the contact lenses in the myopic group could lead to different results for central corneal thickness and therefore axial length. To avoid this problem, we calculated axial length without the cornea by subtracting the central corneal thickness result from the axial length result.

Therefore, three analyses for axial length were performed. These were:

1. *axial length uncorrected:* actual measurement from the LenStar
2. *corrected axial length with cornea:* the axial length measurements for

the accommodated state, corrected for changes in lens refractive index as described above

3. *corrected axial length without cornea:* The axial length measurements corrected for refractive index changes using equation 8.2 with additional subtraction of corneal thickness to avoid bias of the contact lenses. This can be considered to provide the most reliable data in the present study.

The software package SPSS 16.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analysis. Statistical significance was set to $p < 0.05$. In cases of multiple comparisons, the conservative Bonferroni adjustment was applied. Significance level is given individually for each condition.

8.4 Results

The results for 'corrected axial length with cornea' and 'corrected axial length without cornea' were very similar. Therefore, the results are only presented for axial length 'uncorrected' and 'corrected axial length without cornea' data.

8.4.1 Differences between unaccommodated and accommodated state (all subjects)

Measured mean values for corneal thickness, anterior chamber depth, pupil diameter, lens thickness, retinal thickness and axial length are presented in Table 8.1. Unaccommodated and accommodated states of the whole study population (irrespective of refractive error) were compared using repeated measures analysis of variance. Following Bonferroni correction for the ten multiple comparisons, the required significance level is $p = 0.005$. For corneal thickness data, no significant difference was found between the accommodated and non-accommodated conditions ($F_{(1,22)} = 1.19$, $p = 0.29$). Anterior chamber depth, pupil diameter and lens thickness were significantly different between non-accommodated versus accommodated eyes ($F_{(1,23)} = 85.35$, $p = 0.001$; $F_{(1,23)} = 18.64$, $p = 0.001$; $F_{(1,23)} = 81.67$, $p = 0.001$, respectively): as expected, anterior chamber depth and pupil diameter decreased while lens thickness increased with accommodation. No significant difference in retinal thickness was found between the two conditions ($F_{(1,23)} = 0.02$, $p = 0.88$). Accommodation did not change axial length significantly, when either the 'uncorrected' or 'corrected without cornea' values were used ($F_{(1,23)} = 0.37$, $p = 0.55$; $F_{(1,22)} = 6.17$, $p = 0.02$, respectively).

8.4.2 Differences between myopes and non-myopes in the unaccommodated and in the accommodated state

The main biometric parameters (corneal thickness, anterior chamber depth, lens thickness, retinal thickness, axial length, corneal curvatures, pupil diameter and iris diameter) separated for refractive error groups are presented in Table 8.1. To explore the possible differences between the two refractive error groups for these parameters in each of both the accommodated and unaccommodated states, one-way between-groups analysis of variance was applied. The results are also presented in Table 8.1 (column 'Stats'). Bonferroni correction was applied, because of multiple comparisons. In this case there were 20 combinations and the resulting required significance level was $p = 0.0025$. Note that the corneal thickness and 'uncorrected ' axial length estimates for the myopes are increased by the presence of their soft contact lens corrections, which also contribute to their apparently flatter corneal curvatures. Allowing for these effects, only the inter-refractive group differences in the unaccommodated and accommodated 'corrected axial lengths without cornea' can be considered to be significant.

Accommodative responses to the two stimuli, separated for myopes and non-myopes, are presented in Figure 8.1. Mean lags of accommodation were quite large for the 3.0 D target. Accommodative responses were not statistically significantly different between myopes and non-myopes ($F_{(1,23)} = 1.52$, $p = 0.23$). The gradient of the line linking each pair of data points was 0.76 for the myopic group and 0.78 for the non-myopic group. For all subjects, the mean accommodative response change between the two targets was 2.15 $\pm$ 0.58 D. In the myopic group the average accommodative response change was 2.3 $\pm$ 0.53 D and in the non-myopic group 2.01 $\pm$ 0.62 D.

Major biometric changes during accommodation occur in the lens and the anterior chamber. The biometric changes with accommodation are given in Table 8.2 for the whole study population and separately for myopic and non-myopic subjects: although only the parameters of interest are listed, it must be remembered that 10 parameters were assessed, as listed in Table 8.1. Table 8.2 gives also the biometric change per dioptre accommodative response.

		Overall	Myopes	Non-myopes	Stats
Corneal thickness [μm]	unaccommodated	578.6 ± 64.9	633.6 ± 44.2	527.6 ± 28.4	$F_{1,22}$ = 47.7, *p = 0.001*
	accommodated	580.8 ± 67.8	638.5 ± 46.3	527.9 ± 29.3	$F_{1,22}$ = 47.7, *p = 0.001*
Anterior chamber depth [mm]	unaccommodated	3.17 ± 0.31	3.34 ± 0.22	3.01 ± 0.3	$F_{1,23}$ = 9.4, p = 0.01
	accommodated	3.05 ± 0.30	3.21 ± 0.18	2.88 ± 0.32	$F_{1,23}$ = 9.3, p = 0.01
Lens thickness [mm]	unaccommodated	3.62 ± 0.21	3.55 ± 0.21	3.68 ± 0.19	$F_{1,23}$ = 2.5, p = 0.13
	accommodated	3.77 ± 0.23	3.7 ± 0.23	3.83 ± 0.21	$F_{1,23}$ = 2.2, p = 0.15
Retinal thickness [μm]	unaccommodated	202.0 ± 25.1	193.9 ± 26.0	210.2 ± 22.4	$F_{1,23}$ = 2.7, p = 0.12
	accommodated	202.6 ± 21.2	195.3 ± 20.1	209.9 ± 20.6	$F_{1,23}$ = 3.1, p = 0.09
Axial length uncorrected [mm]	unaccommodated	24.44 ± 1.39	25.54 ± 1.02	23.34 ± 0.57	$F_{1,22}$ = 47.9, *p = 0.001*
	accommodated	24.44 ± 1.38	25.53 ± 1.01	23.34 ± 0.58	$F_{1,22}$ = 46.9, *p = 0.001*
Corrected axial length without cornea [mm]	unaccommodated	23.87 ± 1.36	25.02 ± 0.96	22.81 ± 0.56	$F_{1,22}$ = 46.3, *p = 0.001*
	accommodated	23.88 ± 1.35	25.02 ± 0.96	22.84 ± 0.56	$F_{1,22}$ = 45.2, *p = 0.001*
Corneal curvature: flat meridian [D]	unaccommodated	39.7 ± 2.4	38.2 ± 2.1	41.1 ± 1.6	$F_{1,22}$ = 14.8, *p = 0.001*
	accommodated	39.8 ± 2.3	38.3 ± 2.1	41.2 ± 1.6	$F_{1,22}$ = 13.2, *p = 0.002*
Corneal curvature: steep meridian [D]	unaccommodated	40.3 ± 2.4	38.8 ± 1.9	41.8 ± 1.8	$F_{1,23}$ = 15.7, *p = 0.002*
	accommodated	40.4 ± 2.4	38.8 ± 1.9	41.8 ± 1.9	$F_{1,22}$ = 14.3, *p = 0.001*
Pupil diamter [mm]	unaccommodated	6.13 ± 0.85	5.92 ± 1.11	6.33 ± 0.43	$F_{1,23}$ = 1.4, p = 0.25
	accommodated	5.67 ± 1.0	5.58 ± 1.25	5.76 ± 0.71	$F_{1,23}$ = 0.2, p = 0.67
Iris diamter [mm]	unaccommodated	12.39 ± 1.11	12.56 ± 0.94	12.01 ± 1.52	$F_{1,12}$ = 0.67, p = 0.43
	accommodated	12.47 ± 0.63	12.65 ± 0.46	12.15 ± 0.81	$F_{1,13}$ = 2.3, p = 0.16

Table 8.1 – Biometry data separated for the whole study population (overall), for myopes and for non-myopes in the unaccommodated and accommodated state. Values are presented as mean ± standard deviation. The right hand column gives the statistics for the differences between the corresponding values for myopes and non-myopes. Required significance level due to multiple comparison is p = 0.0025. Note that values of corneal thickness, corneal curvature and axial length 'uncorrected' for the myopes are affected by the soft contact lens corrections worn.

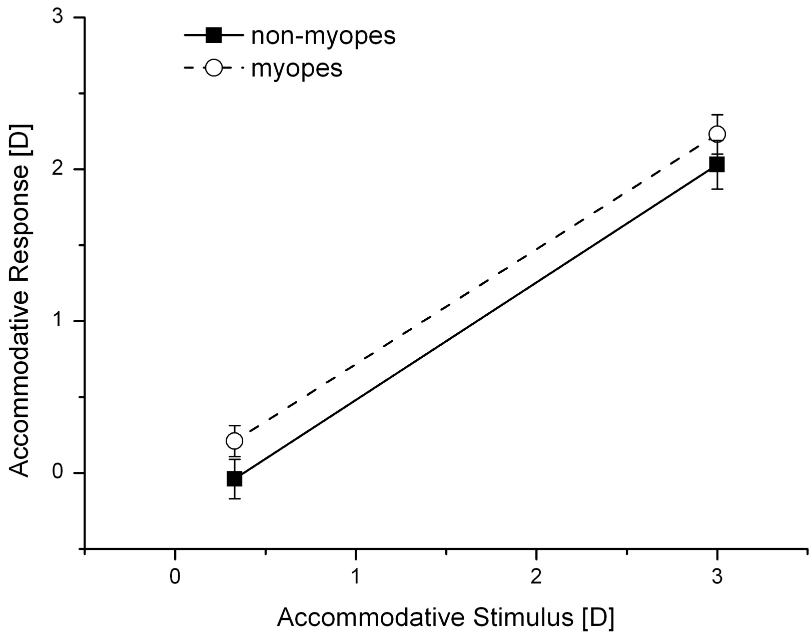

Figure 8.1 – Accommodative responses vs. accommodative stimulus in non-myopes and myopes. Error bars show ± 1 standard deviation.

The overall values have been tested against the hypothesis that their values are zero, and the two refractive groups have been compared using one-way between-groups analysis of variance. After Bonferroni correction for multiple comparisons (10 trials in each case although only 4 are shown in the Table) a p value of <0.005 has been taken as indicating significance.

	Overall			**Myopes**		**Non-myopes**		**Stats for**
	Difference	Diff./D	Stats for difference from 0	Difference	Diff./D	Difference	Diff./D	**difference between myopes and non-myopes**
Lens thickness [μm]	+149 ± 81	+69.3	<0.001	+147 ± 92	+63.9	+152 ± 72	+75.6	0.84
Anterior chamber depth [mm]	-128 ± 68	-59.5	<0.001	-131 ± 76	-60.0	-125 ± 62	-62.2	0.88
Uncorrected axial length [mm]	-0.007 ± 0.026	-0.003	0.216	-0.018 ± 0.028	-0.008	+0.003 ± 0.020	+0.001	0.05
Corrected axial length without cornea [mm]	+0.014 ± 0.027	+0.007	0.021	+0.002 ± 0.028	+0.001	+0.025 ± 0.021	+0.012	0.04

Table 8.2 – Differences in biometric parameters during accommodation for the whole study population (overall), myopes and non-myopes. Values are given as mean ± standard deviation. Positive values indicate an increase, whereas negative values indicate a decrease in length. Diff./D is the difference in microns per dioptre of response. The column 'stats for differences from 0' gives the probability that the recorded difference did not differ from zero. The final column indicates the significance level for the differences between myopes and non-myopes.

Note that, for the whole study population, there is a highly-significant increase in lens thickness and a decrease in anterior chamber depth with accommodation. Most of the increase in lens thickness appears to occur anteriorly. There is a slight increase in the corrected axial length without the cornea (14 microns) but this fails to reach significance.

When the changes found in the myopes were compared with those of the non-myopes, there were no significant differences in any of the parameters.

In separate tests, no significant correlations were found between the changes in accommodative response of individual subjects and their changes in biometric parameters (lens thickness, anterior chamber depth as well as corrected and uncorrected axial length) (p >0.05).

8.5 Discussion

The present study evaluated ocular biometric changes during accommodation and sought for differences between myopic and non-myopic eyes. In general, the overall pattern of changes in biometric parameters during accommodation was as expected. The main effect was an increase in lens thickness and a decrease in anterior chamber depth (ACD), the values found implying that most of the change in ACD was due to forward movement of the anterior pole of the accommodated lens. The results support those of Read *et al.* (2010) in showing that biometric changes during accommodation are similar in myopes and non-myopes. Although our analysis related the biometric changes to the accommodation response change, rather than stimulus change as used by Read *et al.* (2010), the magnitudes and directions of the changes as related to changes in stimulus were similar to those found by Read *et al.* (2010).

Any link between accommodation and refractive error development is, perhaps, most likely to occur through axial length changes, a possible hypothesis being that a less rigid eyeball is more susceptible to length increase under the cumulative stress produced by frequent accommodation, and hence that it might develop axial myopia. Overall changes in axial length during accommodation in the present study were an increase of about 7 μm / D response or 5 μm / D stimulus, based on the corrected data without cornea (Table 8.2). However, this result failed to reach statistical significance (Table 8.2). Others have found significant increases of similar magnitude, variously amounting to about 2 μm / D stimulus (Drexler *et al.*, 1998b), 7 μm / D stimulus (Mallen *et al.*, 2006) and 4 μm / D stimulus (Read *et al.*, 2010). Although length changes of this magnitude have negligible effect on the accommodation response achieved (a 4 μm length change corresponds to only around 0.01 D of refractive change), it is perhaps conceivable that, if sustained, they might have cumulative effect on refractive development.

For differences in axial elongation between myopes and non-myopes, our findings are in line with those of Read *et al.* (2010), who also found no difference between emmetropes and myopes during accommodation, but differ from those of Mallen *et al.* (2006) and Drexler *et al.* (1998b), who found respectively that emmetropes elongated less than myopes or greater than myopes. It is possible that any change in axial length is dependent on the time spent fixating a near target. Subjects in the present study fixated on the near target for less than one minute. The fixation time for near targets in the study conducted by Read *et al.* (2010) is not described. However, in the study conducted by Mallen *et al.* (2006) subjects fixated for 20 seconds on the near target. Larger changes in accommodation stimuli and response might also provoke more consistent changes in axial length.

Given these slightly conflicting results, how reliable is the common finding of an increase in axial length with accommodation? When measuring changes in axial length with accommodation it is important to consider that minimal changes in fixation could account for differences in axial length (Kirschkamp *et al.*, 2004). Fluctuations in axial length correlate with heartbeat and respiration (Van der Heijde *et al.*, 1996). Thus various factors could produce micron-scale changes in axial length measurement. It also needs to be remembered that the measured changes are close to the limits of the capabilities of the instruments used. For example Buckhurst *et al.* (2009) found an intrasession repeatability of 16 μm and an intersession repeatability of 6 μm for the LenStar. For the IOL Master, Sheng *et al.* (2004) found a intrasession repeatability of 80 μm and 100 μm, depending on the observer. In both examples, measurements were taken in non-cycloplegic conditions. We note too that attempts to 'correct' raw estimates of axial length for lens index gradients, as in equations 8.1 and 8.2, are based on very simple models, which are unlikely to be completely valid. At the present time, then, it would be reasonable to regard the suggestions of previous studies (Drexler *et al.*, 1998b; Mallen *et al.*, 2006; Read *et al.*, 2010) that axial lengths increase during accommodation, and possible differences between myopes and emmetropes, as tentative only. Improvements in measurement techniques should clarify this issue. Were a greater accommodation-induced axial elongation to be found in myopic eyes, it could suggest the possibility of a weaker sclera. In this context, it is of interest that recent work on the biomechanical characteristics of the cornea failed to demonstrate any marked differences between myopes and emmetropes (Plakitsi *et al.*, 2011).

As noted earlier, the thicker corneas measured in myopes (Table 8.2) are likely to be caused by a measurement artefact due to the fact the myopes wore their contact lenses during the measurements. Comparing our results to the results obtained by Read *et al.* (2010), who measured myopes without contact lenses, the myopic 'corneas' are thicker in our study population. Anterior chamber depth and lens thickness are similar in both studies. Axial length in unaccommodated myopic eyes was somewhat longer in our study population (axial length uncorrected 25.5 $\pm$ 1.0 mm) than in the Read *et al.* (2010) study population (axial length uncorrected 24.39 $\pm$ 0.62 mm). This was probably caused by the fact that our participants were more myopic (mean spherical equivalent ± SD: -4.3 2.8 D) than the myopes in Read *et al.* (2010) (-1.8 ± 0.8 D). The changes in lens thickness and anterior chamber depth for the 2.67 D accommodation change were comparable to the results from Read *et al.* (2010) for a 3 D change.

Bolz *et al.* (2007) found an increase in lens thickness of 0.06 ± 0.01 mm per dioptre stimulus of accommodation in emmetropes and in myopes. Koretz *et al.* (1997) did not differentiate between myopes and emmetropes. They found in their group of accommodating subjects an increase in lens thickness of 0.043 ± 0.027 mm per dioptre accommodative stimulus. Our results showed an increase of 0.08 mm per dioptre accommodative response for non-myopes and 0.06 mm per dioptre accommodative response for myopes (0.06 mm/D stimulus for both non-myopes and myopes), comparable to both these studies (Koretz *et al.*, 1997; Bolz *et al.*, 2007). Koretz *et al.* (1997) also analysed changes in anterior chamber depth with accommodation. They measured a decrease of -0.037 ± 0.026 mm per dioptre accommodative stimulus. Our overall change in anterior chamber depth is -0.059 mm per dioptre accommodative response, or -0.048 mm per dioptre stimulus, which is comparable to the Koretz value.

A weakness of the study was that accommodative response measurements were not obtained simultaneously with the biometric measurements. The accommodative response measurements were made with a Shin-Nippon autorefractor which is an open field autorefractor allowing the view of the fixation target directly. With the LenStar biometer however, a beamsplitter was placed in front of the eye. These slightly different viewing conditions might have led to some small differences in the measured accommodative responses. These differences are, however, likely to be small and are unlikely to affect the differences seen between the refractive groups.

A further limitation was that we had no data on crystalline lens curvatures. These obviously play a major role in the power changes required for any accommodative response. We note, however, that the in vivo estimation of crystalline lens curvatures by Scheimpflug methods has limitations as, when deriving the curvature of the posterior surface, assumptions need to be made about the refractive index distribution of the lens (Atchison and Smith, 2000a, p. 17).

In conclusion, our findings for a 2.67 D stimulus change support earlier studies in suggesting that the associated changes in biometric parameters during accommodation are similar in myopes and non-myopes (Read *et al.*, 2010). We did not find a significant change in axial length with accommodation

(Drexler *et al.*, 1998b; Mallen *et al.*, 2006; Read *et al.*, 2010). Individual changes in biometric parameters were not significantly correlated with accommodative responses.

Acknowledgment
The authors would like to thank David Atchison for his comments on the manuscript and acknowledge the assistance of Haag-Streit UK Ltd. who provided the LenStar for the duration of this work.

8.6 Remarks

For chapter 8 the data were collected by me and I analysed the data. The first draft of the manuscripts was written by me.

This chapter has been submitted to Optometry and Vision Science for publication (manuscript number: OVS11188) and is currently under review.

Chapter 9

Accommodative response to peripheral stimuli in myopes and emmetropes

9.1 Abstract

Purpose: It has been suggested that peripheral refractive error may influence eye growth and the development of axial refractive error, implying that the peripheral retina is sensitive to defocus. This study aimed to evaluate the steady-state accommodative response to peripheral stimuli in 10 young, adult myopes (mean spherical equivalent error -2.10 ± 1.72 D, median -1.63 D, range -0.83 to -6.00 D) and 10 emmetropes (mean spherical equivalent error -0.02 ± 0.35 D, median +0.08 D, range -0.50 to +0.50 D).

Methods: The subjects were asked to view monocularly the centre of a screen displaying each of a series of eccentric accommodative targets placed at 5, 10 and 15 degrees. An axial target was viewed for comparison purposes. Accommodation was measured using an open-field autorefractor, each stimulus being varied between about 0 and 4 D with spherical trial lenses placed in front of the viewing eye.

Results: The results confirm that the peripheral retina is sensitive to optical focus, up to field angles of at least 15 degrees, with accommodative responses weakening as the peripheral angle increases. There is some evidence that peripheral accommodation may be less effective in myopes than emmetropes.

Conclusions: Although peripheral accommodation can be demonstrated in

the absence of a central stimulus, the accommodation response is normally dominated by the central stimulus and it seems unlikely that peripheral accommodation effects play an important role in refractive development.

9.2 Introduction

It has been suggested that, for some individuals, peripheral refraction may play an important role in myopia development. The typical patterns of peripheral refraction of myopes and emmetropes have been shown to be distinctly different, with some changes taking place before the onset of myopia (Wallman and Winawer, 2004; Mutti *et al.*, 2007; Charman and Radhakrishnan, 2010). Relative to the axial refraction, in the periphery myopes tend to show compound hyperopic astigmatism, whereas emmetropes display mixed astigmatism. The longitudinal study of Hoogerheide *et al.* (1971) indicates that it might be possible to use the pattern of peripheral refraction to identify individual emmetropes or hyperopes who are at risk of developing myopia.

Animal studies have provided further evidence to support the hypothesis that the optical focus in non-foveal areas of the retina can affect refractive development (e.g. Wallman and Winawer (2004); for review see Wildsoet (1997); Smith and Hung (1999); Norton (1999). The animal experiments show that eye growth can be regulated by local regions of the retina, rather than just the fovea, and more recent studies on infant monkeys demonstrate that focus in the peripheral retina can play an important role in modulating overall eye growth (Smith *et al.*, 2005; Charman and Radhakrishnan, 2010).

The possibility that peripheral refractive error can control eye growth implies that defocus, and its sign, can in some way be detected in the peripheral retina and can generate a signal to control ocular growth rates, although such detection need not occur at the conscious level. Several possible mechanisms for directing appropriate eye growth have been suggested, including changes in retinal protein levels, the Stiles Crawford effect and / or ocular aberrations. As yet, there is no conclusive evidence in support of any of these (see Wallman and Winawer (2004) for review). The short-term foveal response to defocus under photopic conditions is accommodation and, if the peripheral retina can detect defocus, it is reasonable to expect that an accommodation response can be elicited by stimuli which fall in the peripheral visual field. Any evidence for such a response would tend to provide some support to the hypothesis of Hoogerheide *et al.* (1971) although absence of response would not negate it, since accommodation involves central as well as local peripheral retinal processes.

Early studies suggested that the accommodation response was controlled by the fovea (Fincham, 1951; Campbell, 1954). Later work showed that stimuli falling outside the central fovea could still cause an accommodation response (Whiteside, 1957; Phillips, 1974; Bullimore and Gilmartin, 1987a,b; Gu and Legge, 1987; Hung and Ciuffreda, 1992), although response accuracy was progressively reduced as the eccentricity of the target increased (see review by Ciuffreda 1991). There was some disagreement on the angular extent over which such peripheral stimuli were effective: although Whiteside (1957) found that stimuli were only effective out to field angles of around 5 degrees, in the study of Gu and Legge (1987) responses continued to be elicited even when the field angles were as large as 30 degrees. Other authors (Hennessy and Leibowitz, 1971; Hennessy, 1975) found that when a target at a fixed distance was viewed foveally through a surrounding concentric circular aperture or annulus of a few degrees in diameter, placed in a dark field at a different distance to provide a potentially conflicting accommodation stimulus, the accommodation response to the fixated target varied with the distance of the surrounding peripheral target. Where, however, the same stimulus vergence is maintained over the available field, changes in the field subtense have no effect on the steady-state accommodation response (Yao *et al.*, 2009).

Overall, then, accommodation studies suggest that stimuli falling on the peripheral retina can alter the accommodation response of the eye and, in the presence of an axial accommodation target, can affect the response to the latter. There is, however, considerable disagreement between authors as to the exact nature of the response and no real understanding as to how the stimuli falling on different regions of the retina might summate in their effects. Of relevance is the finding that depth-of-focus increases and blur sensitivity decreases with increasing eccentricity, suggesting that larger errors in response would be tolerated in the periphery (Charman and Radhakrishnan, 2010). Moreover, for a circular field, depth-of-focus increases with the field radius, up to radii of at least 8 degrees, implying that peripheral imagery influences the nominally axial judgement (Ciuffreda *et al.*, 2005). Studies in which the state of focus is varied in the peripheral retina show that, for normal subjects, changes in spherical focus have little effect on resolution tasks for peripheral angles in the range 10 to 60 degrees (Charman and Radhakrishnan, 2010). However, detection of pattern, movement, and flicker may be markedly affected by changes in focus of as little as 0.5 D, even at eccentricities of 20 to 30 degrees (Charman and Radhakrishnan, 2010).

Some authors have found that myopes exhibit lower and less stable levels of accommodative response to foveal targets when compared to emmetropes (McBrien and Millodot, 1986; Abbott *et al.*, 1998). There are also suggestions that, on axis, myopic eyes are poorer in detecting the presence of blur when compared to emmetropes (Rosenfield and Abraham-Cohen, 1999; Radhakrishnan *et al.*, 2004a,b). If these differences also occurred in the peripheral retina, they could imply that myopes would be less responsive to peripheral accommodation stimuli.

In the light of the possible influence of the relative peripheral refractive error on refractive development and the further possibility that both axial and peripheral accommodation responses differ in myopes and emmetropes, the present study aimed to evaluate the accommodative response to peripheral stimuli in the two refractive groups. Since there is evidence that the variation with field angle in both optical (Atchison *et al.*, 2006b) and neural characteristics is different in the horizontal and vertical meridians (Curcio *et al.*, 1991; Anderson *et al.*, 1992) various combinations of small stimuli located in either the horizontal or vertical visual fields were used, rather than circular targets concentric to the fovea as employed in several earlier studies (Bullimore and Gilmartin, 1987a,b; Gu and Legge, 1987).

9.3 Methods

Twenty subjects (6 male and 14 female) were recruited for the study. The age of the subjects ranged between 19 and 31 years (mean: 24.8 ± 4.5 years). All subjects were free of any ocular pathology and could achieve a visual acuity of 6/5 or better when corrected. Mean spherical equivalent corrections, calculated as spherical power plus half of the cylinder, were in the range -6.00 to +0.50 D (median: -0.55 D; mean -1.06 ± 1.61 D). The group included ten emmetropes (mean spherical equivalent between +0.50 and -0.50 D; median: +0.08 D; mean 0.02 ± 0.35 D) and ten myopes (mean spherical equivalent > -0.50 D; median: -1.63 D; mean -2.10 ± 1.72 D; range -0.83 to -6.00 D). In all cases uncorrected astigmatism was < 1.00 DC. The study followed the tenets of the Declaration of Helsinki and written informed consent was obtained from all participants after the nature of the study and possible consequences of the study had been explained. The project protocol was approved by the Senate

Committee on the Ethics of Research on Human Beings of the University of Manchester.

The subjects were asked to view monocularly a series of targets (Figure 9.1) presented on a monitor placed 60 cm away from the eye (1.67 D stimulus). The targets were generated in a PowerPoint presentation.

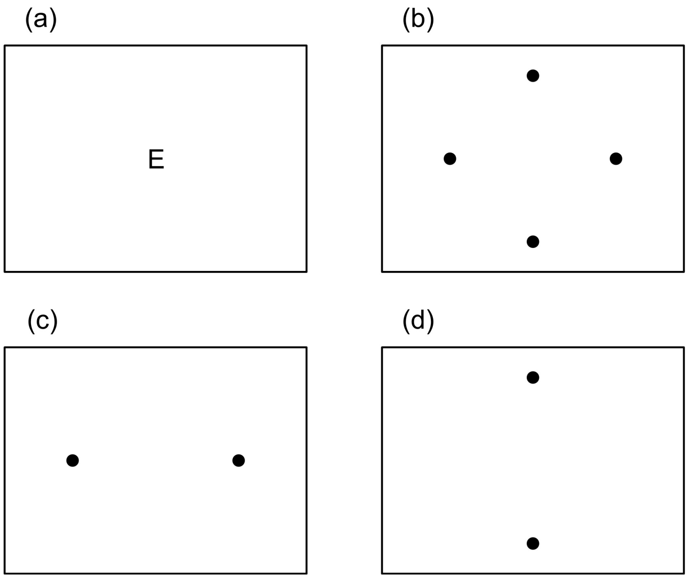

Figure 9.1 – Targets which were presented by a Power Point presentation on a green background.

A single, high-contrast 6/9 Snellen E was used for central accommodation measurements (Figure 9.1 a) since such a target has been widely used in previous work on foveally-driven accommodation. A preliminary pilot study with a subset of eight subjects showed no significant difference between the accommodation responses found when either this Snellen E or a single 0.5 degree subtense, circular, black spot was used as a central target.

The peripheral accommodation targets were circular black spots, each 0.5 degree in diameter, positioned at nominal eccentricities of 5, 10 and 15 degrees. At each eccentricity, three targets were used: four spots, with two in the horizontal meridian and two in the vertical meridian (Figure 9.1 b); two spots separated in the horizontal meridian (Figure 9.1 c); and two spots separated in the vertical meridian (Figure 9.1 d). Fixation was maintained at the centre of each peripheral target by asking the participants to look at the blank centre of the screen and not to move their eyes. Control studies conducted to monitor the extent of eye movements with these instructions, using eight subjects and the Eyelink II eyetracker (SR Research Ltd., Mississauga, Canada in conjunction with Motion Monitor software Innovative Sports training Inc., Chicago, IL, USA), showed the mean and standard deviation of the range of maximal departures from central fixation to be 2.06 ± 2.06 degrees in the horizontal meridian and 2.13 ± 1.27 degrees in the vertical meridian over a 6 second interval.

The targets were presented on a CRT monitor having a green phosphor (chromaticity coordinates x = 0.290, y = 0.611, peak wavelength 547 nm with a bandwidth of about 30 nm, Mitsubishi Diamond Pro 2070SB; Cambridge Research Systems, Rochester, UK). The background luminance of the monitor was 45 cd m^{-2} and the room lights were dimmed. The monitor screen subtended 37 degrees horizontally and 30 degrees vertically and was surrounded by an opaque card, which masked the edge of the screen. A further outer boundary was provided by the viewing aperture of the open-view autorefractor used to make the accommodation measurements. This restricted the open field to approximately 35 degrees vertically and 70 degrees horizontally, the field outside this boundary, defined by the edge of the aperture at a distance of about 0.1 m, appearing dark. These outer boundaries potentially provided fixed, weak, peripheral accommodation stimuli. Pilot studies on two subjects, using the same methods as those described below, showed that accommodative response/stimulus slopes, when the target was a blank screen within these boundaries and fixation was maintained on the centre of the screen, were 0.05 and 0.06, indicating that the accommodative stimulus produced by the surrounds was minimal. The limited screen size meant that, for 15 degrees nominal eccentricities, the eccentricities of the two vertical spots had to be reduced to 14 degrees.

Measurements were taken with a Shin-Nippon SRW 5000 open-field autorefractor (Ajinomoto Trading Inc., Tokyo, Japan). This instrument provides reliable measurements of refractive error (Chat and Edwards, 2001; Mallen *et al.*, 2001). Both eyes of all myopic participants were corrected with soft contact lenses, as it has been shown that wearing contact lenses does not have a significant influence on autorefractor measurements of accommodation (Strang *et al.*, 1997; Day *et al.*, 2008). The measurements of accommodative response were obtained monocularly through the right eye, which was occluded with an IR filter while the left eye viewed the target. Spherical trial lenses of powers +1.50, +0.50, -0.50, -1.50 and -2.50 D at a vertex distance of 13 mm were used in front of the left eye to stimulate accommodation: allowing for lens effectivity and the target distance, the resultant stimuli were 0.20, 1.19, 2.14, 3.08 and 3.99 D. Three readings were taken for each stimulus and each fixation target. Each accommodative response measurement was obtained by averaging the mean spherical equivalents of the three measurements from the Shin-Nippon and reversing the sign.

It was assumed that, as accommodation is driven bilaterally, the responses would be equal in the two eyes (Campbell, 1960; Heron and Winn, 1989; Charman, 2008). Obtaining measurements from the fellow eye rather than the viewing eye had the advantage that problems of lens reflections were avoided, together with the need to correct the autorefractor readings for the effects of the trial lenses when estimating the accommodation responses (Abbott *et al.*, 1998).

Due to spectacle magnification effects, the targets' peripheral angles were altered slightly, by factors between 1.03 and 0.96, when the +1.50 to -2.50 D spectacle lenses were used: it was felt that such changes were small enough to be neglected and, in any case, that effects would apply equally to each of the refractive groups.

9.3.1 Data analysis

Responses were averaged across subjects within each refractive group for each target type, field position and stimulus level.

To yield single-figure indices of accommodative performance for each refractive group, target type and field position, a least-squares regression line fit was made to the accommodative response/stimulus data over the stimulus interval $x_1 = 1.19$ to $x_2 = 3.99$ D (nominally 1.0 - 4.0 D). Visual inspection of the data for each subject and condition confirmed that this range avoided the non-linear region of the response/stimulus curve that is usually found when the stimulus values are small. The slope of each fit was used as one measure of performance. Since a response/stimulus curve may have an 'ideal' slope of unity yet still exhibit lags or leads in accommodation, an additional 'accommodative error index', I, was calculated (Chauhan and Charman, 1995). Using the slope (m), intercept (c) and squared Pearson product-moment correlation coefficient (r^2) of the regression line, the accommodative error index, I, was given by:

$$I = \frac{|(1-m)(\frac{x_2+x_1}{2}) - c|}{r^2} \tag{9.1}$$

9.4 Results

In most participants, accommodative response to the targets decreased with increasing eccentricity of the target. The mean response/stimulus data for the central and peripheral four-spot targets are shown in Figure 9.2. It is evident that, as the target eccentricity increased, the accuracy of accommodative response decreased and lags increased. The myopic group tended to show a lower accommodative response to any given stimulus level at all eccentricities, particularly at higher stimulus levels (compare Figure 9.2 a with Figure 9.2 b).

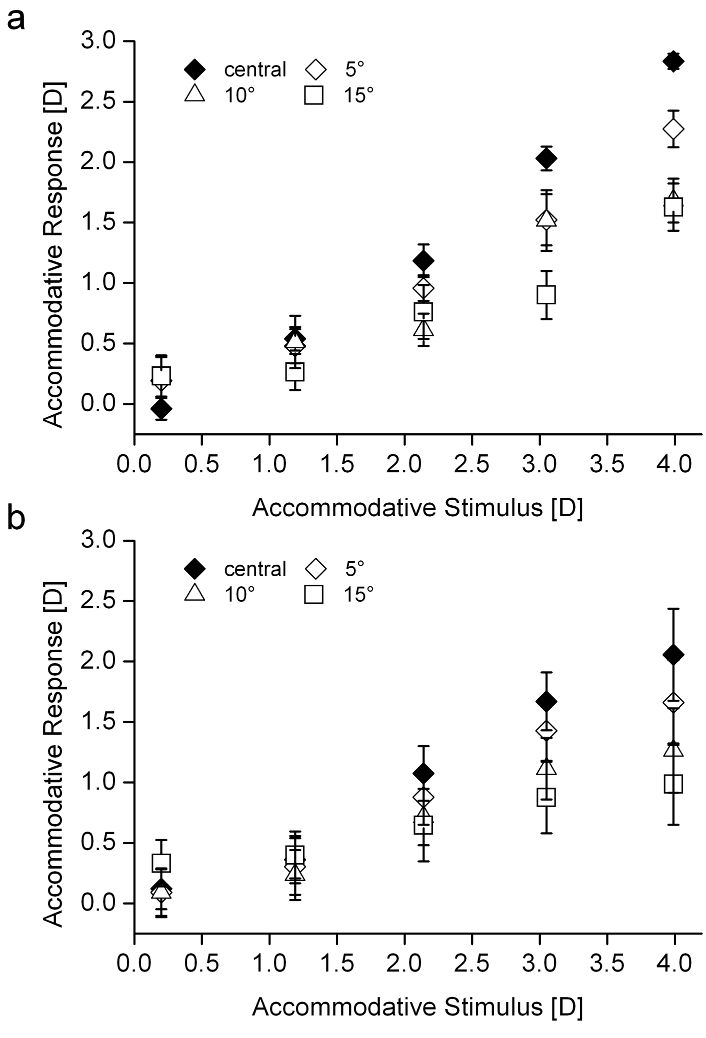

Figure 9.2 – Example of mean accommodative responses to central and peripheral targets for (a) emmetropes and (b) myopes. Data for the eccentric positions were collected using the four-spot target. Error bars show ± 1 standard error of mean.

Figure 9.3 shows the mean accommodative responses for the two refractive groups as a function of accommodative stimulus for 5, 10 and 15 degrees eccentricities, for the four- and two-spot target presentations. Figure 9.3 suggests that accommodative responses to peripheral targets remain similar irrespective of whether the spots of the targets are presented only in the horizontal or vertical meridian or in both meridians. The largest differences between myopes and emmetropes appear at the higher levels of accommodative demand.

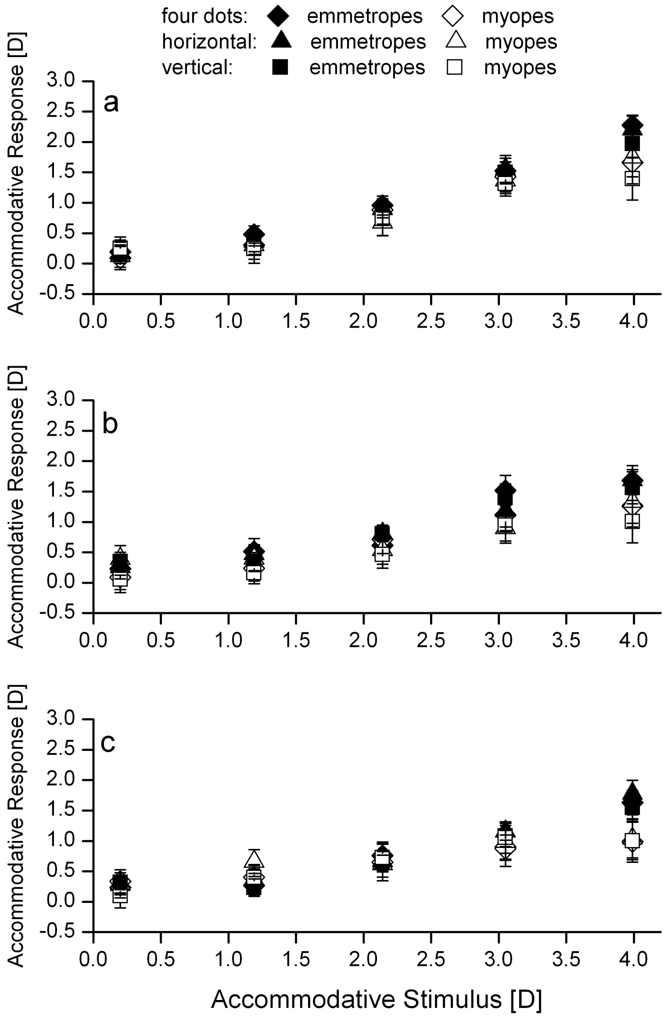

Figure 9.3 – Mean levels of accommodation response for different targets and subject groups at peripheral angles (a) 5 degrees, (b) 10 degrees and (c) 15 degrees. 'Horizontal' and 'Vertical' refer to the two-dot targets illustrated in Figure 9.1 c, d respectively. Vertical bars represent standard errors. Closed symbols represent emmetropes and open symbols myopes. Diamonds: four dot targets; triangles: horizontal targets and squares: vertical targets.

Figure 9.4 shows the means of the individual slopes of the accommodative response function of myopes and emmetropes for all eccentricities and target conditions. As noted earlier, slopes were calculated for the quasi-linear part of the accommodative response curve (nominally 1.0 - 4.0 D), and excluded the 'distance' measurement (Taylor *et al.*, 2009).

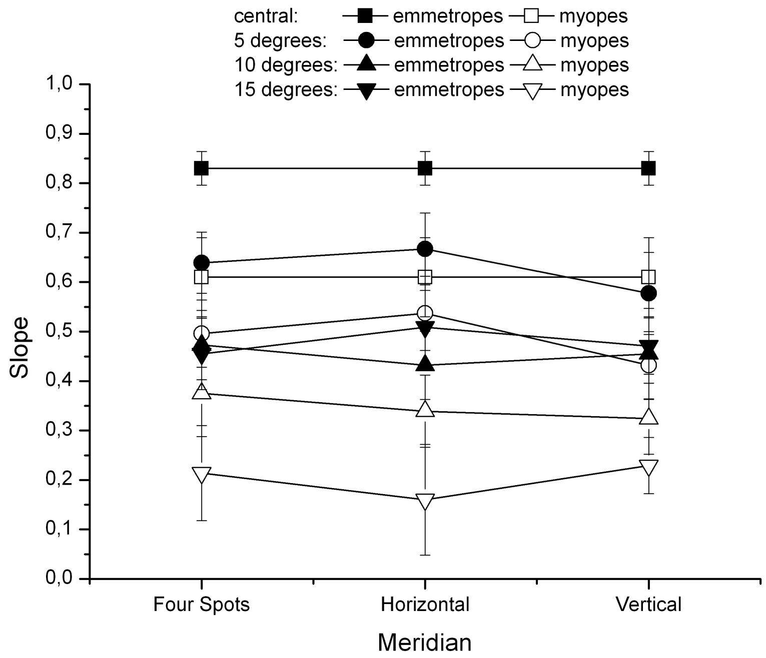

Figure 9.4 – Slopes of the accommodative response functions for the central and three types of peripheral target in emmetropes and myopes with standard error bars.

Generally, the slope for the central target was higher in emmetropes than in myopes. In both refractive groups, the accommodative response slope tended to reduce with increasing eccentricity of the accommodative stimulus. Slopes for stimuli in the horizontal and vertical meridians were similar, indicating that both stimuli elicit similar amounts of accommodation. A one-way analysis of variance with slopes as the dependent variable and refractive error group as the independent variable showed a significant difference between the two refractive groups for central ($F_{(1,18)}$ = 6.1, p = 0.02), four dots at 15 degrees ($F_{(1,18)}$ = 4.46, p = 0.049), horizontal dots at 15 degrees ($F_{(1,18)}$ = 7.6, p = 0.01) and vertical dots at 15 degrees ($F_{(1,18)}$ = 9.9, p = 0.01) targets. A repeated measures analysis of variance showed a significant difference in slopes ($F_{(9,171)}$ = 13.1, p = 0.001) for the 10 different measurement conditions. A Bonferroni post-hoc test revealed significant differences between the central and seven peripheral targets (5 degrees, vertical: p = 0.012; 10 degrees, four dots: p = 0.001; 10 degrees, horizontal: p = 0.001; 10 degrees, vertical: p = 0.001; 15 degrees, four dots: p = 0.001; 15 degrees, horizontal: p = 0.001; 15 degrees, vertical: p = 0.001). The 5 degrees four-dots and 5 degrees horizontal-dots targets compared to the central target were not significantly different (p = 0.055 and p = 1.00, respectively).

The accommodative error index, pooled over all four-dots targets (Figure 9.1), is plotted as a function of target eccentricity in Figure 9.5 for myopes and emmetropes. Both groups show an increase in accommodative error index with target eccentricity. Note the difference in standard errors between myopes and emmetropes and the increasing difference with eccentricity. However, for all three peripheral targets used (four dots, horizontal and vertical dots) a one-way analysis of variance showed no significant statistical difference between the refractive groups (four dots: 5 degrees: p = 0.3, 10 degrees: p = 0.36, 15 degrees: p = 0.1; horizontal dots: 5 degrees: p = 0.97, 10 degrees: p = 0.95, 15 degrees: p = 0.08; vertical dots: 5 degrees: p = 0.14, 10 degrees: p = 0.42, 15 degrees: p = 0.74).

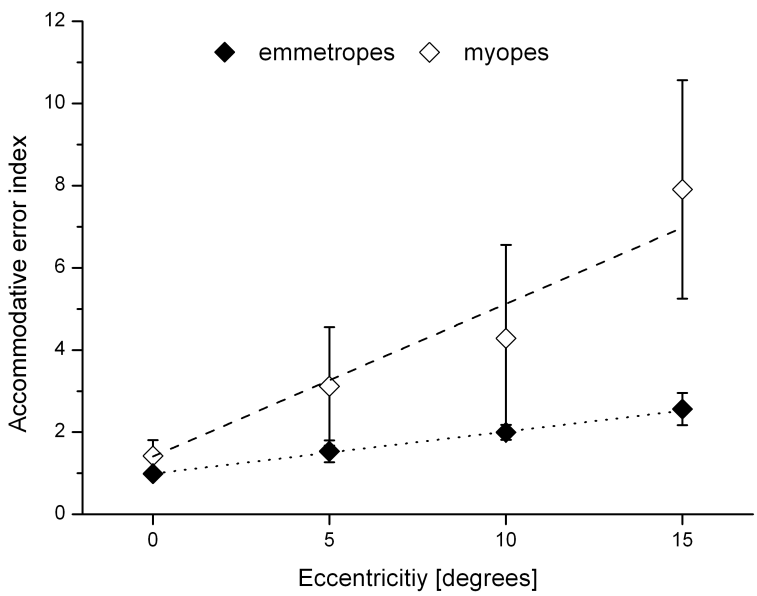

Figure 9.5 – Accommodative error index for four dots targets in myopes and emmetropes with standard error bars (± 1 standard error of mean) and linear trend lines (dashed for myopes and dotted for emmetropes). This shows an apparently large separation between emmetropes and myopes, but the differences at various eccentricities were not statistically significant.

9.5 Discussion

When considering these results, it must be remembered that accommodation was measured in the occluded fellow eye. Thus the apparent responses may be influenced by accommodation-induced vergence of the measured eye, which means that as the stimulus increases its refraction is measured increasingly peripherally. A further factor in relation to the accommodative errors is that, if there is a marked difference between the refraction on axis and in the periphery (relative peripheral ametropia), an axial estimate of the accommodative error will not necessarily indicate the focus error for a peripheral target. The influence of this factor is obviously complicated by the observed dependence of peripheral refractive errors on axial ametropia (Millodot, 1981), the level of accommodation (Smith *et al.*, 1988; Lundström *et al.*, 2009b; Mathur *et al.*, 2009b; Whatham *et al.*, 2009) and the individual. We believe that the combined impact of these effects should be small in the present study, due to the modest range of accommodation stimuli (0 - 4 D) and peripheral target locations (up to 15 degrees) used, which means that the relative peripheral refraction only changes slightly over the field used, but the possibility of some influence cannot be dismissed. Although the proximal accommodation stimulus provided by the target display (Heath, 1956) undoubtedly contributes to the responses, it remains constant and independent of the lens-induced stimulus and the refractive group. However, its effect tends to work against the lens-induced accommodation, and helps to explain the relatively large values of lag observed at the higher lens-induced stimulus levels (Gwiazda *et al.*, 1993).

In the current experimental setting, in which accommodation was stimulated using lenses and the difference between the median spherical equivalent refractions of the myopes and emmetropes was relatively small (-1.63 D compared to +0.08 D), although myopes appeared to have generally lower accommodative response slopes and higher error indices than emmetropes (Figures 9.4 and 9.5), the differences in slope only reached statistical significance for the axial target and for the three targets at 15 degrees. The differences in error index were not significant. Our slope results for axial targets concur with Gwiazda *et al.* (1993), who showed that, for such targets, myopic children exhibit lower accommodative response slopes in comparison to emmetropes for lens-induced accommodation. In contrast, Abbott *et al.* (1998) and Allen and O'Leary (2006) found no statistically-significant differences in lens-induced accommodative response between the two refractive groups in young adults. It may be that the results in studies of this type depend upon the proportions of early-onset, late-onset and progressing myopes among the groups of myopic subjects (Abbott *et al.*, 1998). Previous studies have shown that depth-of-focus increases and blur sensitivity decreases with increasing eccentricity (Wang and Ciuffreda, 2004, 2005). The lower slopes found in our myopic group at 15 degrees may therefore imply that peripheral blur sensitivity is reduced and depth-of-focus increased in myopes as compared to emmetropes, so that they can tolerate larger accommodative errors (Radhakrishnan *et al.*, 2004a,b; Rosenfield and Abraham-Cohen, 1999). Caution should, however, be used in generalising the present monocular results to the case of normal binocular real-world accommodation responses, where a full range of accommodative cues is available and it appears that behavior of myopes and emmetropes is very similar (Ramsdale, 1985; Nakatsuka *et al.*, 2003; Yeo *et al.*, 2006).

The magnitudes of the accommodation response slopes in the present study were broadly similar to those found in prior studies in which annular or disc targets concentric with the fixation point and having different angular diameters were used (Bullimore and Gilmartin 1987a,b; Gu and Legge 1987; see Figure 9.6). The slopes decline approximately linearly with the minimum angle of resolution for the retinal location on which the edge contour falls (Yeo *et al.*, 2006). It is of interest that the overall lengths of the circumferences of the concentric disc or aperture stimuli that were used by the earlier authors were much larger than those of our spot stimuli, which affected much smaller areas of the retina, implying that the strength of the stimulus is not linked in any simple way to the length of the boundary contours which are to be focused. It would, however, be of interest to explore the possible significance of cortical magnification on the results by applying M- or some other form of scaling to the dimensions of the dots of the peripheral targets (Daniel and Whitteridge, 1961; Charman, 1986).

The present study, in which the maximal peripheral angles were restricted to 15 degrees, showed that peripheral targets in the horizontal and vertical meridians produced similar accommodative responses (see Figure 9.4). Although Atchison *et al.* (2006b) found that peripheral refraction differs between the horizontal and vertical meridians of the visual field, differences were small for field angles below 20 degrees. Again, although ganglion cell density and psychophysical measurements provide evidence for a weak human visual streak, i.e. an area of relatively higher ganglion cell density along the nasal-temporal horizontal meridian, the differences between the horizontal and vertical meridians are modest over the central field (Curcio *et al.*, 1991;

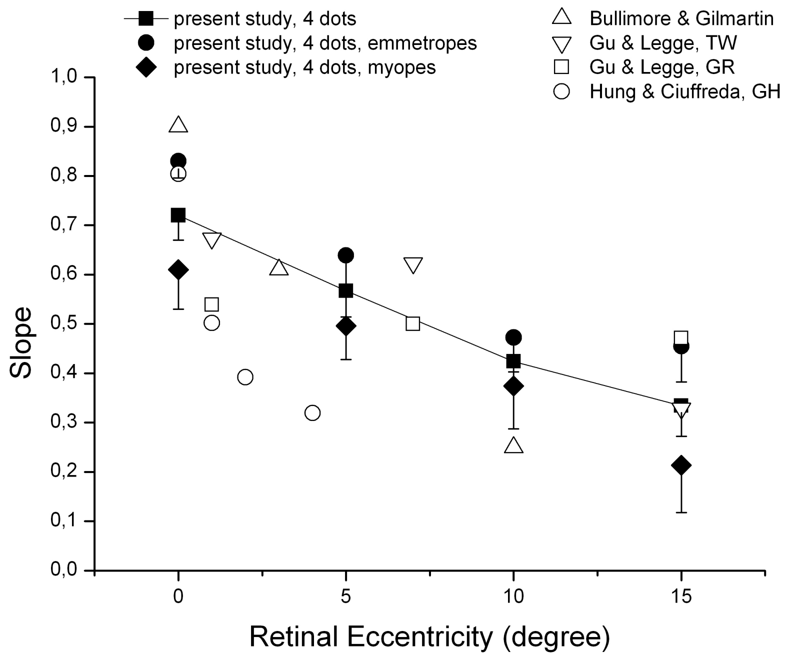

Figure 9.6 – Comparison of slopes for accommodative response functions between studies. The Gu and Legge data are for two individual subjects (TW and GR) and the Hung and Ciuffreda data are also for a single subject (GH). The Bullimore and Gilmartin data are means for seven subjects. The data labelled 'present study, four dots' are the overall means for all the myopic and emmetropic subjects. Error bars represent standard errors.

Anderson *et al.*, 1992). It is, however, striking that in the case of our 15 degrees targets, where one of the horizontal spots must have fallen on or close to the blind spot, the responses to the horizontal and vertical spot targets were still similar, so that one spot was equally effective as a stimulus as two (or even four) spots.

While the present results confirm that a peripheral stimulus can elicit an accommodation response, they give no information over how the effects of stimuli distributed across the visual field may summate. The work of Hennessy and Leibowitz (1971) and Hennessy (1975) shows that additional stimuli at a few degrees in the periphery can substantially affect the response to an axial target. It is clear, however, that, in the real world, it might be disadvantageous, if peripheral stimuli had a too strong effect. Consider for example a stimulus at a distance of 0.4 m (2.5 D) on a textured flat surface, such as a desk top, inclined at 45 degrees to the visual axis. In both the vertical and horizontal field meridians, the accommodation stimulus provided by the surface changes continually with the field angle (Virsu and Hari, 1996). These changes are illustrated in Figure 9.7. Evidently the peripheral accommodation stimulus shows continuous variation with field angle in not only the vertical meridian but also in the horizontal and other meridians, the precise effects depending upon the geometry of the viewing environment, the working distance and other factors. If accommodation is to be appropriate to the fixated object, and the retina and peripheral refraction possess rotational symmetry about the visual axis, it is evidently necessary that the influence of the central stimulus should normally be dominant over that of the varying peripheral stimuli. Arguments of this type have, of course, been used previously to justify the development of 'ramp' retinas and lower field myopia in ground-feeding birds or animals that maintain an approximately constant posture with respect to their environment and have an acuity which is relatively constant across the field (Fitzke *et al.*, 1985; Hodos and Erichsen, 1990). It is of interest that, insofar as the situation assumed in Figure 9.7 approximates to many present-day human working environments involving deskwork, it might actually be advantageous to develop a distance refraction which rather than being emmetropic, was myopic on axis and showed relative peripheral hyperopia along the horizontal meridian. Thus the refractive pattern observed across the retina of todays myopes might simply represent successful adaptation to excessive exposure to the type of near environment shown in Figure 9.7 a.

We can compare the stimulus offered by this near environment (Figure 9.7 a) with that experienced by an individual standing in open horizontal terrain viewing the horizon. In the latter case, only in the lower field will a non-zero dioptric stimulus be experienced, with a value that depends upon the height of the individual. Figure 9.7 b shows the change in the stimulus in the horizontal and vertical field meridians for a typical adult (eye height 1.6 m) and child (eye height 0.8 m). Evidently in this outdoor case the stimulus to accommodation will be small and almost uniform right across the central visual field. If, then, myopia develops as an adaptation to the near accommodation stimuli offered by indoor environments, regular exposure to outdoor environments ought to provide a corrective effect, as observed in several recent surveys, although aspects of outdoor activity other than accommodation demand, such as UV exposure, might also be beneficial (Jones *et al.*, 2007b; Rose *et al.*, 2008b; Dirani *et al.*, 2009).

To summarise, in the absence of a central stimulus, accommodation stimuli falling on the peripheral retina at field angles up to at least 15 degrees are able to elicit accommodation responses, which weaken as the peripheral angle increased. Under the monocular conditions of the present study, with stimuli being varied by the use of spectacle lenses, there is some evidence

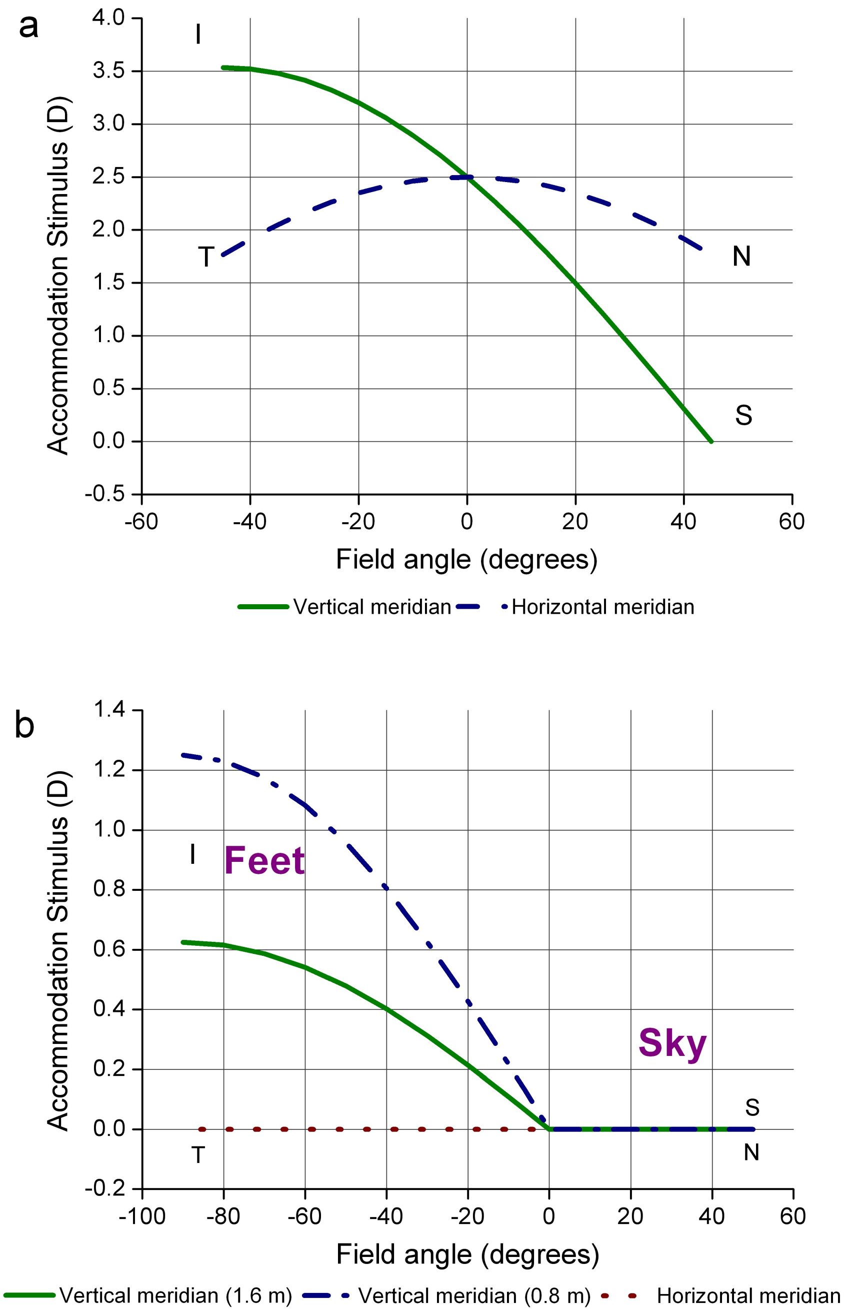

Figure 9.7 – (a) Variation in accommodation stimulus along the vertical and horizontal visual field meridians in a near environment (see text): S,I,T,N represent the superior, inferior, temporal and nasal sectors. (b) Accommodation stimulus in the vertical and horizontal field meridians when a standing individual views the horizon in an open outdoor landscape: results are shown for individuals with eye heights of 1.6 and 0.8 m (see text).

that the accommodation is slightly less effective in myopes than emmetropes but the effect, if any, is marginal. Although the results suggest that the peripheral retina is sensitive to optical focus, and hence provide some support for the suggestion that the state of focus in the periphery could influence refractive development (Hoogerheide *et al.*, 1971), it seems likely that response to accommodative stimuli covering an extended visual field will normally be dominated by the stimulus at the fovea (Yao *et al.*, 2009). This implies that, if imagery and defocus in the peripheral retina play a role in emmetropization, directional cues to growth are unlikely to be provided by peripherally-initiated accommodation (Yao *et al.*, 2009; Mathur *et al.*, 2009a).

9.6 Remarks

For chapter 9 the data were collected by me and I analysed the data. The first draft of the manuscripts was written by me and I dealt with reviewers' comments along with my supervisors.

This chapter has been published: Hartwig, A., W. N. Charman and H. Radhakrishnan (2011). Accommodative response to peripheral stimuli in myopes and emmetropes. *Ophthalmic Physiol Opt* **31**(1): 91-9.

Chapter 10

Peripheral refraction and myopia progression

10.1 Abstract

Purpose: The purpose of the study was to evaluate a possible link between peripheral refraction along the horizontal meridian and refractive error progression during one year.

Methods: Peripheral refractions along the horizontal meridian up to 30 degrees were measured using an open field autorefractor. Additionally axial length measurements and subjective refraction were performed. A year later axial length measurements and subjective refraction were repeated. Progression rates and their relation to peripheral refraction parameters were analysed. Therefore peripheral refraction data, in terms of M, J_{180} and J_{45}, were fitted with polynomial curves.

Results: The change in subjective refraction was 0.04 $\pm$ 0.29 D in myopes and -0.12 $\pm$ 0.38 D in emmetropes. No significant correlations were found between refractive error progression and peripheral refraction parameters. Significant correlations were found between subjective M and B1 fitting coefficient for M and between subjective M and relative peripheral M at 30 degrees temporal retina. The first significant correlation indicates a temporal shift of the polynomial fitting with increasing myopia and the second significant correlation indicates increasing relative hyperopia at 30 degrees temporal retina with increasing central myopia.

Conclusions: There is some further evidence for relative peripheral hyperopia

in myopes. However, the present study failed to show a link between peripheral refraction and refractive error progression. This is possibly due to a low progression rate in our study population.

10.2 Introduction

The prevalence of myopia is increasing dramatically in some countries (Saw *et al.*, 1996; Goldschmidt, 2003; Saw, 2003; Lin *et al.*, 2004; Morgan and Rose, 2005) and various studies have tried to find the reason for this increase (for example Hammond *et al.*, 2004; Charman, 2005; Hartwig *et al.*, 2011a), for review see Young (2009) as well as Charman and Radhakrishnan (2010). Literature suggests that emmetropisation is a visually guided process (Troilo and Wallman, 1991; Norton, 1999; Siegwart and Norton, 1999; Wallman and Winawer, 2004). So far, it appears to be that peripheral refraction may have potential to control myopisation: This idea goes back to Rempt *et al.* (1971) who measured peripheral refraction using a retinoscope in a large population and compared central and peripheral refractions. This comparison showed that central emmetropia or central minor hyperopia was associated with mixed astigmatism peripherally. For central myopia they found mainly hyperopic astigmatism and rarely mixed astigmatism. Hoogerheide *et al.* (1971) measured peripheral refraction using a retinoscope in 20 degree-steps up to 60 degrees in young pilots and related their findings with myopia progression. The time period during which progression data were collected was not given clearly. Their analysis showed that peripheral hyperopia is associated with myopisation. In an animal study, Smith *et al.* (2005) showed that the macula in monkeys is not essential for the process of emmetropisation and that the peripheral retina can contribute to emmetropisation. In an experiment in chickens Schippert and Schaeffel (2006) could not confirm that peripheral refraction might guide central refraction development. This, however, might be caused by selection of the aperture size for the unobstructed central vision. The authors concluded that aperture sizes smaller than 4 mm (at 2 to 3 mm vertex distance) might be capable of altering central refraction. Using an open-field autorfractor, Atchison *et al.* (2006b) compared peripheral refractions along the horizontal and vertical meridian in myopic and emmetropic adults. They found that the link between peripheral refraction along the horizontal meridian and myopia is greater than the link between peripheral refraction along the vertical meridian and myopia. In emmetropes they found relative myopic peripheral refractions along the horizontal meridian and in myopes they found relative hyperopic peripheral refractions, which is in line with previous findings (Rempt *et al.*, 1971; Millodot, 1981; Mutti *et al.*, 2000; Logan *et al.*, 2004; Atchison *et al.*, 2005b; for a detailed review about peripheral refraction, see Charman and Radhakrishnan, 2010).

The link between peripheral refraction and refractive error in both animal and human studies has led to experiments in which spectacle lenses or contact lenses alter the peripheral refraction (Holden *et al.*, 2010; Sankaridurg *et al.*, 2010; Lopes-Ferreira *et al.*, 2011) and found that such lenses can reduce myopia progression within one year. In contrast, Mutti *et al.* (2007) analysed refractive error, axial length and peripheral refraction before, during and after the onset of myopia in children. Peripheral refraction was analysed only in terms of data in one peripheral gaze (30 degrees temporal field) rather than the shape along the horizontal meridian. Based on their long-term observations, they concluded that although peripheral refraction might have an effect, it is likely that more than one factor may influence myopisation.

To evaluate how peripheral refraction can influence refractive error development, it is important to investigate peripheral refraction over a range of eccentricities with refractive error progression. Therefore, the aim of the present study was to determine, if peripheral refraction patterns might have an influence on myopia progression in a group of young adults. We used an open-field autorefractor and measured peripheral refraction over 40 degrees of the horizontal visual field. Also, we incorporated axial length measurements of the eye and measured progression in terms of refractive error and axial length over a one-year period.

10.3 Methods

Fifty-four subjects (20 male and 34 female) were recruited. The age of the subjects ranged between 19 and 38 years (mean ± SD: 24.9 ± 5.1 years; median 24 years). All subjects were free of any ocular pathology and could achieve a visual acuity of 6/6 partially or better when corrected. There were 32 myopes (spherical equivalent from -9.63 D to -0.63; mean -3.46 ± 2.35 D; median -1.38D) and 22 emmetropes (spherical equivalent from -0.50 D to 0.50 D; mean -0.03 ± 0.36 D; median -0.19D). The mean age of the myopes was 25.3 ± 5.5 years and 24.5 ± 4.5 years in the emmetropes. For all the parameters, only the right eye data were analysed.

The study followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants after the nature of the study and possible consequences of the study had been explained. The project protocol was approved by the Senate Committee on the Ethics of Research on Human Beings of the University of Manchester.

The subjects were first seen between February and March 2010. At that time subjective refraction, axial length measurement and peripheral refraction were performed. After a period of one year (March 2011), the same patients were seen again. During this visit a subjective refraction and axial length measurement were performed.

Subjective refraction was performed to an accuracy of ±0.25 DS and ±0.25 DC to obtain maximum plus giving best visual acuity. The cylindrical component, if existent, was found using a cross-cylinder. To refine the spherical component at the end of the routine, the duochrome test was used.

For axial length measurement the LenStar 900 (Haag-Streit, Koeniz, Switzerland) was used. The instrument uses the effect of time domain interferometric or coherent superposition of light waves to measure ocular distances in the eye. It uses an 820 nm superluminescent diode with a Gaussian-shaped spectrum to provide a high axial resolution. It has been shown before that the LenStar is a reliable instrument for axial length measurements (Buckhurst *et al.*, 2009; Holzer *et al.*, 2009; Cruysberg *et al.*, 2010; O'Donnell *et al.*, 2011). The instrument was aligned using the image of the patient's eye on the computer monitor. Subjects were asked to blink just prior to measurements being taken. Blinking or loss of fixation were detected automatically by the instrument and in this case the measurements were repeated. The instrument takes 16 consecutive scans per measurement without the need for realignment and five measurements were taken as recommended by the manufacturer. The internal software calculated the mean of these five readings. The axial length measurements were performed only on 48 subjects (which included 30 myopes and 18 emmetropes).

For peripheral refraction the open-field autorefractor Shin-Nippon SRW 5000 (Ajinomoto Trading Inc., Tokyo, Japan) was used, which was shown to be reliable for central and peripheral refraction (Mallen *et al.*, 2001; Hartwig, 2007). Participants fixated on targets (Maltese crosses) along the horizontal meridian that were placed in 5 degrees steps from 30 degrees nasal to 30 degrees temporal retina which makes a total of 13 different eccentricities. The order of target fixation was randomised. Relative peripheral refraction was computed as the difference between mean spherical equivalent in primary gaze and mean spherical equivalent at each peripheral gaze position.

Eleven ($\sim$ 20%) patients could not be followed up, as they had left the Manchester area or could not be contacted.

Refractive error change was characterised as the difference between second visit spherical equivalent refractive error and first visit spherical equivalent refractive error. Therefore negative values describe a change towards minus, i.e., progression of myopia. For axial length measurements progression was again calculated by subtracting the axial length of the first visit from the second visit axial length. A positive value for this difference indicates axial elongation, i.e. myopia progression.

10.3.1 Data analysis

Subjective refraction and autorefractor refractions in terms of sphere (S), cylinder (C) and axis (α) were converted into vector components by the following formulas (Thibos *et al.*, 1997):

$$M = S + \frac{C}{2} \tag{10.1}$$

$$J_{180} = -C + \frac{\cos(2\alpha)}{2} \tag{10.2}$$

$$J_{45} = -C + \frac{\sin(2\alpha)}{2} \tag{10.3}$$

Each of the three components was fitted against the retinal eccentricity with second order polynomial functions using OriginPro 8 (OriginLab Corporation, Northampton, MA, USA). Peripheral refraction data that was measured at 15 degrees nasal retina (optic disc) was disregarded for the fitting. The polynomial fit formula was:

$$f_{(x)} = B2x^2 + B1x + Intercept \tag{10.4}$$

The polynomial fit data were B2, B1 and intercept. B2 describes the opening of polynomial fit curve (B2 >0; opens upwards; B2 <0: opens downwards, Figure 10.1 for illustration) and B1 describes shifts along the abscissa (B1 >0: shift to the nasal side; B1 <0: shift to the temporal side). These fitting parameters were used for statistical analysis.

Differences between the myopes and emmetropes were assessed using one-way analysis of variance. Values are provided as means ± standard deviations.

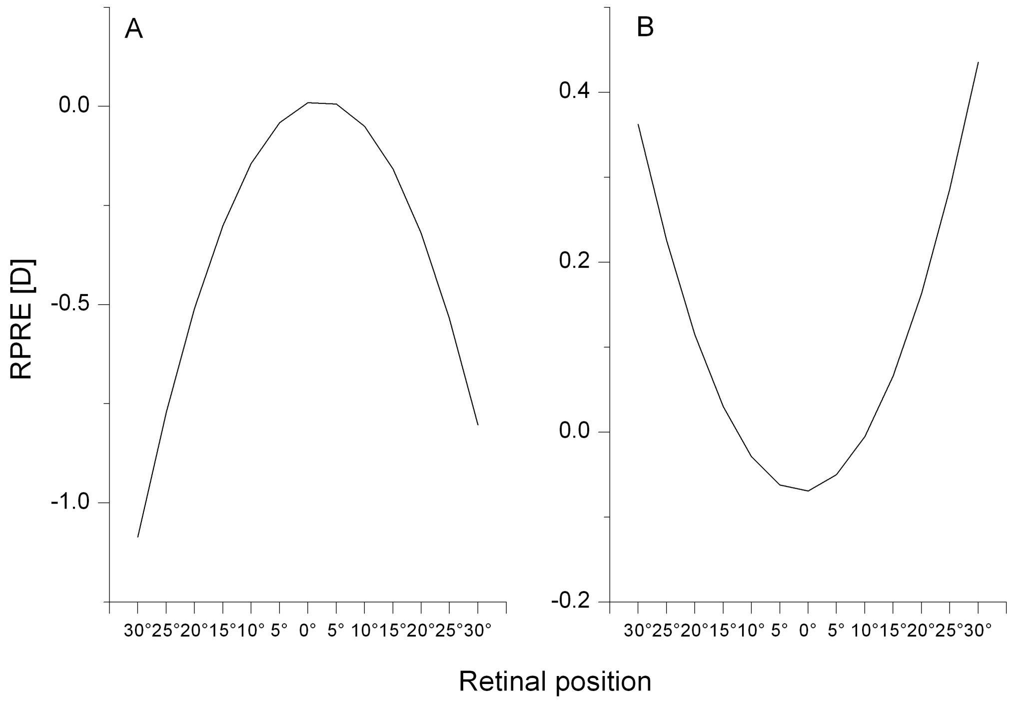

Figure 10.1 – Examples of polynomial fitting in two subjects (A: AS and B: SK) illustrating the effect of B2. In graph A B2 = -0.0011 and in graph B B2 = 0.0005. (RPRE: relative peripheral refractive error)

10.4 Results

10.4.1 Progression during one year

The mean refractive error change within one year was 0.04 ± 0.29 D in myopes and -0.12 ± 0.38 D in emmetropes. Axial length changed by 0.01 ± 0.07 mm in myopes and 0.02 ± 0.07 mm in emmetropes. Changes in refractive error and axial length did not differ significantly between myopes and emmetropes ($F_{(1,41)} = 2.35$; $p = 0.13$; $F_{(1,35)} = 0.03$, $p = 0.87$, respectively).

10.4.2 Peripheral refraction

Peripheral refraction data is presented in Table 10.1. Whereas the M data did not differ between the groups at 30 degrees nasal retina ($F_{(1,52)} = 0.42$; p = 0.52), there was a significant difference at 30 degrees temporal retina ($F_{(1,52)} = 6.17$; p = 0.02). In myopes, M at 30 degrees temporal retina was 0.06 ± 1.13 D and in emmetropes it was -0.60 ± 0.63 D.

Mean relative astigmatic component J_{45} at 30 degrees nasal and temporal retina was not significantly different between the two groups ($F_{(1,52)} = 0.11$; p = 0.74; $F_{(1,52)} = 0.01$; p = 0.99, respectively).

Mean relative astigmatic component J_{180} at 30 degrees nasal and temporal retina were not significantly different in the two groups ($F_{(1,52)} = 2.32$; p = 0.13; $F_{(1,52)} = 0.22$; p = 0.64, respectively).

	M		J_{180}		J_{45}	
Eccentricity	**Myopes**	**Emmetropes**	**Myopes**	**Emmetropes**	**Myopes**	**Emmetropes**
30° nasal	-0.27 ± 1.60	-0.04 ± 0.69	-0.58 ± 0.36	-0.72 ± 0.27	-0.09 ± 0.32	-0.06 ± 0.40
25° nasal	-0.29 ± 1.04	0.15 ± 0.59	-0.41 ± 0.28	-0.51 ± 0.23	-0.16 ± 0.22	-0.06 ± 0.26
20° nasal	-0.36 ± 0.88	0.20 ± 0.54	-0.35 ± 0.38	-0.19 ± 0.25	-0.12 ± 0.38	-0.16 ± 0.38
15° nasal	-0.29 ± 0.62	-0.18 ± 0.73	-0.03 ± 0.35	-0.15 ± 0.36	-0.16 ± 0.30	0.04 ± 0.40
10° nasal	-0.26 ± 0.57	-0.15 ± 0.51	-0.06 ± 0.24	-0.18 ± 0.33	-0.06 ± 0.39	-0.04 ± 0.33
5° nasal	0.00 ± 0.27	0.06 ± 0.28	0.03 ± 0.18	0.02 ± 0.17	-0.04 ± 0.21	-0.08 ± 0.21
5° temporal	0.08 ± 0.24	0.01 ± 0.20	-0.05 ± 0.19	-0.05 ± 0.16	-0.03 ± 0.26	0.01 ± 0.39
10° temporal	0.08 ± 0.47	-0.06 ± 0.30	-0.15 ± 0.20	-0.09 ± 0.15	0.04 ± 0.23	0.03 ± 0.42
15° temporal	-0.06 ± 0.55	-0.28 ± 0.32	-0.31 ± 0.22	-0.26 ± 0.14	0.07 ± 0.24	0.10 ± 0.47
20° temporal	-0.12 ± 0.66	-0.42 ± 0.50	-0.53 ± 0.24	-0.42 ± 0.37	0.08 ± 0.38	0.17 ± 0.32
25° temporal	-0.04 ± 0.90	-0.46 ± 0.49	-0.80 ± 0.26	-0.71 ± 0.33	0.12 ± 0.27	0.18 ± 0.28
30° temporal	0.06 ± 1.13	-0.60 ± 0.63	-1.07 ± 0.44	-1.02 ± 0.32	0.10 ± 0.34	0.10 ± 0.40

Table 10.1 – Peripheral refraction results for M, J_{180} and J_{45} at various retinal eccentricities separated for myopes and emmetropes.

The polynomial fits are presented in Figure 10.2 and the components of the polynomial fitting for the refractive components M, J_{45} and J_{180} separated for myopes and emmetropes are presented in Table 10.2. Whereas J_{180} and J_{45} are symmetric in both groups, there is an asymmetry in M between myopes and emmetropes. Spherical equivalent (M) is significantly different in B1 between the two groups indicating a temporal shift of the fitted curve in myopes and a nasal shift in emmetropes. It is apparent form Figure 10.2 that myopes and emmetropes were myopic in the periphery in terms of M and J_{180}. Only J_{45} was hyperopic in myopes and emmetropes.

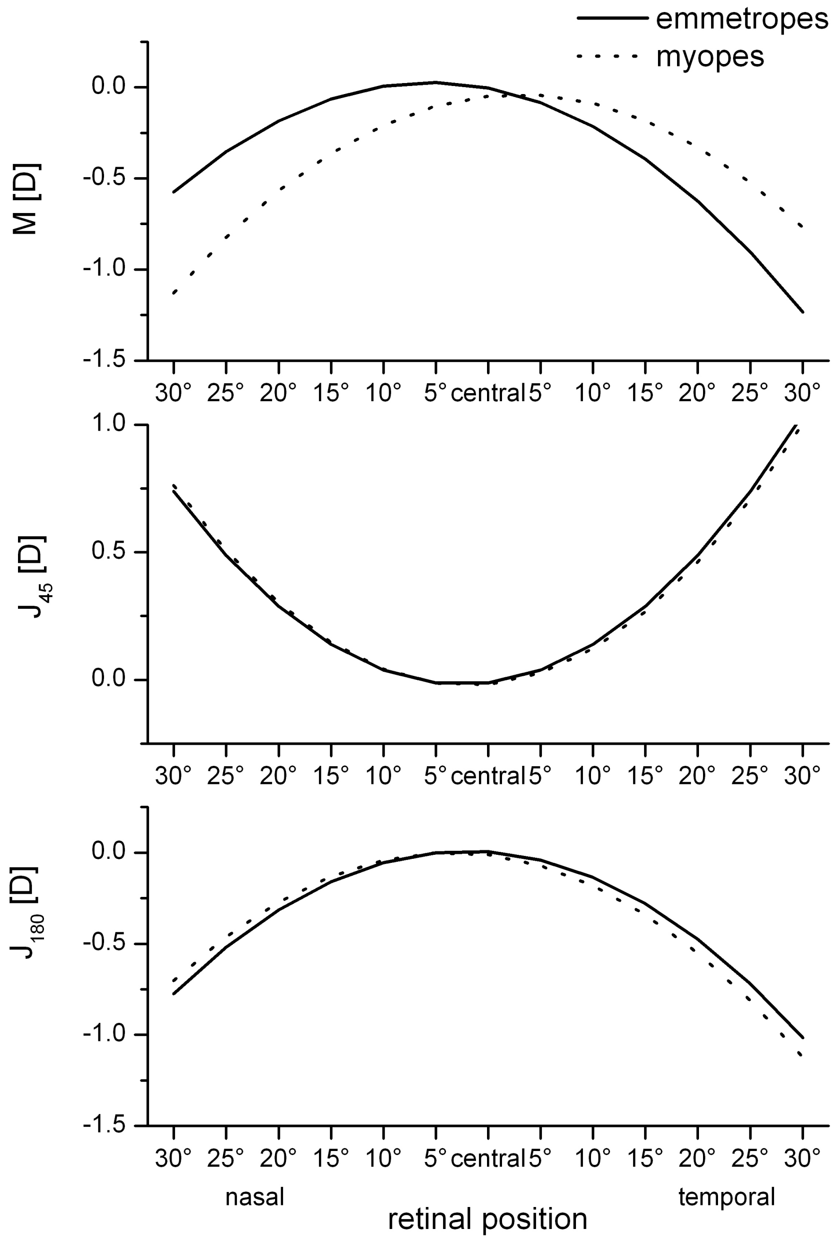

Figure 10.2 – Polynomial curve fittings for M, J_{45} and J_{180} separated for myopes and emmetropes. Note the difference in scaling on the ordinate.

10.4.3 Peripheral refraction, central refraction and progression

To assess the link between peripheral refraction and myopia progression, polynomial fit coefficients for M, J_{45} and J_{180} and relative peripheral refraction at 30 degrees eccentricity were correlated with changes in refractive error and changes in axial length. Also subjective refractions in terms of M, J_{45} and J_{180} were correlated with polynomial fit coefficients and relative peripheral refraction at 30 degrees eccentricity. Due to the multiplicity of correlations

Refraction component	Polynomial fit component	Myopes	Emmetropes	Statistics
	Intercept	-0.048 ± 0.191	-0.004 ± 0.181	$F_{(1,52)} = 0.722$; p = 0.399
M	B1	0.006 ± 0.021	-0.011 ± 0.011	$F_{(1,52)} = 12.208$; p = 0.001
	B2	-0.001 ± 0.001	-0.001 ± 0.001	$F_{(1,52)} = 0.254$; p = 0.617
	Intercept	-0.018 ± 0.151	-0.012 ± 0.206	$F_{(1,52)} = 0.018$; p = 0.895
J_{45}	B1	0.004 ± 0.008	0.005 ± 0.008	$F_{(1,52)} = 0.008$; p = 0.929
	B2	0.001 ± 0.001	0.001 ± 0.001	$F_{(1,52)} = 0.725$; p = 0.398
	Intercept	-0.011 ± 0.125	0.005 ± 0.114	$F_{(1,52)} = 0.243$; p = 0.624
J_{180}	B1	-0.007 ± 0.008	-0.004 ± 0.007	$F_{(1,52)} = 1.648$; p = 0.205
	B2	-0.001 ± 0.001	-0.001 ± 0.001	$F_{(1,52)} = 0.061$; p = 0.805

Table 10.2 – Polynomial fit coefficients for M, J_{45} and J_{180} separated for myopes and emmetropes and analysis of variance results comparing the two groups.

Bonferroni correction was applied. Subjective M and B1 fitting coefficient for M correlated significantly (r = -0.580; n = 54; p <0.001). This indicates a shift of the polynomial fit towards the temporal side with increasing central myopia as evident from Figure 10.2 and 10.3 A. Also, subjective M and relative peripheral M at 30 degrees temporal retina correlated significantly (r = -0.552; n = 54; p <0.001, Figure 10.3 B). This correlation describes an increase in relative peripheral hyperopia with increasing central myopia.

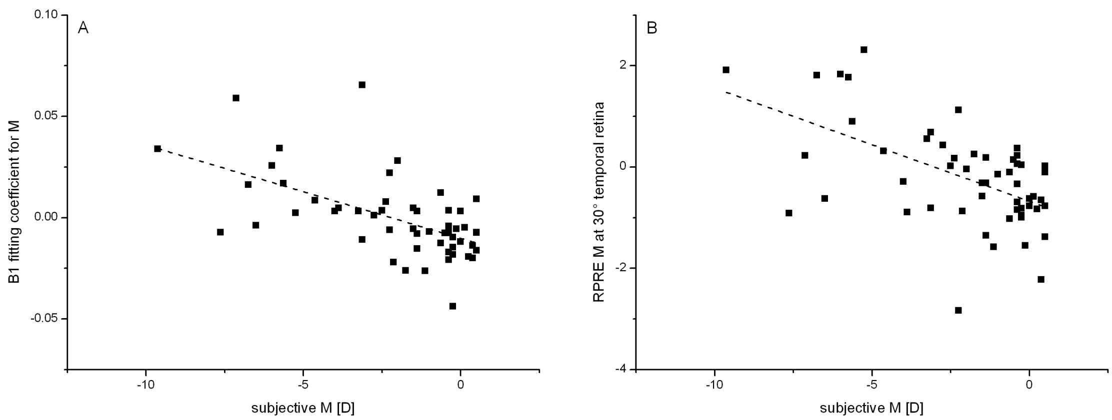

Figure 10.3 – Significant correlations between subjective M and B1 fitting coefficient for M (A) as well as RPRE M at 30 degrees temporal retina (B). Dashed lines represent linear fitting. Details of the correlations are given in text. (RPRE: relative peripheral refractive error)

10.5 Discussion

Based on the assumption that a hyperopic peripheral refraction is a cause for myopisation (Hoogerheide *et al.*, 1971; Smith *et al.*, 2005; Atchison *et al.*, 2006b; Calver *et al.*, 2007; Mutti *et al.*, 2007; Charman and Radhakrishnan, 2010; Mutti *et al.*, 2011) our study gives some further evidence that peripheral refraction and myopisation are linked. In a group of young adults relative peripheral refraction at 30 degrees eccentricity was emmetropic or myopic and refractive error progression was minimal. The low progression rate is possibly due to the age of our subjects. Most myopia progression is usually observed in children rather than in adults (Mutti *et al.*, 2007; Berntsen *et al.*, 2011; Mutti *et al.*, 2011). However, based on previous findings we would have expected to find a higher rate of progression in young adults: during a three year period Blacker *et al.* (2009) found a progression of -0.75 ± 0.76 D in a group of low-Dk/t contact lens wearing myopes. The mean age of that group was similar to our population (23 ± 12 years). In a group of silicone hydrogel lens wearers they found a progression of +0.10 ± 0.60 D over three years, which is comparable to our one year progression data in myopes. The mean-age of this population (38 ± 11 years) was higher than in our population. For a two-year period Jacobsen *et al.* (2008) found a mean progression of -0.25 ± 0.39 D in a group of myopes and non-myopes. The mean age of that population was 23.1 ± 3.3 years. Even though the age is comparable to our study population, the progression of refractive error is higher than in our population.

The myopic peripheral refractions (Figure 10.2) is in line with findings from Seidemann *et al.* (2002). This is underlined by the fact that the age of the subjects is similar in the study of Seidemann *et al.* (range from 21 to 33 years) and in the present study.

Mutti *et al.* (2007) related their peripheral refraction data to the onset of myopia. Therefore a general mean for the peripheral refraction data were not provided. In emmetropic children the relative peripheral refraction at 30 degrees nasal retina was between -0.17 and -0.31 D. In there became-myopic children the peripheral refraction ranged between about -0.2 and +0.5 D. Interestingly the onset of myopia coincided with the most hyperopic peripheral refraction. In our study population of young adults we did not find relative hyperopic refractions in terms of M. In the light of our progression data which is very marginal it would not seem likely to observe relative peripheral hyperopia.

Progression data in children need to be handled with care, as a change in peripheral refraction might go along with the growth of the eye. Our findings are more likely to be comparable with the results from Charman and Jennings (2006) who showed minimal changes in central and peripheral refractions during 26 years of two adult subjects.

Usually most attention for peripheral refraction is drawn to the spherical equivalent (M) (Mutti *et al.*, 2000). However, Hoogerheide *et al.* (1971) found mainly hyperopic astigmatism in the group of progressing myopes. For this reason we also analysed J_{45} and J_{180} for central and peripheral refractions. As we could not find high progression rates in our population, the conclusions from this analysis are limited.

Ideally we wished to find a group with a higher progression rate. However, in reverse we have shown that peripheral myopia is associated with minimal changes in refractive error within one year.

Acknowledgment
The authors acknowledge the assistance of Haag-Streit UK Ltd. who provided the LenStar for the duration of this work.

10.6 Remarks

For chapter 10 the data were collected by me and I analysed the data. The first draft of the manuscripts was written by me.

It is intended to submit this manuscript soon.

Chapter 11

Peripheral aberrations with myopia progression

11.1 Abstract

Purpose: The present study aimed to analyse the possible influence of peripheral higher order aberrations on refractive error progression.

Methods: Higher order aberrations up to the fourth order, subjective refraction and axial length were measured in 32 myopes and 22 emmetropes. Aberrometry was performed along the horizontal meridian for up to 20 degrees eccentricity using the IRX-3. At the same visit, subjective refraction and axial length were measured. After one year subjective refraction and axial length were measured again.

Results: Refractive error progression during one year was 0.04 $\pm$ 0.29 D in myopes and -0.12 $\pm$ 0.38 D in emmetropes. Axial length increased in myopes by 0.01 $\pm$ 0.07 mm and by 0.02 $\pm$ 0.07 mm in emmetropes. Peripheral higher order aberrations were fitted with linear trend lines. Correlations between fitting parameters (slope and intercept) and refractive error progression were not significant. A significant correlation was found between the slope of horizontal coma and corneal curvature ($r = 0.34$, $p = 0.02$).

Conclusions: In the present work no strong evidence was found for the involvement of peripheral higher order aberrations in refractive error development. This is possibly caused by the fact that the progression of refractive error during one year was very low.

11.2 Introduction

The development and progression of myopia has been associated with various factors such as near work (Mutti, 2010 for review), genetics (Young, 2009 for review), peripheral refraction (e.g. Smith *et al.*, 2005), outdoor activities (Rose *et al.*, 2008a), lightning (Ashby *et al.*, 2009) or concentration of vitamin D in the blood (Mutti and Marks, 2011) for examples. Also it has been shown in animal studies that emmetropisation is a visually guided process that could have central (Troilo and Wallman, 1991; Siegwart and Norton, 1999) and local effects (Wallman *et al.*, 1987; Schaeffel *et al.*, 1988; Smith *et al.*, 2010). More recent studies in monkeys have shown that peripheral refraction can guide emmetropisation (Smith *et al.*, 2005). However, Schippert and Schaeffel (2006) could not repeat this outcome in chickens, which is perhaps due to the difference in the size of the central clear zone of the occluder between the two studies.

As peripheral refraction might have an impact on emmetropisation, peripheral refraction data were compared between myopes and emmetropes showing that progressing myopes have a hyperopic defocus in the periphery (e.g. Mutti *et al.*, 2007). This led to trials in humans that reduced peripheral hyperopia using spectacle lenses and showed a minimal, but significant reduction in refractive error progression (Sankaridurg *et al.*, 2010).

As there is some evidence that peripheral refraction influences myopia progression, it is also possible that higher order aberrations in the peripheral visual field have got an effect on myopisation. The study of Mathur *et al.* (2009b) analysed higher order aberrations across the peripheral visual field and compared peripheral aberrations between myopes and emmetropes. They found for example that the slope of the root-mean-square of horizontal and vertical coma was significantly greater in myopes compared to emmetropes. Across the field they also found oblique trefoil to be significantly lower and spherical aberration significantly higher for emmetropes compared to myopes. However, differences between myopes and emmetropes were felt to be minimal.

The examples from Mathur *et al.* (2009b) indicate that some small differences in higher order aberrations between emmetropes and myopes exist. However, more important than the difference between the two groups, is the knowledge if differences in peripheral higher order aberrations may influence myopia progression.

It is the aim of the present study to analyse higher order aberrations along the horizontal meridian in a group of young adults and to determine the relationship between peripheral higher order aberrations and changes in central refractive error during one year.

11.3 Methods

Fifty-four subjects (20 male and 34 female) were recruited. The age of the subjects ranged between 19 and 38 years (mean ± SD: 24.9 ± 5.1 years; median 24 years). All subjects were free of any ocular pathology and could achieve a visual acuity of 6/6 partially or better when corrected. There were 32 myopes (spherical equivalent from -9.63 D to -0.63; mean -3.46 ± 2.35 D; median -1.38D) and 22 emmetropes (spherical equivalent from -0.50 D to 0.50 D; mean -0.03 ± 0.36 D; median -0.19D). For all the parameters, only the right eye data were analysed. The mean age of the myopes was 25.3 ± 5.5 years and 24.5 ± 4.5 years in the emmetropes.

The study followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants after the nature of the study and possible consequences of the study had been explained. The project protocol was approved by the Senate Committee on the Ethics of Research on Human Beings of the University of Manchester.

The subjects were first seen between February and March 2010. At that time subjective refraction, axial length measurement and peripheral aberrometry were performed.

Subjective refraction was performed to an accuracy of ±0.25 DS and ±0.25 DC to obtain maximum plus giving best visual acuity. The cylindrical component, if existent, was found using a cross-cylinder. To refine the spherical component at the end of the routine, the duochrome test was used.

For axial length and corneal curvature measurement the LenStar 900 (Haag-Streit, Koeniz, Switzerland) was used. It was shown before that the LenStar is a reliable instrument for axial length measurements (Buckhurst *et al.*, 2009; Holzer *et al.*, 2009; Cruysberg *et al.*, 2010; O'Donnell *et al.*, 2011). The instrument was aligned using the image of the patient's eye on the computer monitor. Subjects were asked to blink just prior to measurements being taken. Blinking or loss of fixation were detected automatically by the instrument and in this case the measurements were repeated. The instrument takes 16 consecutive scans per measurement without the need for realignment and five measurements were taken as recommended by the manufacturer. The internal software calculated the mean of these five readings. The axial length measurements were performed only on 48 subjects (which included 30 myopes and 18 emmetropes).

Higher order ocular aberrations and pupil diameters were measured with an IRX-3 Shack-Hartmann aberrometer (Imagine Eyes, Orsay, France). This instrument has a 32 $\times$ 32 lens-let array and uses a wavelength of 780 nm. No refractive corrections were worn during the measurements. Habitual contact lens wearers left out their contact lenses from the evening before the measurements. Wavefront errors were recorded from the right eye with the left eye being occluded. No cycloplegia was used. All measurements were taken under dim lighting conditions. The ocular aberration data were analysed for 4.0 mm pupil diameter. If pupil diameter was less than 4.0 mm, these readings were disregarded.

The internal viewing target of the IRX-3 aberrometer is designed for central measurements. To obtain peripheral measurements along the horizontal visual field a modified target system was used. An additional beam splitter was inserted between the subject's eye and the aberrometer. The beam splitter allowed viewing peripheral targets while aberrometry readings could be taken as usual. A custom-made horizontal band with nine LEDs coloured red and green alternatively was used as fixation target. The distance between each LED was 60 mm. The target was placed 690 mm away from the subjects' eye. This made a field angle of 4.97 degrees for each target separation. Therefore measurements were taken at approximately 5, 10, 15 and 20 degrees in the nasal and temporal retina. The sequence of gaze position was randomized and three readings were taken at each position. In total 27 measurements were taken for each subject. The measurements took approximately eight minutes.

After a year (March 2011) the same patients were seen again for subjective refraction and axial length measurement performed as described above.

Eleven ($\sim$ 20%) patients could not be followed up, because they left the Manchester area or could not be contacted.

11.3.1 Data analysis

Refractive error change was characterised as the difference between second visit spherical equivalent and first visit spherical equivalent. Therefore negative values describe a change towards minus, i.e., progression of myopia. For axial length measurement a positive value indicates an axial elongation.

Relative peripheral aberrations were computed as the difference between aberrations coefficient of each eccentricity and the central aberration coefficient.

Higher order aberrations were fitted with linear trend lines. Before performing the fit all higher order aberrations for all subjects were visually inspected to ensure that linear fitting is appropriate.

All statistical analysis was performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). The conservative Bonferroni adjustment was applied for multiple comparisons.

11.4 Results

11.4.1 Progression during one year

The mean subjective refractive error change within one year was 0.04 ± 0.29 D in myopes and -0.12 ± 0.38 D in emmetropes. Axial length changed by 0.01 ± 0.07 mm in myopes and 0.02 ± 0.07 mm in emmetropes. Changes in refractive error and axial length did not differ significantly between myopes and emmetropes ($F_{(1,41)} = 2.35$, $p = 0.13$; $F_{(1,35)} = 0.03$, $p = 0.87$, respectively).

11.4.2 Peripheral higher order aberrations

Peripheral higher order aberration measurements were fitted with linear trend lines. The mean slopes and intercepts of the linear fit for each coefficient are presented in Table 11.1 separated for myopes and emmetropes. No significant difference was found between myopes and emmetropes (column stats in Table 11.1).

Relative higher order aberrations at 20 degrees eccentricity (nasal and temporal retina respectively) were compared between myopes and emmetropes using one-way between groups analysis of variance. After applying Bonferroni adjustment for multiple comparisons the significance level was 0.005. No significant differences were found at this level.

Coefficient	Myopes		Emmetropes		Stats	
	Slope	*Intercept*	*Slope*	*Intercept*	*Slope*	*Intercept*
Oblique Trefoil	0.001 ± 0.001	-0.023 ± 0.041	0.001 ± 0.001	-0.021 ± 0.032	$F_{(1,52)} = 3.23$ p = 0.08	$F_{(1,52)} = 0.04$ p = 0.85
Vertical Coma	-0.001 ± 0.001	0.038 ± 0.058	0.001 ± 0.001	-0.002 ± 0.052	$F_{(1,52)} = 2.75$ p = 0.10	$F_{(1,52)} = 6.99$ p = 0.01
Horizontal Coma	-0.005 ± 0.003	0.001 ± 0.037	-0.005 ± 0.004	-0.008 ± 0.036	$F_{(1,52)} = 0.02$ p = 0.90	$F_{(1,52)} = 0.74$ p = 0.40
Trefoil	-0.001 ± 0.002	0.008 ± 0.027	-0.001 ± 0.001	-0.006 ± 0.027	$F_{(1,52)} = 0.64$ p = 0.43	$F_{(1,52)} = 3.69$ p = 0.06
Oblique Tetrafoil	0.001 ± 0.001	0.002 ± 0.002	0.001 ± 0.001	0.002 ± 0.008	$F_{(1,52)} = 0.79$ p = 0.38	$F_{(1,52)} = 0.01$ p = 0.95
Oblique 2^{nd} Astigmatism	0.001 ± 0.001	0.001 ± 0.009	0.001 ± 0.001	0.002 ± 0.006	$F_{(1,52)} = 0.45$ p = 0.51	$F_{(1,52)} = 0.95$ p = 0.34
Spherical Aberration	0.001 ± 0.001	0.012 ± 0.023	0.001 ± 0.001	0.009 ± 0.018	$F_{(1,52)} = 0.31$ p = 0.58	$F_{(1,52)} = 0.36$ p = 0.55
2^{nd} Astigmatism	0.001 ± 0.001	-0.002 ± 0.018	0.001 ± 0.001	-0.002 ± 0.014	$F_{(1,52)} = 0.01$ p = 0.92	$F_{(1,52)} = 0.04$ p = 0.84
Tetrafoil	0.001 ± 0.001	-0.001 ± 0.010	0.001 ± 0.001	0.002 ± 0.011	$F_{(1,52)} = 0.72$ p = 0.40	$F_{(1,52)} = 0.64$ p = 0.43

Table 11.1 – Linear fitting data for higher order aberrations along the horizontal meridian. The column stats provides one-way between groups analysis of variance results comparing myopes and emmetropes. Due to multiple comparisons the significance level is 0.006 (Bonferroni adjustment).

11.4.3 Aberrations and progression

To analyse the link between refractive error progression and peripheral higher order aberrations along the horizontal meridian fitting parameters (slope and intercept) were correlated with the rate of progression. The results are presented in Table 11.2. All correlations were non-significant.

When correlating progression and relative higher order aberrations at 20 degrees eccentricity (nasal and temporal retina respectively), there was no significant link ($p > 0.006$). When considering absolute higher order aberrations and progression, secondary astigmatism at 20 degrees nasal retina was significant (Pearson product moment correlation: r = 0.48, p = 0.001, Figure 11.1), also after applying Bonferroni correction for multiple comparisons (significance level: p = 0.006). Remaining aberration coefficients were not significant.

As corneal curvature seems to have influence on horizontal coma, we correlated these two parameters, which were significant (Pearson product moment correlation: r = 0.34, p = 0.02, Figure 11.2). Also, corneal curvature differed significantly between myopes and emmetropes (between groups analysis of variance $F_{(1,47)} = 5.09$, p = 0.03).

Coefficient	**Slope**	**Intercept**
Oblique Trefoil	r = -0.05; p = 0.76	r = 0.18; p = 0.26
Vertical Coma	r = 0.16; p = 0.31	r = 0.07; p = 0.65
Horizontal Coma	r = -0.10; p = 0.53	r = 0.02; p = 0.91
Trefoil	r = 0.16; p = 0.30	r = 0.01; p = 0.99
Oblique Tetrafoil	r = 0.10; p = 0.54	r = -0.12; p = 0.46
Oblique 2^{nd} Astigmatism	r = 0.14; p = 0.39	r = 0.04; p = 0.81
Spherical Aberration	r = -0.18; p = 0.24	r = 0.05; p = 0.77
2^{nd} Astigmatism	r = -0.28; p = 0.07	r = 0.36; p = 0.02
Tetrafoil	r = -0.15; p = 0.33	r = -0.27; p = 0.08

Table 11.2 – Correlations between progression data and fitting data for peripheral higher order aberrations. Due to multiple comparisons the significance level is 0.006 (Bonferroni correction).

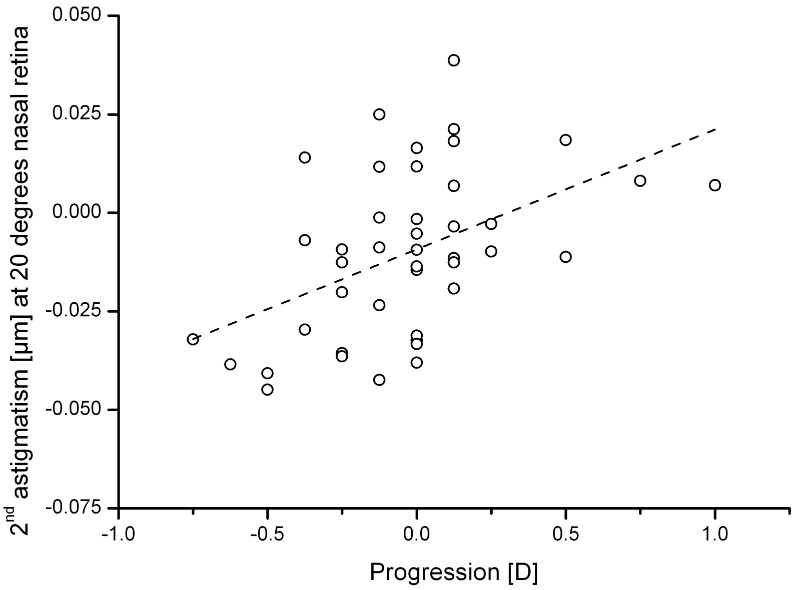

Figure 11.1 – Correlation between progression per year and absolute secondary astigmatism at 20 degrees nasal retina. The line represents the linear fit.

11.5 Discussion

In the present study we analysed, if peripheral higher order aberrations along the horizontal meridian are linked to the progression of refractive error. In general our results indicate similar distributions of higher order aberration along the horizontal meridian in myopes and emmetropes which is in line with findings by Mathur *et al.* (2009b). Rather than comparing higher order

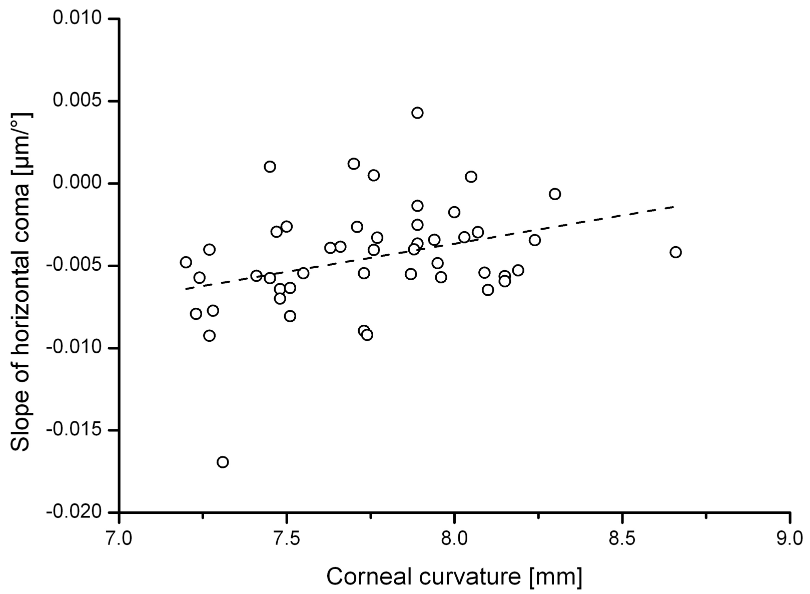

Figure 11.2 – Correlation between central corneal curvature and slope of horizontal coma. The line represents the linear fit.

aberrations between myopes and emmetropes it is more important to analyse the effect of higher order aberrations on refractive error progression. When considering refractive error progression it appears that peripheral higher order aberrations are weakly associated with refractive error progression in young adults, but peripheral higher order aberrations do not seem to be a precursor for progression. In our study population of young adults we found no refractive error progression. To confirm the findings of the present study it would be useful to repeat the analysis in young progressing children.

Convincing differences between myopes and emmetropes in peripheral aberrations were neither found for the nasal nor temporal retina nor for linear fits (slope and intercept, Table 11.1). Nevertheless for further analysis it needs to be considered that different retinal positions could have different consequences on myopisation. This is supported by findings from Smith *et al.* (2010), who showed in primates that peripheral hyperopic defocus across the entire retina lead to elongation of the vitreous along the horizontal meridian with greatest impact on the central and near temporal retina. Temporal retina-only hyperopic defocuses lead to an increase in vitreous which was largely linked to the nasal hemifield. Mathur *et al.* (2009b) analysed higher order aberrations across the visual field comprehensively and they found that the slope of coma (horizontal and vertical coma combined) differed significantly between myopes and emmetropes, which we could not confirm.

Although there is evidence that peripheral refraction might influence myopisation (Smith *et al.*, 2005) our results seem to show that the peripheral retina is more susceptible for blur in terms of defocus rather than higher order aberrations as it was shown that manipulating peripheral refraction could change progression rates (Sankaridurg *et al.*, 2010; Lopes-Ferreira *et al.*, 2011). We did not find important differences between myopes and emmetropes in peripheral higher order aberrations and we did not find a significant association between peripheral higher order aberrations and refractive error progression. That would imply that spectacle lenses or contact lenses, that reduce peripheral hyperopia, do not need to concern about induced peripheral aberrations, as defocus seems to have most impact.

In previous work (Hartwig *et al.*, 2011c) we found various distributions of horizontal coma and speculated that corneal asphericity has an influence. In the present study we showed that corneal curvature and the slope of horizontal coma are linked. This finding is contrary to that of Mathur *et al.* (2009b) who could not find a significant correlation. Possibly this is caused by a smaller number of subjects (n = 20) in their population. Also, they found only negative slopes for horizontal coma, whereas we found a few positive slopes. It was found that corneal curvature also correlates with axial length (O'Donnell *et al.*, 2011). Therefore the present study might give some further evidence for the involvement of horizontal coma in myopisation as it was discussed by other authors (Carkeet *et al.*, 2002; Bakaraju *et al.*, 2008a; Hartwig *et al.*, 2011c).

In conclusion, some minor hints were found that peripheral higher order aberrations might be linked with refractive error progression. A repetition of the study in progressing children would be useful.

11.6 Remarks

For chapter 11 the data were collected by me and I analysed the data. The first draft of the manuscripts was written by me.

It is intended to submit this manuscript soon.

Chapter 12

Higher order aberrations and anisometropia

12.1 Abstract

Purpose: Myopia incidence is increasing around the world. Myopisation is considered to be caused by a variety of factors. One consideration is whether higher order aberrations influence myopisation. More knowledge of optics in anisometropic eyes might give further insight into the development of refractive error. To analyse the possible influence of higher order aberrations on refractive error development, we compared higher order aberrations between anisometropes and isometropes.

Methods: We analysed higher order aberrations up to the fourth order for both eyes of 20 anisometropes (mean age: 42.9 ± 17.0 years) and 20 isometropes (mean age: 33.2 ± 17.0 years). Higher order aberrations were measured with the Shack-Hartman i.Profiler (Carl Zeiss Vision, Aalen, Germany) and were recalculated for a 4 mm pupil. Mean spherical equivalent was based on the subjective refraction. Anisometropia was defined as $\geq$ 1 D interocular difference in mean spherical equivalent. The mean absolute differences between right and left eyes in spherical equivalent were 0.28 ± 0.21 D in the isometropic group and 2.81 ± 2.04 D in the anisometropic group. Interocular differences in higher order aberrations were compared with the interocular difference in mean spherical equivalent using correlations.

Results: For isometropes oblique trefoil, vertical coma, horizontal coma and spherical aberration showed significant correlations between the two eyes. In anisometropes all analysed higher order aberrations correlated

significantly between the two eyes except oblique tetrafoil and secondary astigmatism. When analysing anisometropes and isometropes separately no significant correlations were found between interocular differences of higher order aberrations and mean spherical equivalent. For isometropes and anisometropes combined tetrafoil correlated significantly with mean spherical equivalent in left eyes.

Conclusions: The present study could not show that interocular differences of higher order aberrations increase with increasing interocular difference in mean spherical equivalent.

12.2 Introduction

In the area of myopia research, it has been hypothesised that monochromatic higher order aberrations might have an influence on myopia development and progression (see for example Collins *et al.*, 1995; Charman, 2005; Atchison *et al.*, 2006b; Mathur *et al.*, 2009b). Several studies analysed the relation between higher order aberrations and myopia with equivocal results. Whereas some studies found no increase in higher order aberrations in myopes (Porter *et al.*, 2001; Carkeet *et al.*, 2002; Cheng *et al.*, 2003), other studies found a small increase (He *et al.*, 2002; Paquin *et al.*, 2002). One study showed greater higher order aberrations for hyperopes than for myopes (Llorente *et al.*, 2004). Another study found no effect for overall higher order aberrations root mean square, but for fourth order root mean square and spherical aberration they showed a decrease with increasing myopia (Kwan *et al.*, 2009).

Variations in higher order aberrations can affect accommodative responses (Wilson *et al.*, 2002). The link between accommodation and emmetropisation is not clear (see Charman, 2011b for review), but the link between higher order aberrations and accommodation provides support that higher order aberrations may affect emmetropisation and therefore play a role in refractive error development.

To find more details about the possible link between higher order aberrations and refractive error, it would be interesting to analyse the distribution of higher order aberrations in the special case of anisometropia. Anisometropia is usually defined clinically as a difference of refractive error between both eyes of at least 1 dioptre (Dadeya *et al.*, 2001; Weale, 2003; Robaei *et al.*, 2006). It is an interesting area for research, because the development of refractive error differs between the eyes although both eyes are exposed to the same environmental conditions. A few studies on anisometropes have been conducted that have been aimed to study the genetic influence on myopia development and rule out the influence of environmental factors (see Young, 2009 for review). However, a difference in refractive error between the two eyes does not prove that the environmental factors do not play a role in refractive error development.

Castejón-Mochón *et al.* (2002) compared wave-front aberrations of right and left eyes in a group of subjects with small interocular differences in sphere and cylinder and found significant correlations for oblique trefoil, vertical coma, horizontal coma, spherical aberration, secondary astigmatism and tetrafoil. Studying ocular aberrations in anisometropia might provide evidence for the role of higher order aberrations in myopia development. If higher order aberrations increase with increasing anisometropia, for example elevated higher order aberrations in the eye further away from emmetropia, this indicates a relationship between higher order aberrations and refractive error development. Kwan *et al.* (2009) studied the link between anisometropia and higher order aberrations by examining 26 Chinese participants with anisometropia of 2 dioptres or more and found that the more myopic eyes had lower levels of higher order aberrations than their fellow eyes, particularly for spherical aberration (0.088 $\pm$ 0.055 μm vs. +0.108 $\pm$ 0.062 μm for 5 mm pupils). Haddad *et al.* (2011) compared higher order aberrations in terms of root-mean-square (third and fifth aberrations) between eyes in a group of participants with anisometropia of 2 dioptres or more and did not find a significant difference between eyes for 5 mm pupils. Contrary to Kwan *et al.* (2009), they found that spherical aberration was higher in the more myopic eyes than in the fellow eyes (mean 0.13 μm vs. 0.10 μm, 5 mm pupils). As they analysed anisometropes only, a comparison to isometropic data was not possible. Neither Kwan *et al.* (2009) nor Haddad *et al.* (2011) assessed changes in higher order aberrations as a function of the magnitude of anisometropia.

In the present work we assess the relationship between higher order aberrations and refractive error in isometropes and anisometropes.

12.3 Methods

Retrospective analysis of higher order aberration (HOA) data was based on measurements conducted with the i.Profiler (Carl Zeiss Vision, Aalen, Gemany) on patients from a private optometric practice in Heikendorf, Germany. There were forty subjects, 13 male and 27 female. The age of the subjects ranged between 11 and 73 years (mean ± standard deviation (SD): 38.0 ± 17.5 years; median: 35 years). The group included 20 isometropes and 20 anisometropes (difference in spherical equivalent between right and left eye of 1.0 D or more). The mean age ± SD was 33.2 ± 17.0 years in the isometropic group and 42.9 ± 17.0 years in the anisometropic group. All subjects were free of ocular pathology and achieved visual acuity of 6/8 or better when corrected. None had amblyopia or strabismus. Spherical equivalent corrections for right eyes were 10.25 D to +2.50 D (mean ± SD: -2.06 ± 2.71 D; median: -1.31 D) and for left eyes were -8.88 D to +8.00 D (mean ± SD: -1.43 ± 3.06 D; median: -1.56 D). The mean absolute differences between right and left eyes in spherical equivalent were 0.28 ± 0.21 D in the isometropic group and 2.81 ± 2.04 D in the anisometropic group. In all cases, cylinder was less than 2.25 D. The mean absolute difference in cylinder between eyes was 0.41 ± 0.41 D. In all cases the difference in cylinder between the two eyes was less than 1.25 D.

After an approximate manual alignment, the i.Profiler performed the measurements automatically. The process involved improvement of the alignment and correcting most of the eye's defocus for the measurement. Five consecutive measurements were taken. The i.Profiler changed to the contra lateral eye and took five readings again. Results (mean of five readings) were entered into Excel spreadsheets (Microsoft, Redmond, WA, USA). The i.Profiler provides higher order aberrations in terms of magnitude and axis as described by Campbell (2003), and results were converted into the OSA standard (ANSI, 2004; ISO, 2008). All data were scaled down to a 4 mm pupil using a Matlab (The Mathworks Inc., Natick, MA, USA) program (Lundström and Unsbo, 2007). Before recalculation, mean pupil diameters were 5.1 ± 0.8 mm (range 4.0 mm to 7.2 mm) for right eyes and 5.1 ± 0.8 mm (range 4.0 to 6.8 mm) for left eyes. Higher order aberrations up to the fourth order were analysed. To take the nasal-temporal asymmetry of right and left eyes into account, the signs of the left eye coefficients were altered for Zernike polynomials with either negative, even m indices or with positive, odd m indices (ISO, 2008).

Spherical equivalent refraction was based on subjective refraction obtaining 'maximum plus' giving best visual acuity, and performed to a precision of ±0.25 DS and ±0.25 DC. The cylindrical component was found using the cross-cylinder technique. The duochrome test was used to check the spherical component. Spherical equivalent (SE) was calculated by adding half the cylinder to the spherical component.

SPSS 16.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Pearson correlations were used to compare various parameters. The statistical significance level was set to $p < 0.05$.

Differences between right and left eyes for spherical equivalent and higher order aberrations were given by subtracting left eye data from right eye data.

12.4 Results

Table 12.1 shows correlations between right and left eyes for each of the higher order aberrations. For isometropes, only four of the nine higher order aberrations assessed (oblique trefoil, vertical coma, horizontal coma and spherical aberration) showed significant correlations. However, for the anisometropes seven higher order aberrations showed significant correlations, the exceptions being oblique tetrafoil and secondary astigmatism. Statistically significant positive correlations were found for the aberrations terms ($p < 0.05$) apart from oblique secondary astigmatism.

When higher order aberration interocular differences were correlated with spherical equivalent interocular differences, no significant correlations were found for either group.

	Isometropes		**Anisometropes**	
	Correlation coefficient (r)	**p-value**	**Correlation coefficient (r)**	**p-value**
Oblique trefoil	+0.60	*<0.01*	+0.55	*0.01*
Vertical coma	+0.81	*<0.01*	+0.74	*<0.01*
Horizontal coma	+0.53	*0.02*	+0.76	*<0.01*
Trefoil	+0.30	0.20	+0.58	*<0.01*
Oblique tetrafoil	-0.20	0.41	-0.32	0.17
Oblique secondary astigmatism	-0.26	0.26	-0.56	*0.01*
Spherical aberration	+0.86	*<0.01*	+0.83	*<0.01*
Secondary astigmatism	-0.34	0.14	+0.45	0.05
Tetrafoil	+0.20	0.40	+0.49	*0.03*

Table 12.1 – Correlations between higher order aberrations in right and left eyes, separately for isometropes and anisometropes. Significant p-values are shown in italics.

For combined isometropes and anisometropes, we analysed whether the higher order coefficients are linked to the spherical equivalent refractive error. For right eyes, there were no significant correlations. For left eyes, there was a significant correlation only for tetrafoil (r = 0.38, p = 0.02). Figure 12.1 shows results for spherical aberration.

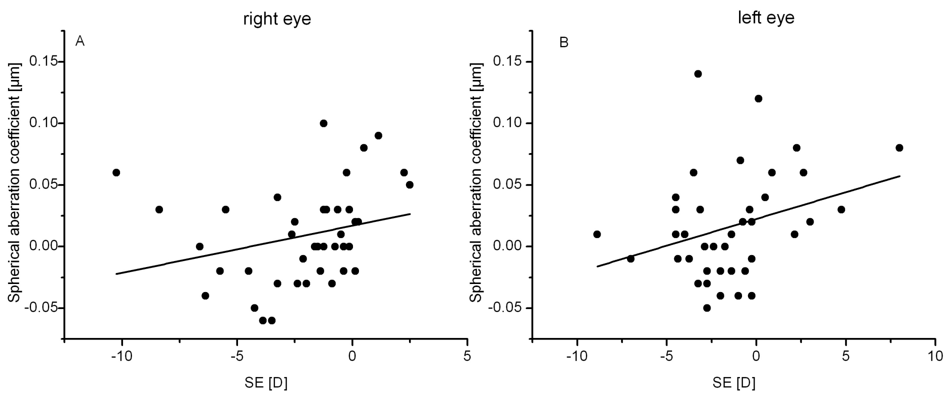

Figure 12.1 – Spherical aberration coefficient versus spherical equivalent (SE) of the total study group for (A) right eyes and (B) left eyes. The lines show the non-significant linear fits (right eye: r = 0.27, p = 0.10; left eye: r = 0.31, p 0.05).

The interocular differences of aberration coefficients were compared with the interocular differences in spherical equivalent in the whole study group. Significant correlations were found only for vertical coma (r = -0.31, p = 0.04) and tetrafoil (r = +0.33, p = 0.04).

12.5 Discussion

This study investigated the relationship between higher order aberrations and refractive error in anisometropia. The interocular correlations are similar in isometropes and anisometropes for most aberrations. The interocular differences in higher order aberrations were not linked to interocular differences in spherical equivalent refraction in either isometropic or anisometropic groups. This indicates that the differences in ocular aberrations are unlikely to be the precursor for the development of anisometropia.

The role of spherical aberration in myopisation has been considered important based on some theoretical calculations (Wilson *et al.*, 2002). Some studies found higher spherical aberration in myopic eyes than in emmetropic eyes (He *et al.*, 2002; Paquin *et al.*, 2002), but other studies did not find this (Collins *et al.*, 1995; McLellan *et al.*, 2001; Carkeet *et al.*, 2002; Atchison *et al.*, 2006c; Kwan *et al.*, 2009). One of the former groups (Paquin *et al.*, 2002) measured aberrations through correcting ophthalmic lenses, which causes overestimation of aberrations for a particular pupil size in myopes (Atchison *et al.*, 2006c).

Higher order aberrations change with age (Artal *et al.*, 2002; see Atchison, 2005 for review), and a limitation of this study was that we did not have age matched groups. However, there is evidence that anisometropia is not affected by age (Czepita *et al.*, 2005). Furthermore, we analysed differences between eyes and therefore we do not expect an effect of age on our results.

Comparing our results to other studies reveals similarities. Kwan *et al.* (2009) correlated higher order aberrations between right and left eyes in anisometropia, and the correlation coefficients are of similar magnitude and sign to those found by us, except for oblique secondary astigmatism (compare Table 12.2 with Table 12.1). A high correlation coefficient for several aberration coefficients, including that of spherical aberration, has been found in several studies as well as our own (Porter *et al.*, 2001; Castejón-Mochón *et al.*, 2002; Kwan *et al.*, 2009).

HOA coefficient	**Correlation coefficient (r)**	**p-value coefficient (r)**
Oblique trefoil	+0.46	*0.02*
Vertical coma	+0.74	*<0.001*
Horizontal coma	+0.68	*<0.001*
Trefoil	+0.75	*<0.001*
Oblique tetrafoil	+0.08	0.72
Oblique secondary astigmatism	+0.09	0.67
Spherical aberration	+0.90	*<0.001*
Secondary astigmatism	+0.39	*0.05*
Tetrafoil	+0.33	*0.01*

Table 12.2 – Comparison of correlations coefficients between right and left eyes in higher order aberrations in anisometropes in the study of Kwan *et al.* (2009). Some coefficient signs have been changed to allow for mirror symmetry between the eyes (horizontal coma, trefoil, oblique tetrafoil and oblique secondary astigmatism). Significant p-values are shown in italics.

In conclusion, our study did not provide evidence that the interocular difference of higher order aberrations increases with increasing anisometropia.

Acknowledgment
The authors thank Ronja Franz for assisting in identifying anisometropia cases

from an optometry practice database.

12.6 Remarks

For chapter 12 the data were collected by me and I analysed the data. The first draft of the manuscripts was written by me.

This chapter has been submitted to Optometry and Vision Science for publication (manuscript number: OVS11195) and is currently under review.

Chapter 13

Summary & Conclusions

In the present project various factors that might influence myopisation were analysed. Before that a few technical issues were addressed. It was shown that the IRX-3 aberrometer is a repeatable instrument for peripheral aberrometry (chapter 2). A second study pointed out that a recalculation of peripheral aberrometry data is not essential for eccentricities up to 20 degrees (chapter 3). Finally the LenStar 900 was accessed and the biometry data were compared to results from other studies. This was important as we correlated axial length measurements with eye movements parameters for example (chapter 4). As an additional outcome of the repeatability study for peripheral higher order aberrations (chapter 2) it was shown that higher order aberrations do not change within short time periods. Therefore it is unlikely that forces of extraocular muscles influence the shape of the eyeball during short time periods.

The analysis of central higher order aberrations in anisometropes and isometropes could not provide evidence that higher order aberrations are linked to the development of refractive error. However, it is still not possible to rule out this relationship (chapter 12).

The comparison of eye and head movements as well as working distances in myopes and emmetropes did not show any differences between the two groups (chapter 5). Similarly the analysis of saccades did not show significant differences between myopes and emmetropes (chapter 6). However, in both cases it remains possible that the stiffness of the sclera is different in myopes and emmetropes. Even though the movements are similar, extraocular muscles could have an impact on myopisation due to differences in scleral stiffness. It was shown that on a short term basis there are no changes in peripheral higher order aberrations (chapter 2), therefore it is important for further studies to analyse the possible influence of extraocular muscles over time.

Peripheral accommodation, peripheral refraction and peripheral higher order aberrations were analysed in myopes and emmetropes. Peripheral accommodation seems to be less effective in myopes compared to emmetropes (chapter 9). In a group of young adults no differences were found neither in peripheral refraction data (chapter 10) nor in peripheral higher order aberrations (chapter 11). Also, there was no significant link between the rate of refractive error progression and peripheral refraction nor peripheral higher order aberrations (chapter 10 and 11). This is possibly caused by a very low refractive error progression rate and it is suggested to repeat these measurements in young progressing myopic children.

Overall, it was found that peripheral vision might influence myopia and its development, which is supported by finding different accommodative responses to peripheral stimuli in myopes and non-myopes.

Eye and head movements did not differ significantly between myopes and non-myopes in the presented study. However, it cannot be ruled out that these factors are involved in myopisation.

13.1 Future work

13.1.1 MRI studies

It has been speculated that forces of extraocular muscles have an impact on refractive error development. Therefore an imaging technique such as MRI would be useful to analyse the possible influence of extraocular muscles on refractive error development. MRI images could be used to find out, if extraocular muscles have an influence on the shape of the eyeball in general or if only certain positions might affect the shape. With MRI images it was possible to derive useful information in terms of different eye shapes in myopes and emmetropes (Atchison *et al.*, 2004), so this approach could be used to analyse the shape of the eyeball fixating at different positions. Also the position of muscle attachment to the eyeball could be measured with high precision and used as an additional determinant for refractive error development.

13.1.2 Studies in children

Progression of refractive error especially in myopia is high in children. Therefore it would be useful to analyse the link between refractive error progression and peripheral refraction data as well as peripheral aberration data in children. This would provide important information, if peripheral refraction is involved in emmetropisation.

13.1.3 Peripheral higher order aberration

A link between the slope of horizontal coma and corneal curvature was found and based on model eye data it was speculated that corneal asphericity has an impact on the slope of horizontal coma. To gain more knowledge about the role of horizontal coma on refractive error development and its link to corneal curvature, it would be useful to measure peripheral aberrations and corneal curvature including corneal asphericity.

13.1.4 Eye and head movements

Using a head mounted eye-tracker could influence the results due to the weight of the helmet. Therefore it would be important to repeat the analysis using an eye-tracker that is not head mounted to reduce the possible bias. Also, in a future project it would be useful to extend the recording period, especially, because a link between progression of myopia and forward bending of the head over time was found (chapter 7), indicating that time might be an important factor. It would be interesting to see, if this link persists for longer period of near work.

When analysing saccades again it might be interesting to analyse saccadic eye movements for a pattern like a star. The target-presentation should then be randomised.

13.1.5 Peripheral accommodation

To gain more knowledge about peripheral accommodation it would be useful to measure responses to peripheral stimuli with peripheral targets that were M-scaled (Rovamo and Virsu, 1979; Virsu and Hari, 1996; Nasanen and O'Leary, 1998). However, preliminary trials showed that an increased size of peripheral accommodation targets leads to accommodative responses that were comparable to accommodative responses for central targets. Analysis to find out the threshold for the size of peripheral accommodation targets would be a useful first step for a further project. It is possible that peripheral accommodative target size correlates to accommodative responses.

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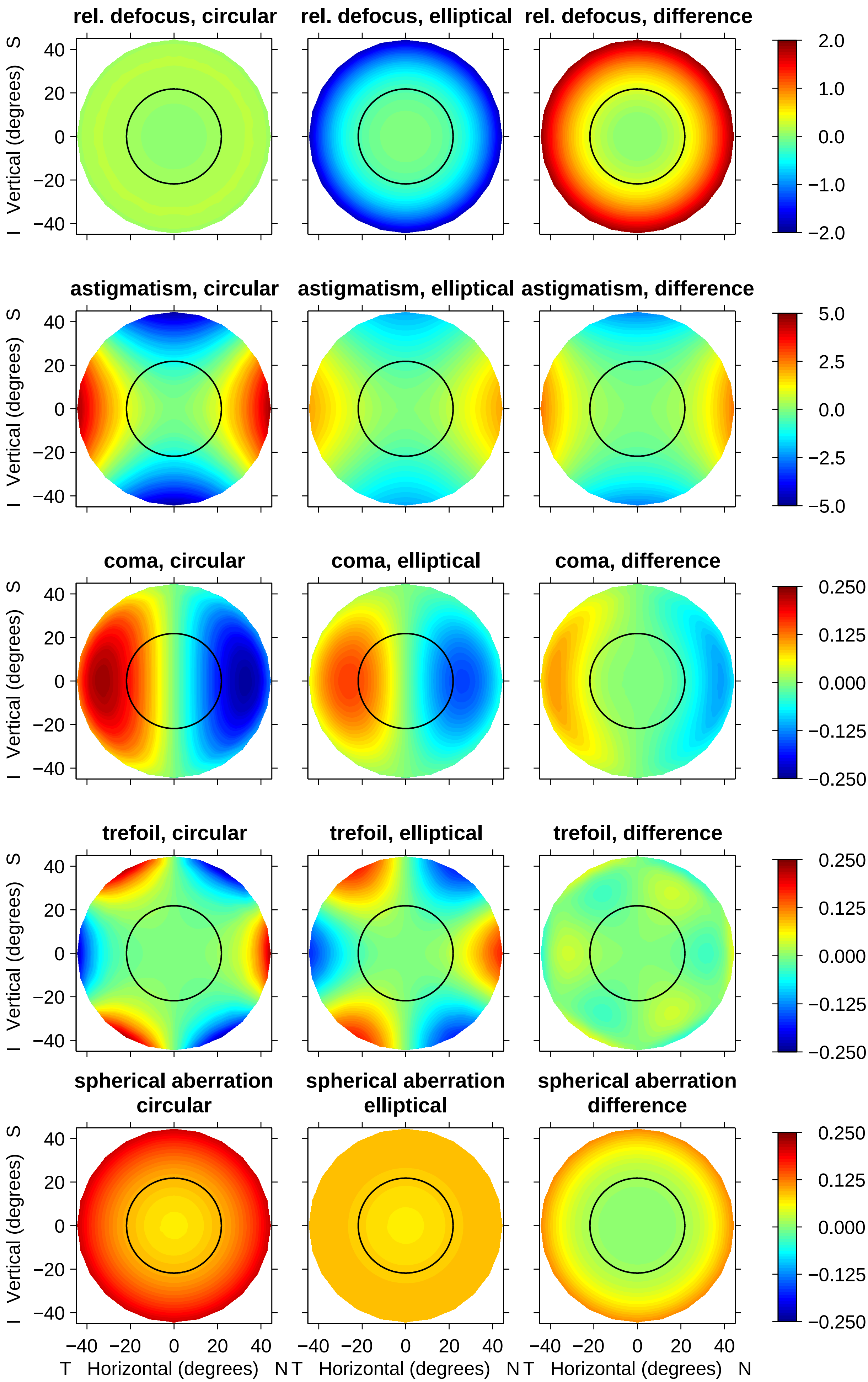
Appendix A

Model eye simulations

Circular (first column) and elliptical (second column) representation of selected aberration coefficients. The third column represents the difference between circular and elliptical data. The black circle shows the 20 degrees eccentricity.

Acknowledgement

The following figure has been prepared with the help of Prof. David Atchison, Queensland University of Technology, Brisbane, Australia.



rel. defocus, circular
rel. defocus, elliptical
rel. defocus, difference
astigmatism, circular
astigmatism, elliptical
astigmatism, difference
coma, circular
coma, elliptical
coma, difference
trefoil, circular
trefoil, elliptical
trefoil, difference
spherical aberration circular
spherical aberration elliptical
spherical aberration difference
2.0
1.0
0.0
−1.0
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5.0
2.5
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−2.5
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Appendix B

Ethical approval

MANCHESTER
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The University
of Manchester

Secretary to the Ethics Committee
Room 2.005 John Owens Building

Tel: 0161 275 2206/2046
Fax: 0161 275 5697
Email: timothy.stibbs@manchester.ac.uk

Office of the Registrar and Secretary
University of Manchester
Oxford Road
Manchester, M13 9PL

ref: TPCS/ethics/09250

Andreas Hartwig,
Vision Sciences,
Faculty of Life Sciences,
Moffat Building

4th January 2010

Dear Andreas,

Committee on the Ethics of Research on Human Beings
Hartwig, Radhakrishnan, Murray: Influence of peripheral refraction and posture on refractive error development (ref 09250)

I write to confirm that the amendments made in the revised application and documentation in your email of 16 December satisfy the concerns of the Committee and that the project therefore has full ethical approval.

The general conditions remain as set out in my letter of 14th December.

We hope the research goes well.

Yours sincerely,

Timothy Stibbs

Dr T P C Stibbs
Secretary to the Committee

cc. Dr Hema Radhakrishnan