ACCOMMODATION, REFRACTIVE SURGERY AND OCULAR ABERRATIONS

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Accommodation, Refractive Surgery and Ocular Aberrations

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Abstract

The principal work in this thesis describes the investigation of the impact that alterations to ocular aberrations following refractive surgery have on the accommodative mechanism. A series of prospective studies were conducted with healthy adults (n=36) that had chosen to undergo refractive surgery at Manchester Royal Eye Hospital. A variety of monocular accommodative functions were assessed prior to surgery and then at one and three months following surgery on the same cohort of patients. Accommodative functions included amplitude of accommodation, accommodative facility (at 6m and 0.4m) including positive and negative response times, and accommodative stimulus-response functions. Dynamic accommodation responses were examined in a subgroup (n=10) at three months following refractive surgery and compared to an age-matched emmetropic control group (n=10) to evaluate differences in latency, amplitude, time constant and peak velocity of accommodation and disaccommodation. During the studies, ocular aberrations were concurrently measured to determine whether alterations to aberrations could help explain any observed changes in accommodative functions. Evaluation of visual, refractive and questionnaire outcome measures indicated that the patient cohort underwent successful surgery. Following surgery, significant alterations to a number of accommodative functions were discovered. Mean subjective ocular amplitude of accommodation increased by approximately 0.50D ($p<0.05$), mean stimulus-response function gradient decreased by approximately 10% ($p<0.05$) and distance facility rate increased by approximately 2-3 cycles/minute ($p<0.05$). Significant correlation was found between the change in accommodative stimulus-response function gradient, and the change in spherical aberration following surgery ($p<0.05$). Significant differences were also found in the parameters of accommodative dynamics, although some of these factors may be explained by refractive error differences between the refractive surgery patients (pre-operative myopes) and the emmetropic control group. The results suggest that alterations to aberrations following refractive surgery may be capable of influencing elements of the accommodation response. Additional studies were conducted to investigate the changes in aberrations during accommodation (n=31 subjects), and explore the contribution of the tear film (n=19 subjects) to higher order aberrations in eyes that have undergone refractive surgery. The results suggested that the rate of change in aberrations during accommodation is not affected by refractive surgery, but that the pattern of aberrations induced by post-blink tear film changes may differ in patients that have undergone refractive surgery. A further study is presented which investigated the form of the accommodative stimulus-response function to grating target of different spatial frequencies in groups of myopic (n=10) and emmetropic (n=10) participants recruited from among the staff and students at the University of Manchester. Both refractive groups appeared to show similar accommodative behavior, however the dominant feature of the data in both groups was between subject variation.

Declaration

No portion of the work referred to in this 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

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CHAPTER 1
INTRODUCTION

The principal work in this thesis investigates the impact of altered aberrations following refractive surgery on the accommodative mechanism. This introduction is split into three broad areas as a precursor to the experimental work that follows. The first section introduces monochromatic aberrations. It mentions how they are measured and represented before going on to describe normal ocular aberrations. The second section covers refractive surgery. It provides an overview of relevant surgical techniques before examining the structural and optical changes that take place following refractive surgery. The third section covers accommodation and describes the key aspects of the accommodation response of relevance to the subsequent experimental chapters.

1.1 Normal ocular aberrations

A perfect optical system would produce a point image of a point object. In reality, all optical systems suffer from various defects or aberrations, each of which tends to degrade the quality of the image in some way (see Charman, 1991; 2005 for reviews). The aberrations of the eye can be broadly classified as chromatic aberrations or monochromatic aberrations. This introduction concentrates on monochromatic ocular aberrations. The eye consists of a series of optical components, anatomical variations in which are expected to contribute to the monochromatic aberration profile of the visual system.

1.1.1 Measurement of ocular aberrations

Several methods have been developed to measure the aberrations of the human eye (see e.g. Howland, 2000; Applegate *et al.*, 2001; Atchison, 2005 for reviews). Two of these methods that have been incorporated into commercially available aberrometers are the Shack-Hartmann method and the Tscherning method. An overview of each of these two methods is provided in Chapter 2 (sections 2.2 and 2.3).

1.1.2 Representation of ocular aberrations

The aberrations present in the eye can be represented in a number of ways (see Atchison, 2004 for a review). The most common way of doing this is to represent the wave-front across the pupil in Zernike polynomial terms (Thibos *et al.*, 2002a). In this system, each polynomial term represents a particular component of the total wave-front aberration profile. The coefficient of each term quantifies its contribution to the overall wavefront aberration, and will vary with the aberration profile of the particular eye. The equations for each of the first 15 Zernike terms are presented in Table 1.1. The mathematical advantage of the Zernike system is that the terms are orthogonal. This means that they are independent of one another over a unit pupil. In practical terms this allows investigation of individual aberrations and their relative importance for vision. There are two disadvantages of the Zernike system. Firstly, the coefficients calculated for one pupil diameter are not valid for smaller pupil diameters and therefore the analysis has to be repeated by either calculating new coefficients over the required pupil diameter, or by applying mathematical conversions (Schwiegerling, 2002; Campbell, 2003). Secondly, the Zernike analysis can only be directly applied when the pupil is circular. This is not usually a problem as the pupil is generally circular, but could be an issue in cases of an irregular pupil.

Mode	Radial order	Angular frequency	Zernike Polynomial Equation	Optical aberration
0	0	0	1	Piston
1	1	-1	$2\ r\ \sin(\theta)$	Tilt/Prism (x-axis)
2	1	+1	$2\ r\ \cos(\theta)$	Tilt/Prism (y-axis)
3	2	-2	$\sqrt{6}\ r^2 \sin(2\theta)$	Astigmatism (axis 45, 135)
4	2	0	$\sqrt{3}\ (2r^2 -1)$	Spherical defocus
5	2	+2	$\sqrt{6}\ r^2 \cos(2\theta)$	Astigmatism (axis 0, 90)
6	3	-3	$\sqrt{8}\ r^3 \sin(3\theta)$	Trefoil (x-axis)
7	3	-1	$\sqrt{8}\ 3r^3 \sin(\theta)$- $2r \sin(\theta)$	Vertical Coma
8	3	+1	$\sqrt{8}\ 3r^3 \cos(\theta)$- $2r \cos(\theta)$	Horizontal Coma
9	3	+3	$\sqrt{8}\ r^3 \cos(3\theta)$	Trefoil (y-axis)
10	4	-4	$\sqrt{10}\ r^4 \sin(4\theta)$	
11	4	-2	$\sqrt{10}\ 4r^4 \sin(2\theta)$- $3r^2 \sin(2\theta)$	
12	4	0	$\sqrt{5}\ 6r^4$-$6r^2$+1	Primary spherical aberration
13	4	+2	$\sqrt{10}\ 4r^4 \cos(2\theta)$- $3r^2 \cos(2\theta)$	
14	4	+4	$\sqrt{10}\ r^4 \cos(4\theta)$	

Table 1.1: Zernike polynomials up to the fourth order (after Charman, 2005).

The polynomial series is often presented in a pyramidal manner (Figure 1.1) in which higher-order Zernike modes represent patterns of aberrations with increasing complexity. The lower Zernike orders can be broadly classified according to traditional concepts of refractive error, with first-order terms representing prismatic effects and second-order terms representing spherical defocus and astigmatism. Third order aberrations and higher are often collectively referred to as “higher order aberrations”. Third and fifth-order terms represent coma-like aberrations and forth and sixth-order terms represent spherical-like aberrations. Root-mean-square (RMS) values can be calculated to give one value that represents a series of individual aberration values (i.e. 4th order RMS, or total higher order RMS). The RMS value gives an approximation of the wavefront error from that source and is calculated as the square root of the sum of squares of the component aberrations (Roorda, 2004).

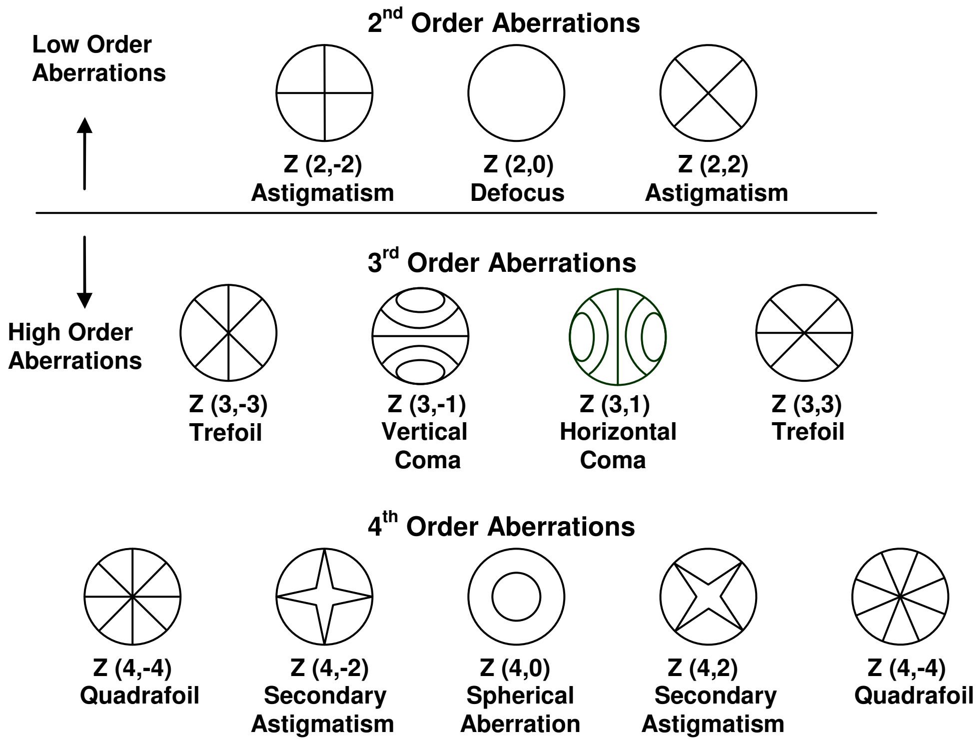


Figure 1.1: Pyramid representation of first 15 Zernike coefficients along-side the contour maps that illustrate the form of the wave-front aberration associated with each coefficient.

1.1.3 Distance resting aberrations

There have been a number of studies to quantify the ocular monochromatic aberrations in the normal population (Porter *et al*., 2001; Thibos *et al*., 2002b; Castejon-Mochon *et al*., 2002; Wang *et al*., 2003; Brunette *et al*., 2003). Despite methodological differences in these studies, a clear picture is emerging of the normal aberration profile of the human eye. One of the largest studies in this area is the study by Porter *et al*. (2001). They used a Shack-Hartmann wave-front sensor to measure the monochromatic wave-aberrations in both eyes of 109 normal subjects, across a 5.7mm pupil, while viewing a distant target. The wave aberration was calculated up to and including the 5th order. Figure 1.2 presents some of the results of their study to illustrate some commonly reported trends. Their results showed that approximately 92-93% of the total variance of the wave aberration is produced by the 2nd order aberrations. These represent spherical defocus (80%) and astigmatism (12-13%) and are correctable with spectacles or contact lenses. This leaves a residual error of approximately 7-8% in the wave-front aberration which results from higher order aberrations (Zernike coefficients of 3rd order and above).

The higher order aberrations that contribute most to the wave-aberration profile are 3rd and 4th order aberrations (principally spherical aberration and coma); with diminishing contributions from aberrations with increasing Zernike order. This general trend of high levels of 2nd order aberrations and progressively decreasing levels of higher order aberrations is consistent with the results of later studies (Thibos *et al*., 2002b; Castejon-Mochon *et al*., 2002). Beyond the sixth order the coefficients are generally very small, and investigation of such terms is consequently limited in value.

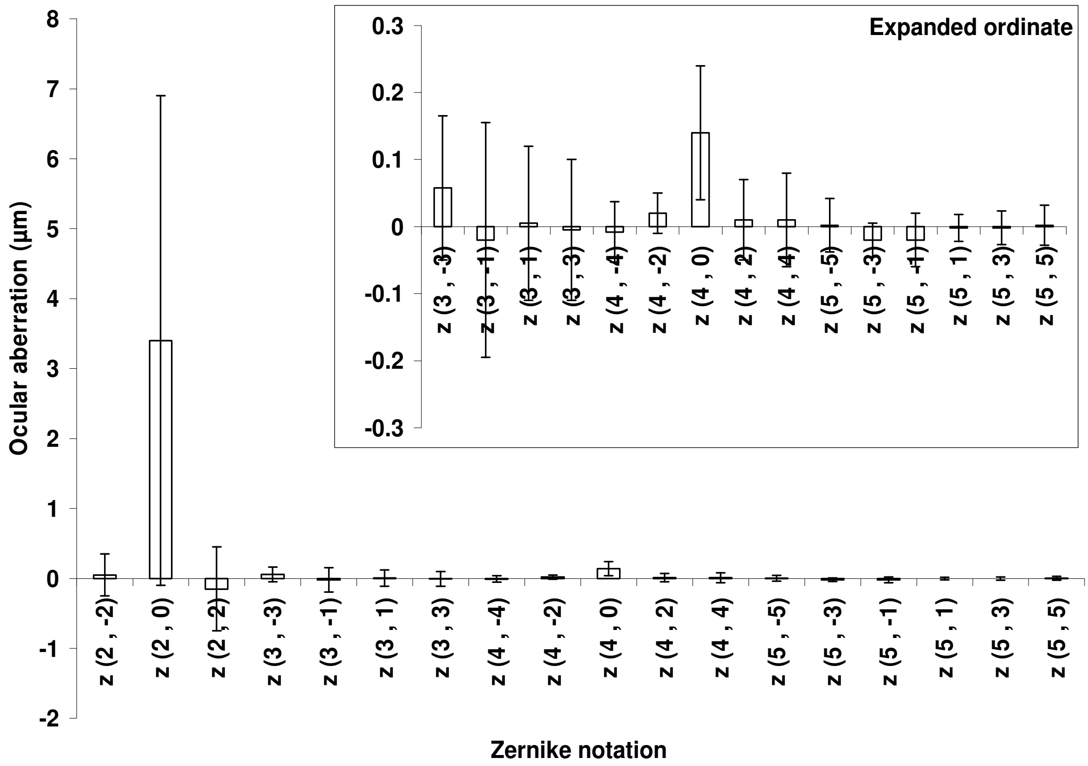


Figure 1.2: Mean (±SD) of the Zernike coefficients (2nd to the 5th order) for 109 normal subjects, across a 5.7mm pupil diameter, observing a distant target. Inset shows an expanded ordinate of the higher order aberrations (3rd to 5th order). Data re-plotted from Porter *et al.* (2001).

In any individual eye the Zernike coefficients can be positive or negative and vary in magnitude: meaning any given eye may suffer from low levels of higher order aberration, or high levels of higher order aberration. The aberrations of right and left eyes of any individual person often show high levels of correlation and the two eyes sometimes exhibit mirror-symmetry (Liang and Williams, 1997; Porter *et al.*, 2001; Castejon-Mochon *et al.*, 2002; Wang and Koch, 2003), probably resulting from genetic and anatomical factors.

Most studies suggest that higher order aberrations exhibit large between-subject variability (Porter *et al.*, 2001; Thibos *et al.*, 2002b; Castejon-Mochon *et al.*, 2002;

Brunette *et al*., 2003) which is thought to result from natural biological variation. When a group of individuals is considered (as in Figure 1.2) the average value of most higher-order aberrations is approximately zero, indicating a natural tendency for the human eye to be free of high order aberration. The exception is primary spherical aberration (Z_4^0), which tends to exhibit low positive values and is the only coefficient to show a tendency to differ significantly from zero.

Another important finding in studies of ocular aberrations is that the magnitude of aberrations increases with increasing pupil size (Castejon-Mochon *et al*., 2002; Wang *et al*., 2003). With decreasing pupil sizes, the levels of higher order aberration become negligible for pupil diameters below 3.0mm. Aberrations therefore have minimal effect on image quality at small pupil sizes. Image quality for a pupil diameter below 3.0mm is largely governed by diffraction.

1.1.4 Aberrations during accommodation

Whole-eye wave aberrations are expected to alter during accommodation due to the changes that occur in the shape, position and refractive index gradient of the crystalline lens (Garner and Smith, 1997; Garner and Yap, 1997). Debate exists as to whether or not the cornea also changes shape during accommodation, with some authors suggesting a change of corneal curvature (Pierscionek *et al*., 2001; Yasuda *et al*., 2003), while others suggest no change in corneal curvature occurs (Buehren *et al*., 2003). Despite this controversy, it is thought that the change in corneal aberrations during accommodation is relatively small, and that the changes in optical aberrations with accommodation are primarily a result of the crystalline lens changes (He *et al.*, 2003).

Study of the change in aberration with accommodation can be traced back many years. Early studies reported a trend for the levels of spherical aberration to change in a negative direction with increasing accommodation (Ivanoff, 1956; Koomen *et al.*, 1956; Van Den Brink, 1962; Jenkins, 1963). This change in spherical aberration can be explained by changes in the crystalline lens shape. During the accommodative response the central portion of the crystalline lens shows an increase in curvature, and this is thought to be accompanied by a flattening of the lens periphery (Garner and Yap, 1997).

The increasing availability of aberrometers as a research tool has allowed more recent studies to investigate how spherical aberration and other higher order aberrations alter during accommodation. Cheng *et al.* (2004) measured monocular wave-front aberrations using a Shack-Hartmann wave-front sensor in a large young normal adult population (n=76), across a pupil diameter of 5.0mm, over an accommodative range of 0-6D. The wave-front aberration was calculated up to and including the 6th order. Their results demonstrated that among higher-order aberrations, spherical aberration (Z_4^0) shows the greatest change with accommodation. Spherical aberration changed in a negative direction, and in a manner that was proportional to the change in accommodative response. Their results suggest that spherical aberration is the only higher order aberration to undergo a systematic and relatively predictable change during accommodation. The changes in other aberrations appeared to be smaller and more variable in both magnitude and direction (positive or negative).

These changes in higher order aberrations during accommodation are in agreement with other studies which also show that spherical aberration tends to shift towards negative values, and that other aberrations can change but the magnitude and direction of the change is less predicable and varies widely between individuals (He *et al*., 2000; Ninomiya *et al*., 2002; Plainis *et al*., 2005; Radhakrishnan and Charman, 2007a).

Change in astigmatism during accommodation is another area that has received the attention of researchers. A recent study by Radhakrishnan and Charman (2007b) used a Shack-Hartmann aberrometer to measure the monocular changes in astigmatism during accommodation over a 0-4D range in a group of young normal subjects (n=31). Although some of the subjects showed no significant change in astigmatism during accommodation, overall the group showed a mean change in astigmatism of 0.036DC per dioptre of accommodation in a *with-the-rule* direction (axis 176 degrees). The results of Radhakrishnan and Charman (2007b) are in broad agreement with other studies in this area which typically report that some subjects show stable astigmatism during accommodation and other subjects show small changes in astigmatism with accommodation (Ukai and Ichihashi, 1991; Mutti *et al*., 2001; Cheng *et al.*, 2004). These changes are generally in the order of 0.2DC or less over the range of accommodation typically used for near vision tasks (i.e. approximately 0-4D range).

It has been suggested by several authors that a change in astigmatism during accommodation could result from lens or corneal distortion during accommodation (Fletcher, 1951; Brzezinski, 1982; Garzia and Nicholson, 1988; Nicholson and Garcia, 1988). Theoretically, lens distortion could result from inhomogeneous changes in lens or ciliary muscle contraction during accommodation, and corneal distortion could result from the effects of the extra-ocular muscles (Brzezinski, 1982). The likely anatomical variation between subjects in the lens, ciliary body and extra-ocular muscle insertions may account for some of the between-subject variability in magnitude and direction (axis) of astigmatism change found during accommodation in several of these studies (e.g. Ukai and Ichihashi, 1991). Despite the likelihood of only small changes in astigmatism occurring during accommodation, this is another factor that could potentially affect image quality during accommodation.

1.1.5 Aberrations of the tear film

One of the principal functions of the tear film is to provide a smooth optical surface which contributes to production of a good quality retinal image and normal vision. The smooth surface of the anterior eye is maintained by the intermittent re-surfacing of the tear film by the blink reflex. However, between blinks the tear film does not remain stable. The tear film rapidly builds-up once the eye-lids are opened, it then stabilizes, reaching its most uniform state for a few seconds and then begins to thin, and eventually exhibit areas of localized disruption known as tear break-up (Benedetto *et al*., 1984; Wong *et al*., 1996; Nemeth *et al*., 2002). If the eye-lids remained permanently open following a blink then drainage and evaporation of the tear film would cause the formation of further areas of tear break-up which progressively increase in size, and coalesce to form larger dry areas (Liu *et al*., 2006). This would continue until eventually the exposed corneal surface epithelium represented the most anterior ocular surface. In reality, the intermittent blink reflex interrupts this process, and re-surfaces the corneal epithelium with a smooth optical tear film, and the cycle is repeated.

The tear film has the greatest refractive power of any ocular surface due to the large change in refractive index that occurs at the transition between the air and the tear film. In the presence of a smooth tear film of uniform thickness, the combination of tear film and cornea has been shown to have the same optical power as the cornea alone (Albarran *et al*., 1997). However, during tear-break-up the localized areas of disruption will produce localized variations in thickness and curvature of the tear film which may introduce aberrations to the optical system of the eye (Tutt *et al*., 2000).

A number of studies have been carried out to investigate the changes in higher order optical aberrations that occur due to the tear film break-up between blinks (e.g. Albarran *et al*., 1997; Koh *et al*., 2002; Montes-Mico *et al*., 2004a; b; c; 2005a; b; Lin *et al*., 2005). These studies typically show that aberrations tend to increase with increasing time following a blink and suggest that changes in the tear film are capable of introducing measurable changes in the optical quality of the eye.

Koh *et al*. (2002) measured ocular aberrations before and after tear break up under topical anesthesia in 20 normal subjects. Topical anesthesia was used to control reflex tearing and reduce discomfort during the measurements. The authors found a significant increase in ocular aberrations during tear break up, although no details on the temporal characteristics of these changes were provided.

Montes-Mico *et al*. (2004b) measured anterior and total ocular aberrations at discrete intervals of up to 20 seconds after a blink in normal emmetropic subjects. They found an increase in both anterior surface and total ocular aberrations after 20 seconds post-blink. The magnitude of this increase in aberrations was greater with increasing pupil size. Montes-Mico *et al*. (2004a) measured anterior surface aberrations during a period of non-blinking at a temporal frequency of 1Hz for 15 seconds following a complete blink. Aberrations (3^{rd}-6^{th} order) were obtained for pupil diameters of 3.0mm and 7.0mm. Subjects (n=15) were healthy adult emmetropes with a mean age of 26 years and fluorescein TBUT of between 8-15 seconds. They found that the total (RMS) aberrations initially decreased to a minimum value at approximately 6 seconds post-blink. The total aberrations then began to increase, reaching the immediate post-blink level at around 10 seconds post-blink and then continued to increase further between 10 and 15 seconds post-blink. The authors suggested that this pattern of aberration change represents the initial stabilization and subsequent dispersion of the tear fluid. Although the total aberrations were of greater magnitude for a large pupil (7.0mm), the results suggest that the pattern of aberration change is qualitatively similar for small pupil diameters (3.0mm). The results they present also suggest that these patterns of aberration change exhibit high levels of both intra-subject and inter-subject repeatability. Further work by the same research group has suggested that the changes in aberrations during tear film break-up appear accelerated in dry eye patients (Montes-Mico *et al*., 2005a) and, conversely, that the use of artificial tears in dry eye patients can reduce optical aberrations (Montes-Mico *et al*., 2004c).

More recent research by Mihashi *et al.* (2006) measured ocular aberrations over a longer time period following a blink. Aberrations (3^{rd}-6^{th} order) were measured under topical anesthesia for a 4.0mm natural pupil at a rate of 1Hz for up to 50 seconds following a blink. Subjects (n=6) were healthy adults with a mean age of 27.3 years with fluorescein TBUT below 10 seconds for all subjects. In broad agreement with previous research, their results showed that ocular aberrations increased over a 50 second period following a blink. However, closer observation of their results indicates that during the initial 15 seconds after a blink, for some subjects the ocular aberrations decreased or remained stable. It was only after around 25 seconds that aberrations appeared to show an increase for all subjects. In contrast to the earlier work of Montes-Mico *et al*. (2004a) this study suggests that the aberrations due to tear film changes can be relatively stable and show high between-subject variability during the early post-blink period.

While objective measures showing an increase in aberrations during tear-film break-up imply a decrease in visual function, subjective measures are required to establish the magnitude of effect that such a change in optical quality would have on visual function. Studies that examine the effect that tear film changes and break up have on subjective measures of visual performance provide evidence that supports the idea that the tear film plays an important optical role. These studies tend to monitor subjective measures of visual function during periods of non-blinking. Evidence suggests that tear break-up is capable of decreasing high and low contrast visual acuity (Timberlake *et al.*, 1992), decreasing contrast sensitivity (Tutt *et al*., 2000), adversely affecting threshold values during automated perimetry (Reiger, 1992), and can give rise to subjectively noticeable symptoms of blurred vision (Bjerrum, 1996; Shimmura *et al*., 1999).

1.1.6 Tear break-up time and blink rate

The tear break-up time (TBUT) can be defined as the time interval between a blink and the appearance of the first rupture of the tear film within the corneal region and is often used as a measure of tear stability: with lower values indicating a less stable tear film. Normal TBUT typically falls between 10 and 25 seconds for healthy adults, although the measurements of tear film stability can vary widely between individuals and measurement techniques (see e.g. Cho and Brown, 1993; Tsubota, 1998; Nichols *et al*., 2004; Johnson and Murphy, 2006; Liu *et al*., 2006).

A steady blink rate is necessary to regularly spread the tear film across the cornea, keeping it moist and preventing desiccation of the ocular surface (Tsubota and Nakamori, 1995). The intrinsic blink rate for a healthy adult under relaxed normal viewing conditions is approximately 12 blinks/minute (King and Michels, 1957; Carney and Hill, 1982). This translates in to a typical inter-blink interval in the region of 5 seconds. The blink rate can show wide variation between different individuals and different environmental conditions (King and Michels, 1957; York *et al*., 1971; Collins *et al*., 1989; Patel *et al*., 1991; Nakamori *et al*., 1997; Cho *et al*., 1997; 2000). For example, during concentrated tasks the blink rate can be reduced to as low as 3-4 blinks per minute, corresponding to an inter-blink interval of approximately 15-20 seconds (Patel *et al.*, 1991).

A dynamic relationship therefore exists between the TBUT and blink rate. For the tears to break-up between blinks, the TBUT has to be less than the interval between blinks. As the TBUT is typically greater than the inter-blink interval, the tears will frequently never actually break-up between blinks. This means that increases in aberrations due to disruption of the tear film are typically masked by the blink reflex. In this situation it is unlikely that changes in optical quality caused by the tear film changes during the normal inter-blink phase will be sufficient to cause a noticeable decrease in visual performance. However, if this dynamic relationship breaks down, then aberrations from tear-break-up may become more significant. This could occur if either the TBUT decreases to below the blink interval or the blink interval increases to beyond the TBUT.

1.2 Refractive surgery

Over the past 30 years refractive surgery has gone through a rapid evolution. This progress has involved innervations in technology, improvements in surgical equipment and the introduction of a number of new surgical techniques (for reviews see Seiler and McDonnell, 1995; Stulting *et al.*, 2000; Taneri *et al.*, 2004b; Sakimoto *et al.*, 2006). These advances have led to dramatic improvements in the safety and the efficacy of refractive surgery. Consequently increasing numbers of people are undergoing refractive surgery as an alternative to spectacles and contact lenses to manage refractive error. Studies estimate that globally over 1 million refractive surgery procedures are performed annually, and that to date over 16 million people have undergone refractive surgery (Hammond *et al.*, 2005; Solomon *et al.*, 2009). The most popular surgical techniques are currently LASIK and LASEK which together account for the vast majority of refractive procedures performed in the United States and UK (Duffy and Leaming, 2004; Ewbank, 2009). These techniques are based on the idea that an excimer laser can be used to mould corneal shape, modify the anterior curvature profile, and hence alter the refractive state of the eye.

1.2.1 Overview of LASIK surgical procedure

An overview of the LASIK surgical procedure is provided here (for detailed reviews see Rama *et al.*, 1997; Sutton and Kim, 2010). During the procedure a microkeratome or femtosecond laser is used to cut a superficial incomplete circular incision of approximately 8mm diameter in the cornea. This creates a superior (or nasal) hinge by which a lamellar flap can be folded backwards revealing the underlying corneal stroma. The flap typically has a thickness in the range 100-200μm and therefore consists of the surface epithelium, Bowman's layer, and an anterior portion of the stroma. As the flap is of uniform thickness it has no refractive power. During the laser ablation phase a 193nm excimer laser is used to re-shape the exposed corneal stroma. Tissue is removed in a way that corrects the ametropia. In standard LASIK procedures the ablation aims to correct spherical defocus, and regular astigmatic error (if applicable). The exact ablation diameter, depth and profile used to correct the ametropia is calculated from nomograms which describe the relationships between corneal thickness, pupil size, optical zone diameter, ablation depth and intended correction (Munnerlyn *et al.*, 1988). Usual ablation zone diameter and depth are approximately 6.0mm and 80-100µm respectively, leaving a residual bed thickness in the region of 250-300µm. Once the laser ablation phase is complete, the epithelial flap is replaced over the remodeled stroma.

1.2.2 Overview of LASEK surgical procedure

An overview of the LASEK surgical procedure is provided here (for detailed reviews see Camellin, 2003; Taneri *et al.*, 2004b; O'Keefe and Kirwan, 2010; Reynolds *et al.*, 2010). During the procedure a microtrephine is used to create an epithelial incision which is 60-80µm deep and approximately 8mm wide, with a superior 90º hinge. Dilute ethanol solution (18-20% concentration) is then applied to the corneal surface, over the incision, in a 8.5mm diameter circular well for between approximately 20-25 seconds to loosen the epithelium. A microhoe is used to detach the epithelium sheet, which is then dragged intact across the cornea towards the superior (hinge) position. The laser ablation procedure is then applied to the exposed (anterior) stroma to re-shape the corneal profile and correct the ametropia. Following the laser ablation, the epithelial sheet is re-positioned to cover the ablated area. A soft contact lens is applied for approximately 3-5 days while the epithelium heals.

1.2.3 Wavefront-guided surgery

Wavefront-guided refractive surgery comprises the same basic surgical procedure involved in standard LASIK or LASEK with the difference occurring at the laser-ablation stage. Evolving technology and the application of adaptive optics, has led to the use of wavefront-guided procedures to detect and correct higher-order aberrations in addition to conventional refractive error (Doane and Slade, 2003). This is in contrast to standard LASIK or LASEK that aims to correct only second order aberrations such as myopia, hyperopia and astigmatism.

1.2.4 Structural changes following refractive surgery

A large number of structural changes take place in the eye as a result of refractive surgery. These principally involve the cornea, tear film and ocular surface. This section covers the structural changes which have the greatest consequence for ocular aberrations (which are covered in section 1.2.5). As a pre-cursor to the experimental work this review concentrates on structural changes occurring during LASIK/LASEK for myopia.

1.2.4.1 Changes to anterior surface topography

Topography is an investigative technique used to evaluate the shape characteristics of the anterior (and sometimes posterior) corneal surface (e.g. see Naroo and Cervino, 2004). A 3-Dimensional diagram of the corneal surface is presented on a 2-Dimensional plot using colors to highlight power or curvature changes. Steep areas are represented by *hot* colors (e.g. yellow/orange/red) and flat areas are represented by *cool* colors (e.g. green/blue). Figure 1.3 shows typical anterior corneal topography plots for three patients: before, and at one month and three months after undergoing LASEK for myopia and myopic astigmatism.

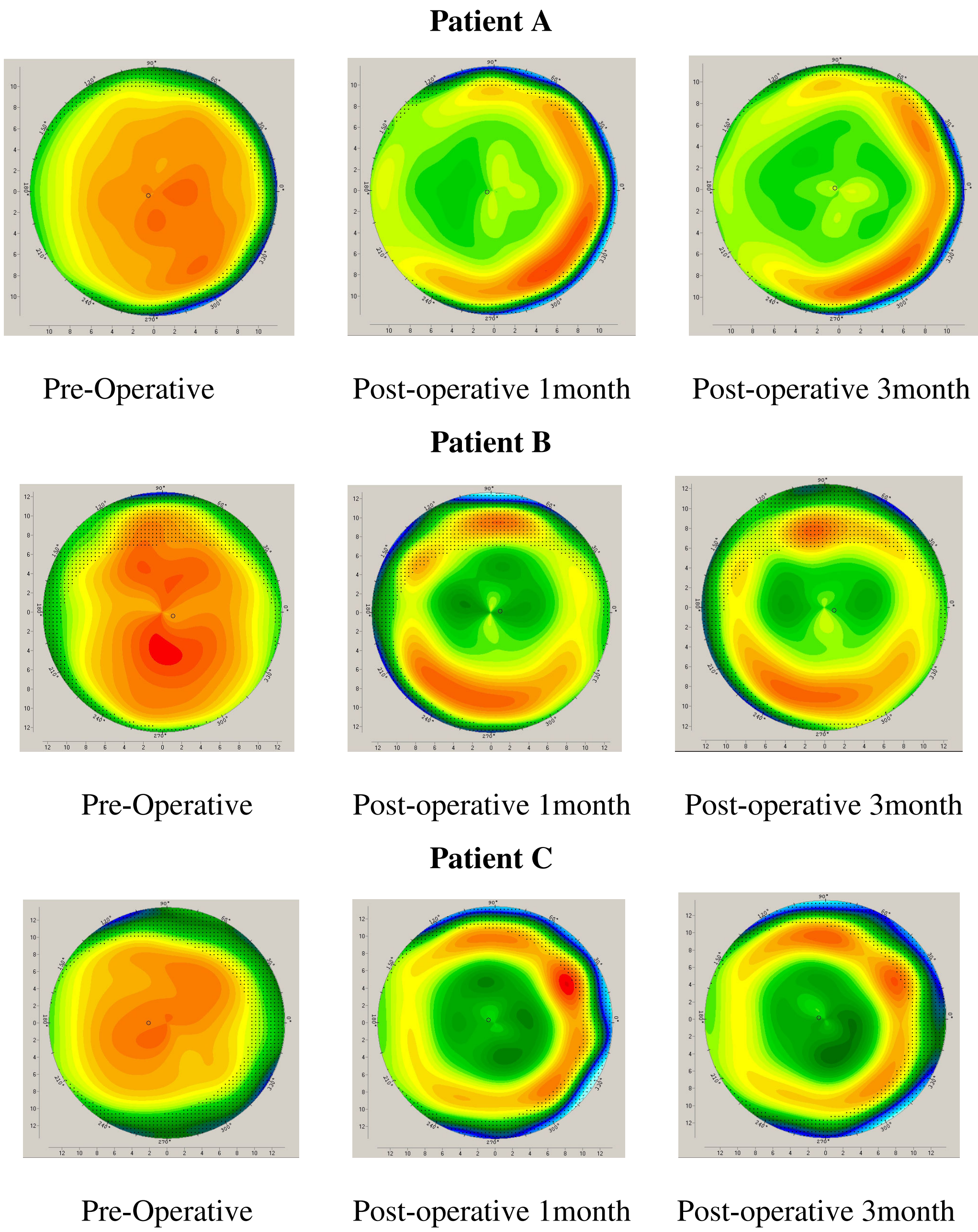


Figure 1.3: Anterior corneal topography plots for three different patients (A-C) undergoing refractive surgery for myopia. For each patient plots are shown for the same eye pre-operatively (left plot), at then at one month (centre plot) and three months post-operatively (right plot). Patient A underwent wavefront-guided LASEK (pre-operative mean sphere -4.75D), patient B underwent standard LASEK (pre-operative mean sphere -6.75D) and patient C underwent standard LASEK (pre-operative mean sphere -9.12D). At all post-operative visits residual mean sphere was less than ±0.75D for each patient.

The anterior surface of a normal cornea is usually steepest centrally and then gradually flattens towards the periphery (Pipe and Rapley, 1997). This is clearly represented in the pre-operative topography plots for each patient. During LASIK and LASEK for myopia, the ablation profile involves removing a large area of central corneal stroma and blending this with the peripheral cornea. This systematic removal of stromal tissue causes a flattening of the anterior corneal surface over the area of ablation. This is clearly represented in the post-operative topography plots which show a large, approximately circular, flattened central region surrounded by a relatively steeper peripheral region.

Due to the similarities in the laser ablation phase between LASIK and LASEK, the overall changes to anterior topography are expected to be broadly similar in both procedures. The exact characteristics of the change in topography will depend on the ablation diameter and profile used, the patient's pre-operative refractive error (hence amount of tissue ablated), and the success of the procedure. Tilted or decentered ablations, and/or irregular corneal topography can result from variations in the success of the surgical procedure or from surgical complications.

1.2.4.2 Changes to posterior surface topography

The posterior surface topography is not directly altered during refractive surgery because the surgical procedures of LASEK/LASIK involve structures anterior to this region. The posterior surface is therefore often assumed to remain relatively unaltered, however there is increasing evidence that alterations do occur in the topography of this region. The majority of studies investigating this issue report that there is an anterior shift of the posterior corneal surface leading to a generalized steepening of the posterior surface topography (Wang *et al.*, 1999; Naroo and Charman, 2000; Baek *et al.*, 2001; Seitz *et al.*, 2001; Marcos *et al.*, 2001; Rani *et al.*, 2002). There is limited evidence however to suggest that no change occurs (Nishimura *et al.*, 2007) or even that a flattening of the posterior corneal surface is possible (Hernandez-Quintela *et al.*, 2001). Flattening could theoretically result from edematous changes in the cornea in response to surgery. The studies that suggest a steepening of the posterior corneal surface generally report an anterior shift of the central cornea in the region of 20-40µm occurring over the weeks and months following surgery (see e.g. Wang *et al.*, 1999; Baek *et al.*, 2001). This forward movement has been shown to correlate negatively with the pre-operative and post-operative corneal thickness, and positively with the pre-operative refraction, amount of laser ablation and pre-operative intra-ocular pressure (IOP) (Baek *et al.*, 2001). Taken as a whole these relationships indicate that the thinner the post-operative cornea is, and the higher the level of IOP, the greater the anterior shift of the posterior corneal surface. This evidence suggests that the anterior shift occurs due to the thinner post-operative cornea being less resistant to the forces exerted on it by the IOP: hence the posterior cornea becomes steeper by means of mechanical pressure.

1.2.4.3 Tear film and ocular surface after refractive surgery

The prevalence of dry eye in the general population it estimated to be approximately 6-15%, depending on the diagnostic criteria used and precise characteristics of the population studied (Lemp, 1995; Schein *et al.*, 1997; Bjerrum, 1997; McCarty *et al.*, 1998). The prevalence of dry eye tends to show a dramatic increase in those having undergone refractive surgery, with studies estimating that around 60-70% of individuals can experience dry eye in the immediate 2-4 week post-operative period (Yu *et al.*, 2000; Albietz *et al.*, 2002). The prevalence of dry eye then tends to gradually subside, although for a number of people it can persist, and may develop into a chronic issue.

The ocular surface, lacrimal gland, accessory lacrimal glands, and the neural network connecting them forms an integrated neural reflex loop (see Beuerman *et al.*, 2004 for a detailed description). It is thought that this neural network between the ocular surface and the lacrimal system is responsible for the regulation of tear film secretion and plays a critical role in the maintenance of the ocular surface (Stern *et al.*, 1998). During refractive surgery corneal nerves are damaged as a result of the surgical formation of the flap (LASIK) and the ablation procedure (LASIK and LASEK). This disrupts the normal corneal nerve plexus and induces a degree of anesthesia which is typically most extreme during the immediate post-operative period (Battat *et al.*, 2001; Benitez-del-Castillo *et al.*, 2001). Confocal microscopy has been used to monitor the apparent recovery of corneal nerve structural morphology. This tends to parallel the return of corneal sensitivity which approaches the levels seen pre-operatively by approximately 6-9months following surgery (Linna *et al*., 1998; 2000a; Benitez-del-Castillo *et al*., 2001; Perez-Gomez and Efron, 2003). The loss of corneal sensitivity and consequent disruption of the neural network between corneal surface and lacrimal system is considered to be the principal cause of tear film anomalies and surface irregularity after refractive surgery, and hence the major causative factor in the increased prevalence of dry eye (Mathers, 2000; Battat *et al*., 2001; Donnenfeld *et al*., 2004).

Reported alterations to the tear film after refractive surgery include decreases in tear secretion (Benitez-del-Castillo *et al*., 2001), tear volume (Albietz *et al*., 2002), tear stability (Yu *et al*., 2000), and tear clearance (Battat *et al*., 2001), and an increase in tear osmolarity (Lee *et al*., 2000).

In addition to the alterations to the tear film, there are a number of small scale structural changes that can occur at the corneal surface itself, and to some of the surrounding structures. Such changes may result from trauma during the surgical procedure. Recognized alterations to the ocular surface include increases in corneal surface irregularity (Battat *et al*., 2001), ocular surface staining (Battat *et al*., 2001; Albietz *et al*., 2002), and corneal epithelial permeability (Polunin *et al*., 1999). There is also limited evidence to suggest a decrease in conjuctival goblet cell density (Albietz *et al*., 2002), an increase in tarsal gland anomalies in the eyelids (Patel *et al*., 2001), and a decrease in blink rate (Toda *et al*., 2001).

This array of inter-linked structural changes to the tear film and ocular surface has the potential to create a series of alterations in both the physiological and optical performance of the eye's anterior surface.

1.2.4.4 Structural changes within the cornea after refractive surgery

There has been extensive research in to the structural changes within the various corneal layers as a result of refractive surgery (see e.g. Perez-Satonja *et al.*, 1997; Jones *et al.*, 1998; Vesaluoma *et al.*, 2000; Collins *et al.*, 2001; Kim *et al.*, 2001; Pisella *et al.*, 2001; Kramer *et al.*, 2002; Perez-Gomez and Efron, 2003; Erie *et al.*, 2006). Perhaps the most relevant of these structural changes in relation to the aberrations of the eye is the existence of microfolds at the level of Bowman's membrane or the anterior stroma. Reported prevalence figures for microfolds can be as high as 90% (Vesaluoma *et al.*, 2000; Perez-Gomez and Efron, 2003). Using confocal microscopy they appear as long dark lines with varying length, thickness, curvature and orientation (Perez-Gomez and Efron, 2003). Suggested causes for microfolds after LASIK include stretching of the flap during surgery, and impaired compatibility between the flap and the new ablated residual stromal bed (Vesaluoma *et al.*, 2000). Microfolds are thought to have little clinical significance, however if severe, they may affect corneal topography and contribute to irregular astigmatism (Linna *et al.*, 2000b; Perez-Gomez and Efron, 2003).

1.2.5 Changes to ocular aberrations following refractive surgery

Successful refractive surgery results in a dramatic decrease (or elimination) of second order aberrations (spherical defocus and astigmatism) as this is the primary aim of the procedure. However, it has been extensively documented and is well known that refractive surgery tends to cause an increase in the magnitude and variability of higher order aberrations (e.g. Applegate *et al.*, 1996; 1998; Oshika *et al.*, 1999; Seiler *et al.*, 2000; Mrochen *et al.*, 2001a; Marcos *et al.*, 2001; Marcos, 2001; Moreno-Barriuso *et al.*, 2001; Straub and Schwiegerling, 2003; Yamane *et al.*, 2004; Buzzonetti *et al.*, 2004; Kohnen *et al.*, 2005; Porter *et al.*, 2006; Kirwan and O'Keefe, 2009). The levels of aberrations induced due to surgery are invariably found to be pupil size dependant, with higher levels of aberration induced for larger pupil sizes. Another common observation is that higher levels of aberration are induced for higher levels of attempted refractive correction. The increased levels of post-operative aberrations, particularly at large pupil sizes, have been linked with reports of decreased contrast sensitivity (Holladay *et al.*, 1999; Marcos *et al.*, 2001; Nakamura *et al.*, 2001; Chan *et al.*, 2002), decreased low contrast visual acuity (Holladay *et al.*, 1999; Bailey *et al.*, 2004) and symptoms of glare and haloes (Tuan *et al.*, 2006). Wavefront-guided refractive surgery procedures were introduced in an attempt to remove higher order aberrations while still correcting the refractive error. However, aberrations are still found to increase in patients receiving wavefront-guided refractive surgery (see e.g. Mrochen *et al.*, 2001b; Aizawa *et al.*, 2003; Porter *et al.*, 2006).

1.2.5.1 Nature and magnitude of changes in aberrations

A relatively early study by Moreno-Barriuso *et al.* (2001) used a laser ray tracing technique to objectively measure the change in higher order ocular aberrations caused by refractive surgery. Subjects (n=22 eyes of 12 patients) had a mean age of 28 ± 5 years and pre-operative refractive error between -2.00DS and -13.00DS, with astigmatism of less than 2.50DC. All subjects underwent conventional LASIK. Aberrations were measured before, and then at approximately two months post-operatively for 6.5mm and 3.0mm pupil diameters (up to 7^{th} order). The results showed that the total higher order RMS error (3^{rd}-7^{th} order) increased significantly in the vast majority of eyes (20/22). One eye showed a small decrease in RMS error. The increases in RMS error ranged from -0.06µm to 1.84µm. On average, this represented a 1.9-fold increase in RMS error for a 6.5mm pupil (i.e. RMS almost doubled for the group as a whole). However, the inter-subject variability was found to be very high with some subjects showing up to 4-fold increases in total higher order RMS following surgery and one subject showing a 10-fold increase in certain individual aberration coefficients. By far the largest increases occurred for 3^{rd} and 4^{th} order aberrations. There was no significant increase in the aberrations beyond 4^{th} order (collectively 5^{th} order or higher). Spherical aberration dominated the change in 4^{th} order aberrations, showing increases between 0.002µm and 0.97µm, which represented a 4-fold increase on average for a 6.5mm pupil. The coma-like aberrations (3^{rd} order RMS) showed a 2.1-fold increase for the same pupil size. The results for the smaller pupil size (3.0mm) were similar in nature but smaller in magnitude in comparison to those found at the larger pupil size (6.5mm).

These results are in broad agreement with other studies which tend to show that the total higher order RMS tend to increase by approximately 1.2-fold to 3-fold in comparison to the pre-operative level depending on the surgical procedure used and pupil size examined (Marcos *et al*., 2001; Marcos, 2001; Moreno-Barriuso *et al*., 2001). However, the increase in aberrations is found to vary widely between individuals (see e.g. Buzzonetti *et al*., 2004; Kirwan and O'Keefe, 2009). The 3rd and 4th order aberrations are frequently found to undergo the largest changes during refractive surgery (Oshika *et al*., 1999; Moreno-Barriuso *et al*., 2001). Spherical aberration is generally found to undergo the largest changes, with coma tending to increase by a lesser magnitude, although this can also vary between individuals and refractive error group (see e.g. Buzzonetti *et al*., 2004; Kohnen *et al*., 2005). The changes in spherical aberration and coma levels following surgery generally lead to an alteration in the ratio of coma:spherical aberration, and hence to the relative contribution of each to the total wave-front profile. For example, in one study coma-like aberration was dominant before surgery, but spherical aberration became dominant post-operatively (Oshika *et al*., 1999).

1.2.5.2 Causes of increased aberrations after refractive surgery

The principal location for the increase in higher order ocular aberrations is thought to be the anterior corneal surface (Marcos *et al*., 2001). A variety of causes have been suggested for the increase in higher order aberrations. Following surgery the cornea undergoes a large change in anterior curvature which is clearly demonstrated in the changes to anterior corneal topography (see section 1.2.4.1). This change in corneal asphericity is thought to be a major source of the increase in spherical aberration found post-operatively (Yoon *et al*., 2005). Tilted, asymmetric or decentered ablation patterns have also been shown to increase the level of post-operative higher order aberrations (Mrochen *et al*., 2001a). Decentration of the ablation pattern is thought to be a major source of increased post-operative coma levels. A variety of other factors could play a role in the final post-operative aberrational outcome. Surgical factors such as ablation zone and transition zone diameters, presence or absence of an eye tracker, type of laser used, efficacy of the laser during treatment, type of microkeratome used and flap cutting procedure may be expected to influence the aberrations caused by surgery (see e.g. Pallikaris *et al*., 2002). The final post-operative aberration profile will also be influenced by the patient's pre-operative aberration profile. Some studies have suggested that the re-modeling of the cornea during the post-operative healing process can cause further alterations to ocular higher order aberrations (Kirwan and O'Keefe, 2009). In contrast, other research indicates that aberrations remain stable during the first post-operative year (Straub and Schwiegerling, 2003), suggesting that the aberration changes due to surgery could be permanent.

Marcos *et al*. (2001) conducted a study in which they measured the corneal anterior surface aberrations and whole-eye aberrations, before and after refractive surgery (LASIK for myopia). Subtracting the change in anterior corneal aberrations from the change in whole-eye aberrations gave an estimate of the change in the internal aberrations of the eye. These internal aberrations showed an increase in negative spherical aberration for the majority of subjects in the study. The authors concluded that the most likely source of this change was the posterior corneal surface. They found an increase in negative spherical aberration which agreed well with the levels predicted from the forward shift in the posterior corneal surface found in studies investigating structural corneal changes in response to refractive surgery (see e.g. Wang *et al*., 1999; Baek *et al*., 2001; Seitz *et al*., 2001). Interestingly, Marcos *et al*. (2001) also suggested that spherical aberration was the only higher order aberration to alter as a result of the posterior corneal topography changes. The study also found a strong correlation ($r = 0.97$, $p<0.0001$) between the increase in aberrations at the anterior corneal surface and the increase in whole-eye aberrations, confirming that the principal location for the increase in higher order aberration due to refractive surgery was the anterior corneal surface, and that the changes at the posterior corneal surface had a minor contribution to the overall increase in aberrations.

Although there is general agreement that changes in the tear film are capable of influencing the optical quality of the eye, relatively little is known as to the extent of this within the refractive surgery population. The increased prevalence of post-operative dry eye may make this in this population particularly susceptible to visual degradation from this source. A review of the literature revealed only one study that investigated the effect of tear break up on higher order aberrations in eyes that have undergone refractive surgery. Lin *et al*. (2005) measured anterior surface aberrations during a period of non-blinking at three discrete time intervals following a blink. The time intervals were: immediately after a blink, at ½TBUT and at TBUT. Aberrations were also measured at 10 seconds after saline installation. Aberrations (3^{rd}-6^{th} order) were obtained for a 6.0mm pupil only. The refractive surgery subjects (n=28) were adults that had undergone complication-free LASIK for myopia between 1-6 months before the study. Mean pre-operative refractive error was -5.62D (range -2.5D to -10.25D) and mean fluorescein TBUT was 11.3 seconds among subjects. This study also included normal control subjects that had not undergone refractive surgery (n=50) and dry eye patients (n=42) for comparison purposes. The results of this study showed that aberrations increased during TBUT for the normal and dry eye group and decreased following the installation of saline. The results for the refractive surgery group however showed that aberrations did not vary significantly over time and suggest that aberrations remain stable throughout the TBUT.

1.2.6 Treatment outcomes for refractive surgery

The principal reason for measuring treatment outcome following refractive surgery is to provide information about the success and safety of the procedure. Having a method to assess the success and safety of a particular refractive surgery procedure allows comparison between different techniques. This helps optimize treatment regimes for individual patients by identifying surgical approaches that provide the best results in a given situation and also allows new surgical techniques and equipment to be assessed to examine whether or not they offer improvements over existing technologies. Surgical outcome data is also essential to help prospective patients make informed decisions about refractive surgery.

Over the years a number of ways to report the outcomes of refractive surgery have been suggested (Waring, 1992; Koch *et al.*, 1998; Waring, 2000; Koch, 2001). These suggestions have been an attempt to standardize the reporting of refractive surgery outcome, allow clear communication of the findings, and more direct comparison across the literature. Unfortunately, these standardized methods for reporting outcome have not been universally adopted and refractive surgery companies and independent researchers continue to report their results in a variety of different ways. Broadly speaking, the various methods used to assess the outcome of refractive surgery are aimed at obtaining information about the stability, efficacy or safety of treatment. Despite differences across the literature in the actual measures used, the results presented can normally be placed in to one of these three categories.

1.2.6.1 Typical surgical outcome results

There are a large number of studies reporting the surgical outcome of refractive surgery. When comparing these studies there is inevitable variation in the sample size, age, and pre-operative refractive error distribution of the patients studied, in addition to variations in surgical technique, surgeon experience, surgical equipment used, post-operative care regime, length of follow-up, and methods used to report outcome.

To account for some of this variability there have been a number of control-matched studies that have directly compared outcome results for LASIK and LASEK (Scerrati, 2001; Kim *et al*., 2004; Kaya *et al*., 2004; Tobaigy *et al*., 2006; Teus *et al*., 2007). These studies have typically found that LASIK and LASEK provide similar outcome results at 1-3 months post-operatively across a broad range of pre-operative myopia. In terms of outcome, the major differences between these two surgical techniques appears to be during the first few days and weeks following the procedure: with LASIK tending to show a rapid visual and refractive recovery over the first few days (Aizawa *et al*., 2003) and LASEK tending to show a longer refractive and visual recovery period extending over several weeks (Claringbold, 2002). Because the outcome results of LASIK and LASEK tend to be similar after this initial early post-operative recovery period, the following outcome statistics broadly refer to both surgical procedures.

Successful LASIK or LASEK surgery for myopia tends to result in a large initial reduction in the refractive error due to the laser ablation process. At one month post-operatively approximately 85-95% of patients achieve residual refraction (mean sphere) within ±1.00D of emmetropia and approximately 65-80% achieve residual refraction (mean sphere) within ±0.50D of emmetropia (Pop and Payette, 2000; Shahinian, 2002; Taneri *et al*., 2004a; 2004b). Refractive outcome figures tend to remain comparable at 3 months, 6 months and 12 months post-operatively with approximately 85-95% and 60-85% of patients achieving residual refractive error (mean sphere) within ±1.00D and ±0.50D of emmetropia respectively (Pop and Payette, 2000; Shahinian, 2002; Partal *et al*., 2004; Taneri *et al*., 2004a; 2004b; O'Doherty *et al*., 2006; Bailey and Zadnik, 2007). Although there can large variation between patients in the time taken for the refraction to stabilize, these residual refraction outcome statistics suggest that for the majority of patients the refraction is largely stable at one month following surgery. Others suggest that refractive stability is achieved at between one and three months post-operatively (Pop and Payette, 2000; Aizawa *et al*., 2003; Camellin, 2003).

In terms of visual recovery, studies report that at one month post-operatively approximately 90-100% of patients achieve uncorrected visual acuity (UCVA) of 6/12 or better and 40-70% achieve UCVA of 6/6 or better (Shahinian, 2002; Taneri *et al*., 2004a; 2004b). Further minor improvements in UCVA tend to follow as the eye heals, and the percentage of patients achieving UCVA of 6/6 or better improves to approximately 50-75% at three months post-operatively, and approximately 60-80% at 6-12 months post-operatively (Shahinian, 2002; Partal *et al*., 2004; Taneri *et al*., 2004a; 2004b). The percentage of patients losing more than two lines of best spectacle corrected visual acuity (BSCVA) is typically less than 5% at one month post-operatively (Taneri *et al*., 2004a; 2004b). As the eye heals and vision recovers, this decreases to around 0-1% at three months post-operatively and thereafter (Shahinian, 2002; Partal *et al*., 2004; Taneri *et al*., 2004a; 2004b).

A recent literature review by Netto *et al*. (2006) examined studies which compared the refractive outcomes of wavefront-guided procedures against conventional ablation procedures. They concluded that while wavefront-guided procedures may hold a promising future, there is only limited evidence that they currently outperform conventional procedures. This suggests that standard measures of outcome (discussed above) are likely to be comparable for both conventional treatments and wavefront-guided procedures.

1.2.6.2 Questionnaires

It seems reasonable to assume that someone achieving good surgical results based on all of the above criteria (no residual refractive error, good uncorrected visual acuity and stable refraction) would be happy with the result. However, evidence suggests that standard measures of outcome based on residual refraction and or unaided visual acuity do not necessarily correlate well with the patient's post-operative subjective impressions (Halliday, 1995; Schein, 2000; Schein *et al.*, 2001). The use of questionnaires offers another way of obtaining information to assess health intervention. Over the past 10 years a number of vision-specific questionnaires have been developed, validated and used to assess treatment outcome following refractive surgery. These include the Refractive Status and Vision Profile (RSVP) (Schein, 2000), the National Eye Institute Refractive Error Quality of Life Instrument (NEI-RQL) (Berry *et al.*, 2003), and more recently the Quality of Life Impact of Refractive Correction (QIRC) (Pesudovs *et al.*, 2004). Over this period, there have also been a number of more informal non-validated satisfaction questionnaires used to gauge the subjective opinions of patients following refractive surgery (see e.g. McGhee *et al.*, 2000; Hill, 2002). These non-validated questionnaires have tended to be administered at a more local level to assess and report refractive surgery outcomes at a particular clinical facility.

1.2.6.3 Quality of Life Impact of Refractive Correction (QIRC) questionnaire

The Quality of Life Impact of Refractive Correction (QIRC) questionnaire was developed through question selection involving literature search and extensive work with focus groups (Pesudovs *et al.*, 2004). The QIRC questionnaire consists of 20 fixed questions that cover a variety of vision specific quality of life issues. The 20 questions consist of six subscales that cover issues relating to visual function

(1 question), symptoms (1 question), convenience (5 questions), cost (2 questions), health concerns (4 questions), and well being (7 questions). The questionnaire consists of closed questions with fixed response category answers. The responses are analyzed to give an overall QIRC score based on a scale of 0-100 that represents refractive error related quality of life. Higher scores indicate better quality of life measures.

The QIRC questionnaire has been shown to be a valid and reliable way to assess quality of life related to refractive error and its correction in the pre-presbyopic population (Pesudovs *et al*., 2004). The QIRC has also been shown to be sensitive to the mode of refractive correction (Pesudovs *et al*., 2006) and sensitive to the changes in vision related quality of life that occur due to refractive surgery intervention (Garamendi *et al*., 2005).

1.3 Fundamental aspects of accommodation

The accommodative system provides the eye with a mechanism to adjust its power in response to objects at different distances from the eye. The accommodative response involves a complex sequence of events that culminate in the neurological control of the ciliary muscle and corresponding, appropriate changes in the power of the crystalline lens to improve an out-of-focus image (see Atchison, 1995; Croft *et al*., 2001; Schachar and Bax, 2001; Glasser, 2006, for detailed reviews). The following sections introduce some of the key aspects of the accommodative response as a precursor to the experimental studies that follow.

1.3.1 Amplitude of accommodation

The amplitude of accommodation is the dioptric distance between the point at which accommodation is fully relaxed (far point) and the point at which accommodation is fully exerted (near point). It therefore gives a measure of the maximum focusing range of the accommodative system. One area of research that has received considerable attention is the link between age, reduction in amplitude, and presbyopia (see Atchison, 1995; Charman, 2008 for reviews). Figure 1.4 shows typical data reported for the amplitude of accommodation as a function of age (after Rosenfield, 1997). These data suggest that the decrease in amplitude of accommodation with age follows a second order polynomial function with the rate of decline reducing with increasing age. However, these results were derived from cross-sectional studies which may mask the age-related decrease in amplitude for individual people. Longitudinal studies that follow the same individuals over time have found that there is a linear decrease in amplitude of accommodation with age (Hofstetter, 1965; Ramsdale and Charman, 1989). It has been suggested that the non-linear association found in cross-sectional studies is due to artifacts introduced by the averaging process (Charman, 1989). Amplitude of accommodation is typically around 10D at 20 years of age, reducing to around 2-4D at 40-50 years of age (Duane 1912; Hofstetter, 1944; Hamasaki *et al.*, 1956; Turner, 1958). This suggests an average annual decline of approximately 0.30D/year. At around the age of 45 years the amplitude becomes insufficient for near work in a condition termed presbyopia.

In addition to the well documented alteration of amplitude with age, there are a variety of other factors that have been shown to have a potential influence on the amplitude of accommodation. There are a variety of methods by which amplitude can be measured (see Rosenfield, 1997 for a detailed account of techniques). The most commonly used methods cover the subjective measurement of amplitude by altering target distance ("push up" and "push down" techniques) or by altering target vergence ("minus lens" technique). The amplitude can also be measured objectively by using an auto-refractor to measure the accommodation response over a range of increasing stimulus levels. The method of measurement may affect the amplitude result (Kragha, 1986; 1989; Rosenfield, 1997). Subjective techniques invariably show higher amplitudes than those measured objectively due to depth of focus effects.

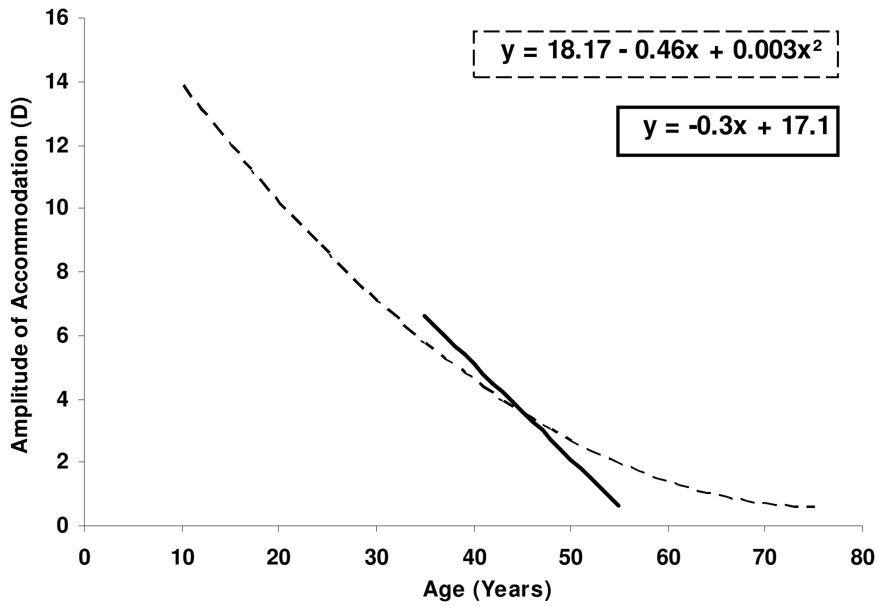


Figure 1.4: Amplitude of accommodation (D) as a function of age (years). Data re-plotted from Rosenfield (1997) (dotted line) and Ramsdale and Charman (1989) (solid line).

In the presence of refractive error the amplitude of accommodation is known to vary with the plane in which it is measured (see e.g. Douthwaite, 1995). For example, if a -6.00D myope corrected with spectacle lenses at a vertex distance of 14mm views an object at 0.40m, then they will exert 2.50D of accommodation at the spectacle plane (spectacle accommodation), yet only 2.07D of accommodation at the eye (ocular accommodation). Studies suggest that amplitude of accommodation is slightly higher when measured binocularly in comparison to monocular measurements (Duane, 1922; Schapero and Nadell, 1957; Fitch, 1971; Otake *et al*., 1993). There is some evidence that amplitude of accommodation can vary with refractive group (Fledelius, 1981; Maddock *et al*., 1981; McBrien and Millodot, 1986a; Fisher *et al*., 1987) and angle of gaze (Ripple, 1952; Atchison *et al*., 1994b).

The amplitude of accommodation measurement may also vary with the target used. Higher estimates of amplitude are found with targets of increasing letter size (Rosenfield and Cohen, 1995). This is thought to occur due to depth of focus effects, as the depth of focus has been shown to increase as the angular size of the target increases (Tucker and Charman, 1975). Amplitude of accommodation is typically measured clinically using a target of fixed size (often a line of N5 letters) which is moved towards the subject (“push-up” method). These letters get bigger as they are moved towards the subject leading to an alteration in the target size used to measure amplitudes of different magnitude. Atchison *et al*. (1994a) argue that using targets of fixed letter size leads to an increasing over-estimation of the amplitude with increasing amplitude levels (i.e. younger patients). They advocate the use of a letter chart which provides targets that maintain constant angular magnification, in an attempt to provide more accurate amplitude measurements.

1.3.2 Static aspects of accommodation

1.3.2.1 The accommodative stimulus-response function

The static accommodation response is usually characterized in terms of the stimulus-response function. This provides a measure of steady-state accommodation over a range of fixed stimulus levels. Experimentally, the stimulus levels can be created by altering the optical vergence of the target using a series of lenses, or by physically altering target distance. The accommodation response is then measured at each stimulus level and the accommodative response plotted as a function of the accommodative stimulus.

It has been extensively documented and is well known that the accommodative response exerted by the eye rarely matches the accommodative stimulus precisely (see e.g. Ward and Charman, 1985; Ramsdale and Charman, 1989; Gwaizda *et al*., 1993; Abbott *et al*., 1998). Figure 1.5 shows a schematic diagram of a typical stimulus-response function. At low stimulus levels (below approximately 1.0-1.5D) there is an initial non-linear zone which ordinarily exhibits a lead of accommodation. With increasing stimulus levels the accommodative stimulus-response function is characterized by a linear region. Over this linear region the accommodative response shows a lag of accommodation which increases with increasing near vision demand. The effects of depth of focus of the eye allows an individual to maintain a clear image of the object despite these slight inaccuracies (leads or lags) of accommodation (Wang and Ciuffreda, 2006; Charman, 2008). At higher accommodative demands, the maximum amplitude of accommodation is approached (i.e. beyond 8-9D in Figure 1.5) and the accommodative system becomes progressively less capable of eliciting an adequate response. At these high stimulus levels the stimulus-response function subsequently becomes non-linear once more and eventually plateaus to a level representing the objective amplitude of accommodation.

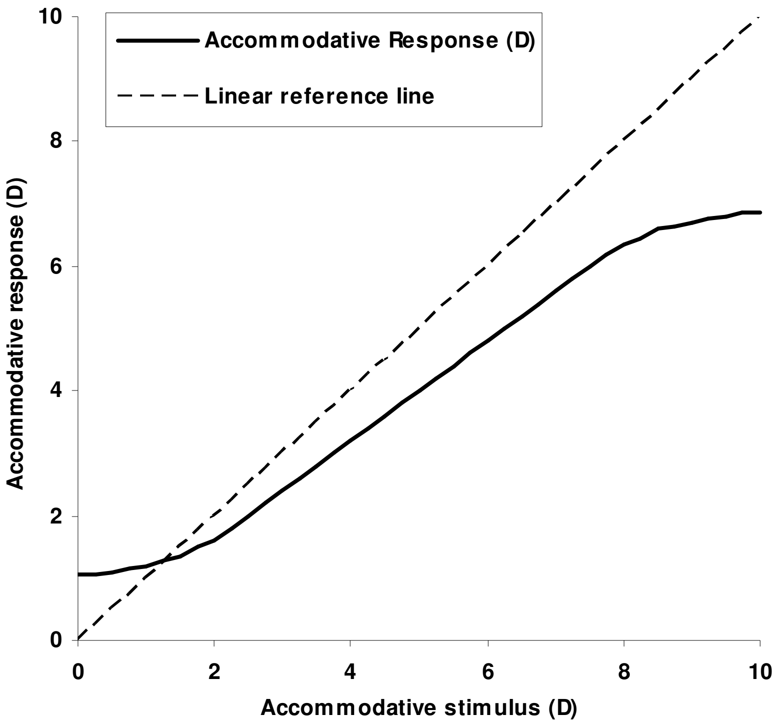


Figure 1.5: Schematic diagram of a typical stimulus-response function (after Ramsdale and Charman, 1989).

The linear region of the stimulus-response function is the principal region over which steady state accommodation is assessed. The stimulus-response function is often summarized by the gradient of the linear regression line covering the points measured over the linear region of the function. This generally provides gradients in the region of 0.5 to 1.0, although gradients can vary widely between individuals and test conditions (Johnson, 1976; Ward and Charman, 1985; Kalsi *et al.*, 2001; Gwiazda *et al.*, 1993; Radhakrishnan and Charman, 2007c).

Chauhan and Charman (1995) criticize the use of gradient alone to represent the accommodative stimulus-response function because of its failure to accurately represent errors in the accommodation response under certain circumstances. In addition they suggest the use of an additional metric, the *accommodative error index* that also takes account of the horizontal and vertical position of the stimulus-response function and the level of correlation between the accommodative response and stimulus values.

One further area of the stimulus-response function that has received attention is the point at which the stimulus-response function crosses the linear reference line. This is the only point at which the accommodative response exactly matches the accommodative stimulus. It has been suggested that this point is related to the tonic accommodation level although there seems to be only limited evidence to support this view (see Rosenfield *et al.*, 1993 for a review).

1.3.2.2 Factors affecting the accommodative stimulus-response function

While Figure 1.5 represents the generic form of the stimulus-response function, the exact characteristics of any individual function may depend on a number of factors covering both observer characteristics and a variety of experimental conditions.

1.3.2.2.1 Observer characteristics

It is generally thought that the stimulus-response function gradient is relatively resistant to the effects of age during the pre-presbyopic years. Studies have shown that the gradient remains relatively stable during adulthood up to the age of approximately 45 years and tends to show a marked and rapid decrease thereafter (Ramsdale and Charman, 1989; Mordi and Ciuffreda, 1998; Kalsi *et al*., 2001).

There is evidence to suggest that the refractive error of the observer may influence the stimulus-response function gradient. A tendency for myopes to exhibit lower gradients than emmetropes has been reported for both adults (McBrien and Millodot, 1986b) and children (Gwiazda *et al*., 1993). Later work by Abbott *et al*. (1998) was unable to confirm a link between stimulus-response function gradient and refractive error although they did find that progressing myopes exhibited lower gradients than stable myopes and emmetropes.

An early study by Heath (1956) showed that progressively decreasing visual acuity resulted in less accurate accommodation responses with progressively lower stimulus-response function gradients. Further evidence that reduced visual acuity can adversely affect static accommodation has come from studies showing reduced stimulus-response function gradients in those with amblyopia (Ciuffreda *et al*., 1983; Ciuffreda and Rumpf, 1985). A recent study by Leat and Mohr (2007) presented evidence that young individuals with visual impairment from a wide variety of different disease processes can show reduced stimulus-response function gradients in comparison to healthy controls.

1.3.2.2.2 Experimental conditions

There is considerable evidence to suggest that the stimulus-response function gradient is affected by the method of measurement, with the use of a negative lens series producing functions with lower gradients than when physically altering stimulus distance (Gwiazda *et al*., 1993; 1995; Abbott *et al*., 1998; Chen and O'Leary, 2000; Anderson *et al*., 2009; Theagarayan *et al*., 2009).

An area that has received attention is the effect that the spatial frequency distribution of the target has on the accommodative response. An early study by Charman and Tucker (1977) investigated the characteristics of the monocular accommodative stimulus-response function (over a 5D range) to grating targets of different spatial frequencies (ranging between 0.4-30 cyc/deg). They found that the gradient of the stimulus-response function increased as the spatial frequency of the target increased, indicating that the accommodative response became more accurate with increasing target spatial frequency.

Research on amblyopic eyes has provided further evidence that high spatial frequencies are important in the accommodative response. Reduced visual acuity is found in amblyopia, and amblyopes have been shown to exhibit lower accommodative responses (Wood and Tomlinson, 1975), suggesting that the lack of high spatial frequency information has a detrimental effect on accommodation.

A later study by Owens (1980) investigated the characteristics of the monocular accommodative stimulus-response function at different distances (0-5D range), to grating targets of different spatial frequencies (ranging from 0.5-19.2 cyc/deg). In contrast to the study by Charman and Tucker (1977), the results showed that the highest stimulus-response function gradients occurred for mid-spatial frequencies (3-5cyc/deg), with progressively lower stimulus-response function gradients for gratings of lower and higher spatial frequencies. The author concluded that these results showed similarities to the subject's sensitivity to contrast over a range of spatial frequencies (described in the contrast sensitivity function). This highlighted the possibility that the control of accommodation may depend on the same processes involved in foveal contrast resolution.

The early work of these investigators led to alternate hypotheses as to which regions of the spatial frequency spectrum are most important in relation to the accommodative response. The "*fine-focus*" hypothesis suggests that the initial accommodation response to a blurred target is based on the available low spatial frequency information and that high spatial frequencies (up to 30cyc/deg) are subsequently necessary to fine tune accommodation (Charman and Tucker, 1977; 1978). An alternative "*contrast-control*" hypothesis proposes that mid-spatial frequencies in the region of the peak of the contrast sensitivity function are most important to the accommodative response, since the highest sensitivity to changes in spatial contrast occurs in this region (Owens, 1980).

The effects of target luminance levels on the stimulus-response gradient have been investigated by Johnson (1976). It was found that decreasing the target luminance levels caused a decrease in the gradient of the stimulus-response function indicating decreased accommodative accuracy.

1.3.3 Dynamic aspects of accommodation

The accommodative dynamics of young pre-presbyopic adults have been well documented (see Ciuffreda and Kenyon, 1983; Ciuffreda, 1991; 1998; Hung *et al.*, 2002 for detailed reviews). The experimental work on the dynamics of accommodation in this thesis concentrates on dynamic responses to a static target with step presentation. Figure 1.6 shows a schematic diagram of the accommodation responses expected in such an experimental situation.

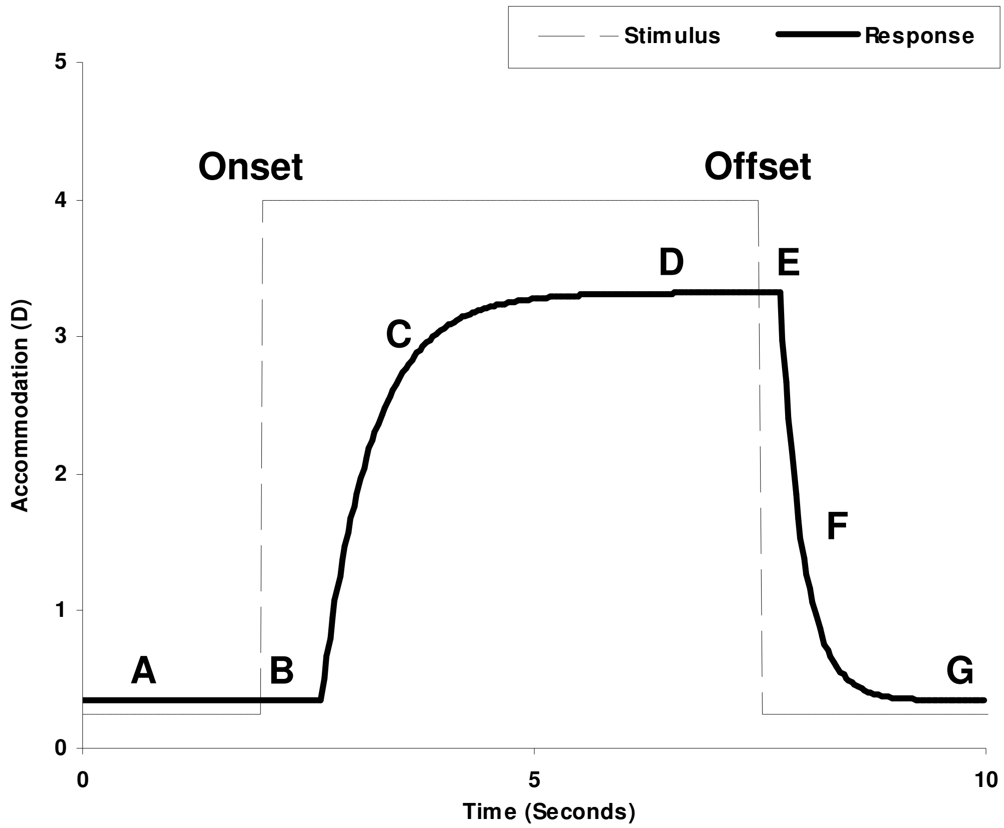


Figure 1.6: Schematic diagram of the accommodation response as a function of time to a static target with step presentation (after Ciuffreda, 1998).

Figure 1.6 shows an accommodative response trace to a target presented at 0.25m (4D stimulus) and then removed. Region **A** represents the resting accommodation level to a distant stimulus. Region **B** represents the latency time of accommodation. This is the time delay between the onset of a near stimulus and the start of the accommodation response to that stimulus.

Region **C** represents the accommodation response (distance to near). This is the time period over which the accommodation response changes from the initial resting state to the final accommodated state at region **D**. The vertical separation between the initial accommodation response at region **A** and the final accommodation response at region **D** represents the amplitude of the accommodation response produced to the near stimulus. Region **E** represents the latency time for the disaccommodation response. This is the time delay between the offset of the near stimulus and the start of the disaccommodation response. Region **F** represents the disaccommodation response (near to distance). This is the time period over which the accommodation response changes from the accommodated state to the distance resting state at region **G**.

The latency time for both the accommodation and disaccommodation response can show large between subject variation, but generally fall in the range 200-500ms (Campbell and Westheimer, 1960; Tucker and Charman, 1979; Heron *et al*., 2001; Mordi and Ciuffreda, 2004). The time over which the lens is altering shape is known as the response time. The accommodation and disaccommodation response times are typically around 450-650ms (Campbell and Westheimer, 1960). The total time interval between the onset of a near stimulus and the attainment of a new level of steady-state accommodation (i.e. latency + accommodation response/lens movement time) is therefore approximately one second for a single response. The gradient of regions **C** and **F** give the rate of change of accommodation over time, and therefore provide measures of velocity for accommodation (gradient of region **C**) and disaccommodation (gradient of region **F**). The region with the steepest gradient provides a measure of the peak velocity of each response. For a near vision stimulus of 4.0D (i.e. focusing from 0.0D to 4.0D and 4.0D to 0D), the peak velocity is usually around 5-10 D/s for accommodation and 10-15 D/s for disaccommodation, although these values can vary widely between individuals and with the magnitude of the accommodation response (Kasthurirangan *et al*., 2003). The accommodation response tends to initially increase rapidly and then level off to a steady state where clear near vision is achieved. Similarly, the disaccommodation response tends to initially decrease rapidly and then level off to a steady state where clear distance vision is achieved (see e.g. Kasthurirangan *et al*., 2003; Kasthurirangan and Glasser, 2006). Research has shown that the accommodative and disaccommodative responses can be well modeled using exponential functions (Beers and Van Der Heijde, 1994; 1996; Kasthurirangan *et al*., 2003; Kasthurirangan and Glasser, 2005; 2006). The equations used to model the response take the form:

$$\mathbf{y = y_0 + a\,(1 - e^{-x/\tau})} \qquad \text{for accommodation}$$

and $$\mathbf{y = y_0 - a\,(1 - e^{-x/\tau})} \qquad \text{for disaccommodation}$$

Where:

$\mathbf{y}$ = Accommodation

$\mathbf{y_0}$ = Initial amplitude of accommodation at the start of the response

$\mathbf{a}$ = Total amplitude change during the response

$\mathbf{x}$ = Time in seconds

$\boldsymbol{\tau}$ = Time constant

The peak velocity of response can be calculated using the formula:

$$\mathbf{v = a / \tau}$$

(Radhakrishnan *et al.*, 2007)

Where:

$\mathbf{v}$ = Peak velocity

$\mathbf{a}$ = Total amplitude change during the response

$\boldsymbol{\tau}$ = Time constant

1.3.4 Microfluctuations

If a young observer views a fixed stimulus, the usual steady-state accommodation response shows small involuntary oscillations about the mean level of accommodation that are known as microfluctuations (see Charman and Heron, 1988, for a detailed review). Microfluctuations typically have an amplitude of about 0.1-0.5D and a temporal frequency of about 0.5-2.5Hz (Campbell *et al.*, 1959). The exact amplitude and temporal frequency observed varies with the experimental viewing conditions and observer characteristics (Alpern, 1958; Campbell *et al*., 1959; Bour, 1981; Denieul, 1982; Grey *et al*., 1993a; 1993b).

Research on microfluctuations has tended to bracket them in to two categories: low temporal frequency microfluctuations (<0.6Hz) and high temporal frequency microfluctuations (around 2Hz). There is evidence for a strong correlation between high temporal frequency microfluctuations and arterial pulse (Winn *et al*., 1990; Winn and Gilmartin, 1992; Collins *et al*., 1995) and between low temporal frequency microfluctuations and respiration rate (Collins *et al*., 1995). It has therefore been suggested that microfluctuations could result from these cyclic biological processes and their effects on the mechanical and elastic properties of the lens and its associated structures (Winn *et al*., 1990; Winn and Gilmartin, 1992; Collins *et al*., 1995).

Some research suggests that microfluctuations simply represent inherent variability or "noise" in the accommodative system and have little or no functional significance to the control of the accommodative response (Stark *et al*., 1965). However, it seems logical to assume that a microfluctuation in one direction would improve an out-of-focus image while a microfluctuation in the opposite direction would make an out-of-focus image worse. Therefore it has been suggested that microfluctuations could provide a directional cue that helps guide the accommodative response (Alpern, 1958; Fender, 1964). After a review of the available evidence Charman and Heron (1988) conclude that high temporal frequency microfluctuations (around 2Hz) are probably too small and variable to have an important role in controlling the accommodative response. However, they suggest that low temporal frequency microfluctuations (around 0.5Hz) may play a role in maintaining the steady-state accommodative response but are too slow to have any useful influence on the dynamic accommodation response: the components of which usually occur much more rapidly. The exact role (if any) of microfluctuations in the accommodative response remains a matter of debate.

1.3.5 Accommodative facility

Accommodative facility gives a measure of the ability of the eye to focus on a sequence of stimuli at various distances or vergences in a given period of time. Low accommodative facility can be used as a measure of accommodative insufficiency and can be a source of visual discomfort (Henessey *et al*., 1984).

Accommodative facility is usually measured by instructing the subject to observe (monocularly or binocularly) a target at a fixed distance alternately through positive and negative lenses. Distance facility rate is typically measured using a distance stimulus (often at 6.0m or 4.0m) and a "plano/-2.00D" lens combination, and near facility rate is typically measured using a near stimulus (often at 0.40m) and a "± 2.00D" lens combination (e.g. see Zellers *et al*., 1984; Allen and O'Leary, 2006). The lenses are interchanged as soon as the subject reports that the target is clear. This process is repeated continuously for a period of one minute and the result recorded as the number of cycles completed in the one minute period (one cycle indicates that the images through both the positive and negative lenses were brought in to focus). Normal facility rates can show considerable between subject variation but typically fall between 12-18 cycles/min and 9-13 cycles/min for distance and near facility respectively (Hennessey *et al*., 1984; Zellers *et al*., 1984; McKenzie *et al*., 1987; Allen and O'Leary, 2006; Radhakrishnan *et al*., 2007).

1.3.6 Link between aberrations and accommodation

Over the years the potential cues for the accommodation reflex have received much attention. A large number of potential cues have been suggested including chromatic aberration (Fincham, 1953), target size (Kruger and Pola, 1985), Stiles-Crawford effect (Fincham, 1951), convergence (Toates, 1972) and microfluctuations (Charman and Heron, 1988). While the precise relative contributions from each of the potential accommodative cues remains unknown, it has emerged and is widely accepted that defocus blur provides the principal cue for the accommodative mechanism to change focus (Phillips and Stark, 1977; Kruger and Pola, 1986). However, if an object is defocused by the same amount either side of the retina then a symmetrical shape of blur is perceived in the presence of defocus blur alone. The even-error nature of defocus blur therefore offers no directional cues to aid the accommodative mechanism (Fincham, 1953; Stark and Takahashi, 1965; Smithline 1974). Therefore other possible cues are thought to combine with defocus blur to provide the eye with the necessary cues for accommodation.

The levels of higher order aberration typically found in the eye can appear modest and may only have a small effect on image quality. However, the eye can display high sensitivity to them when they are combined with defocus. There is increasing evidence to show that higher order aberrations can have an important role in helping to control and drive the accommodative system.

Wilson *et al.* (2002) conducted a psychophysical experiment (n=8 subjects) to examine whether people could use higher order aberrations to provide a directional cue for the accommodative mechanism. A two-alternative-forced-choice task was used to determine whether a blurred target was presented in front of or behind the retina. The experiment was conducted with 1mm, 2mm and 5mm artificial pupil diameters. Their results showed that as the pupil size increased, the subject's levels of higher order aberration increased and they got concurrently better at discriminating the direction of defocus. The authors concluded that even-order aberrations could combine with defocus to provide asymmetries between the images produced with positive and negative defocus blur, and that this created an odd-error cue which could be used by the eye to help guide the direction of the accommodative mechanism.

Fernandez and Artal (2005) were the first to use adaptive optics to investigate accommodative control. They conducted an experiment (n=2 subjects) in which they measured the dynamic accommodation response to a single step-change in stimulus (0-1.5D for one subject and 0-2D for the other subject) with the subject's normal ocular aberrations present. They repeated the measurements while using an adaptive optics system to continuously correct for asymmetric higher order aberrations (astigmatism, coma, and trefoil) in real-time during accommodation. The dynamic function data was used to look for differences in: accommodative latency, response time, amplitude and peak velocity between the two measurement conditions (normal aberrations present versus aberrations corrected). The results showed that when the higher order aberrations were corrected the accommodation response latency and magnitude were unaffected, but the velocity of response was reduced and there was a concurrent increase in accommodative response time (lens-movement time). They concluded that the correction of asymmetric higher order aberrations produced deterioration in the accommodative response for both subjects.

A similar study by Chen *et al*. (2006) also used adaptive optics to investigate the impact of higher order monochromatic aberrations on the accommodative response. They measured accommodation responses to a randomly selected single step-change in stimulus of 0.50D: either from zero to far, or from zero to near (n=6 subjects). Accommodation responses were measured with the subject's normal ocular aberrations present, and then with their higher order aberrations corrected using an adaptive optics system. The adaptive optics system they used achieved a 95% reduction in all higher order aberrations (up to the 10^{th} order). They found that the majority of subjects (n=4) could accommodate equally well with or without the aberrations present (there was no significant difference in amplitude of response, or response time after aberrations were corrected). However, one subject accommodated normally in the presence of aberrations, but could not accommodate at all, in either direction, after higher order aberrations had been removed. The remaining subject accommodated poorly under both conditions. The results suggest that some subjects rely heavily on higher order aberrations to control accommodation.

A recent study by Chin *et al*. (2009) examined the dynamic accommodation response to a single step-change in stimulus of ±0.50D (i.e. 0.0D to 0.50D in either inward or outward steps) (n=4 subjects). Accommodation was measured with the subject's normal ocular aberrations present, and then with various higher order aberrations corrected, and then with various higher order aberrations inverted using an adaptive optics system. The dynamic responses were examined for gain, latency and total response time (latency + lens movement time). The results showed that correcting aberrations did not have a significant effect on dynamic accommodation responses. However, inversion of higher order aberrations produced a decrease in gain and an increase in latency for accommodation responses to outward stimulus steps, and caused an increase in the number of times subjects showed an initial accommodation response in the wrong direction (i.e. an initial inward response to an outward stimulus change). These errors of accommodation were most obvious when even-order terms were inverted. The authors concluded that disaccommodation appears to derive a cue from even-order aberrations which helps guide the initial direction of the accommodative response.

Adaptive optics has also been used by Gambra *et al.* (2009) to investigate the affect of higher order aberrations on accommodation. They measured the accommodative response of five normal subjects to a stimulus that was altered in 1D steps over a 0-6D range in the presence of different levels of higher order aberration. They found that inducing 1µm of negative spherical aberration produced a decrease in lag and more accurate accommodation responses, and inducing 1µm of positive spherical aberration produced an increase in lag and less accurate accommodation responses. They also found that correction of higher order aberrations improved the accommodation response (decreased lag) in four of the subjects. Their results suggest that induced aberrations are capable of influencing lag of accommodation, and that the effects are most apparent for alterations in spherical aberration.

A different approach that has been used to investigate the effect of higher order aberrations on the accommodative system has been to measure accommodative functions while using contact lenses that induce various levels of aberration. A potential problem with this method is that rotation or decentration of the contact lens (due to fitting issues), or movement of the contact lens during a blink, may alter the induced aberrations (Guirao *et al.*, 2001).

Lopez-Gil *et al*. (2007) examined the dynamic accommodation response to a sinusoidal change in stimulus (1.0-3.0D, 0.2Hz), in a group of normal subjects (n=10). They repeated the measurements with custom made contact lenses that induced various levels of RMS coma (0.34µm and 0.94µm) and RMS trefoil (0.25µm and 1.03µm). The results showed that the highest levels of coma and trefoil appeared to cause a small reduction in accommodative gain but this decrease did not reach statistical significance. Conversely, their data suggests that the accommodative system is relatively resistant to changes in 3^{rd} order aberrations of up to 0.8µm-1.0µm (5.7mm pupil).

Using a similar approach, Theagarayan *et al*. (2009) showed that the manipulation of spherical aberration with custom made contact lenses could cause predicable changes in the static accommodative stimulus-response function (n=10 subjects). They showed that increasing positive spherical aberration (via contact lenses with +0.10µm and +0.20µm spherical aberration for a 5mm pupil diameter) caused a decrease in the stimulus-response function gradient, and increasing the negative spherical aberration (via contact lenses with -0.10µm and -0.20µm spherical aberration for a 5mm pupil diameter) caused an increase in the stimulus-response function gradient. They also showed that this effect was maintained over a period of 30-60 minutes.

It has been suggested that manipulating spherical aberration to improve accommodative accuracy could be used as a possible way to slow myopia progression (Allen *et al.*, 2009).

Plainis *et al.* (2005) conducted a study to investigate the relationship between monocular steady-state errors of accommodation and changes in ocular aberrations during accommodation. They measured accommodative stimulus-response functions over a stimulus range of 0-8D (n=7 healthy subjects, mean age 28 years). Aberrations were measured up to and including the 4th order for natural pupils. They found a linear relationship between the levels of spherical aberration during accommodation and errors of focus inherent in the stimulus-response function. Positive spherical aberration was found to accompany a lead of accommodation for distant targets and negative spherical aberration was found to accompany a lag of accommodation for near targets. Zero error focus (stimulus-response function crossing point) was found to occur for zero levels of spherical aberration. The authors concluded that spherical aberration is the main higher order aberration that contributes to image quality changes during accommodation, and that spherical aberration is used to maximize image quality.

Considered collectively, the results of these studies suggest that higher order aberrations have a role in accommodative control. However, the precise role of higher order ocular aberrations in the performance of the accommodative system remains unknown.

1.4 Aims and scope of thesis

The aim of this thesis is to investigate the impact of refractive surgery on the accommodative mechanism. The rationale that underpins a lot of this research is as follows. Previous reports have shown that higher order aberrations alter significantly due to refractive surgery. There is also increasing evidence that higher order aberrations could have an important role in controlling the accommodative mechanism. It is therefore hypothesized that the change in ocular aberrations following refractive surgery will alter an individual's ability to detect blur and hence to facilitate accommodative functions. The impact of refractive surgery on the accommodative mechanism is currently unknown. With large numbers of people undergoing refractive surgery, it is important to have a better understanding of the consequences of altering higher order aberrations on the accommodative mechanism. The current attempts to control higher order aberrations surgically with wavefront-guided procedures makes this research particularly timely.

To investigate this issue a number of experiments will be conducted to measure a series of accommodative functions in a group of individuals prior to and following refractive surgery, while concurrently measuring the changes that take place in ocular aberrations. More specifically, studies will be conducted to investigate the effects of altered aberrations on:

1. Amplitude of accommodation
2. Stimulus-response function
3. Accommodative facility rates
4. Dynamic aspects of accommodation

Previous studies have shown that ocular aberrations can alter during accommodation and can be influenced by tear film disruption. To find out more about the levels of ocular aberration in eyes that have undergone refractive surgery, studies will be performed to investigate how aberrations change during accommodation, and to examine temporal characteristics of any aberrational change due to tear film disruption in those undergoing refractive surgery.

Initially, prior to the recruitment of any refractive surgery patients a study was performed to investigate possible differences in the accommodative stimulus-response function between emmetropes and myopes. This initial study introduced important aspects of the accommodative response, and data collection and analysis techniques that would be used during the study involving the refractive surgery patients.

CHAPTER 2
INSTRUMENTATION AND APPARATUS

This chapter describes the instruments used during the experimental studies.

2.1 Shin-Nippon SRW-5000 auto-refractor

The Shin-Nippon SRW-5000 is a commercially available auto-refractor for the objective measurement of refractive error (Aijinomoto Trading Inc., Toyko, Japan). The auto-refractor incorporates an open-field design which makes it a valuable instrument for use in accommodation research. In static mode the auto-refractor provides discrete individual readings of refractive error in approximately one second. Previous studies have included a description of how the auto-refractor works (e.g. see Mallen *et al*., 2001; Wolffsohn *et al*., 2004). Briefly, during the measurement procedure a set of two horizontal and two vertical infrared bars surrounding fixation are reflected to/from the patient's retina. The reflected image of the bars is focused by a lens system on to a CCD camera. The separation of each pair of bars is analyzed by the internal software of the instrument to calculate the refractive error.

The Shin-Nippon SRW-5000 auto-refractor has been shown to be valid (compared to subjective refraction) and repeatable over a range of +6.50D to -15.00D (Mallen *et al*., 2001).

Specifications of the Shin-Nippon SRW-5000 (Mallen *et al*., 2001):

- Available measurement range: Sphere ±22.00DS, Cylinder ±10.00DC, precision choice of 0.12D or 0.25D, axis specified to 1 degree.

- Available back vertex correction: choice of 0, 10, 12, 13.5, 15, or 16.5mm.
- Minimum pupil size = 2.9mm.
- Open-field design allows 80 degree horizontal field.
- Viewing screen to allow real-time instrument alignment.
- Built in printer to print off refraction results.

The Shin-Nippon SRW-5000 is capable of continuous measurement of accommodation and hence investigation of accommodative dynamics. Several previous studies have included descriptions of how to link the Shin-Nippon to a personal computer (PC) and how to take continuous measurements using the Shin-Nippon auto-refractor (see Li and Edwards, 2001; Wolffsohn *et al.*, 2001; 2004).
During the experimental study of dynamic accommodation described in Chapter 8 the Shin-Nippon was linked to a desktop PC. This connection allowed the horizontal and vertical measurement bars to be imaged on the computer. To allow continuous accommodation readings with the Shin-Nippon it is necessary for the horizontal and vertical infrared measurement bars to be permanently illuminated. This is achieved by changing an option in the Shin-Nippon's internal menu system. Under the "*set system items*" menu, option "*Ref.Led*" is changed from "*Auto*" to "*On*". Installed on the desktop PC was an image analysis program. The computer program was designed and written by Professor James Wolffsohn (Aston University, Birmingham) using Labview programming and Vision software Version 1.4 (National Instruments, Austin, TX, USA, see Wolffsohn *et al.*, 2004). The software converts the image of the measurement bars to a digital image. It then detects the edges of the measurement

bars and records the distance between the measurement bars in pixels. This separation distance is then converted in to a dioptric refraction measurement which is saved in a computer file.

Specifications during dynamic measurements (Wolffsohn *et al.*, 2001; 2004):

- Range 6.5D.
- Temporal frequency up to 60Hz.
- Pupil size greater than 2.9mm.
- Accuracy 0.001D.
- Unaffected by eye movements of ±10 degrees from instrument axis.
- Relatively resistant to machine focusing errors (10mm towards, and 5mm away from the eye).

Prior to each of the experimental study sessions in which the Shin-Nippon auto-refractor was used calibration of the machine was checked against a model eye of known refraction (-5.00DS). Errors of up to ± 0.12D were accepted.

2.2 IRX-3 Shack-Hartmann aberrometer

The IRX-3 Shack-Hartmann aberrometer is a commercially available aberrometer (Imagine eyes, Paris, France) for the objective measurement of whole-eye ocular aberrations. The IRX-3 uses Shack-Hartmann principles in the measurement of aberrations. A brief description of this method is provided here (see Atchison, 2005; for detailed review). In the Shack-Hartmann method (*out-of-the-eye aberrometry)* a narrow wave-front of light (approximately 1mm wide) is generated and then

projected through the eye to a point focus on the macula. This light is reflected back out through the eyes optics and the emerging wave-front is focused by a lenslet array of identical small lenses on to a charged couple device (CDD) sensor. If the eye were free from aberration, the wave-front would exit the eye as a plane wave-front, just as it entered, and the lenslet array would form a regular lattice of spot images on the sensor. If the eye contains aberrations, the flat wave-front entering the eye will exit as an irregular wave-front after passing through the eye's optics. These deviations in the wave-front exiting the eye produce displacements in the pattern of spot images on the sensor. The aberration profile can be calculated from the direction and magnitude of displacement of the spot images from their corresponding reference position.
Shack-Hartmann aberrometry has been shown to be a valid (Salmon *et al*., 1998; Cheng *et al*., 2003; Hong *et al*., 2003) and repeatable (Miranda *et al*., 2009) method to evaluate ocular aberrations.

Specifications of the IRX-3 Shack-Hartmann aberrometer (IRX-3 User Guide/Product Manual, Imagine Eyes):

- Available measurement range: Sphere -15.00DS to +20.00DS, Cylinder ±10.00DC.
- Wavelength 780nm.
- Area of analysis at the pupil plane 7.2 x 7.2 mm^2.
- Number of sub-apertures 32 x 32.

2.3 Allegretto Wave Analyzer

The Allegretto Wave Analyzer is a commercially available aberrometer (Wavelight Laser Technologies AG, Erlanger, Germany) for the objective measurement of whole-eye ocular aberrations. The Allegretto Wave Analyzer uses Tscherning principles in the measurement of aberrations. A brief description of this method is provided here (see Atchison, 2005; for detailed review). In the Tscherning method (*into-the-eye aberrometry)* a wave-front is generated and passed through a matrix of holes to create a group of parallel light rays in a grid pattern. These rays then enter the eye, passing through the eye's optics, and are imaged in the form of a grid-like pattern of spots on the retina. If the eye were free of aberrations, the grid pattern on the retina would have the same regularity as the rays entering the eye. Any aberrations present in the eye cause deviations in the spot pattern on the retina. The retinal spot pattern is captured by a video camera and the aberrational profile calculated from the direction and magnitude of deviation of the spot images from their reference position.

Tscherning aberrometry has been shown to be a valid (Rozema *et al*., 2006) and repeatable (Mrochen *et al*., 2000) method to evaluate ocular aberrations. The Allegretto Wave Analyzer Excimer Laser System received FDA approval in October 2003 (Bailey and Zadnik, 2007).

Specifications of the Allegretto Wave Analyzer (Allegretto Analyzer Procedure Manual, Wavelight Laser Technologies):

- Available measurement range: Sphere -12.00DS to +6.00DS, Cylinder ±6.00DC.

- Wavelength 660nm.
- Grid size at the cornea 10 x 10mm, spot pattern approximately $1mm^2$ on the retina.
- Grid projector creates array of 168 red laser rays for measurements.
- 3-Dimensional eye tracking system ensures that image acquisition only occurs if the pupil is properly centered and focused.

Calibration of the aberrometer was checked (and performed if necessary) weekly by trained hospital staff prior to surgical assessments. In addition, the machine also performs a self-calibration checking procedure during start-up when switched on.

CHAPTER 3

EFFECT OF TARGET SPATIAL FREQUENCY ON ACCOMMODATIVE RESPONSE IN MYOPES AND EMMETROPES

3.1 Introduction

Several studies have suggested that myopes exhibit lower monocular stimulus-response function gradients than emmetropes (see e.g. McBrien and Millodot, 1986b; Gwiazda *et al*., 1993; Abbott *et al*., 1998). The largest differences in lag of accommodation have been found for higher accommodative demands (McBrien and Millodot, 1986b) and when accommodation was stimulated with negative lenses (Gwiazda *et al*., 1993; 1995; Drobe and de Saint-Andre, 1995; Abbott *et al*., 1998).

Why might myopes exhibit lower stimulus-response function gradients? It has been suggested that larger accommodative lags might be tolerated by myopes, as compared to emmetropes, because of their reduced sensitivity to defocus blur (Jiang, 1997; Rosenfield and Abraham-Cohen, 1999; Collins *et al*., 2006; Vasudevan *et al*., 2006). When grating objects are observed, the degrading effect of any given level of defocus blur on the contrast of the retinal image increases with the spatial frequency of the target, although the exact contrast changes vary with such factors as the pupil diameter, wavelength and ocular aberration (e.g. Green and Campbell, 1965; Charman and Jennings, 1976; Charman, 1979; Legge *et al*., 1987; Atchison *et al*., 1998; Marcos *et al*., 1999). If, then, myopes have reduced sensitivity to defocus blur and less accurate accommodation responses (compared to emmetropes) to targets consisting of a broad range of spatial frequencies, this may be because they place a greater importance on the lower spatial frequency components of the retinal image than on those of higher spatial frequency. If this is true, it might be expected that myopes would have greater problems than emmetropes when asked to accommodate to targets containing mainly high spatial frequencies.

Many earlier authors have explored the accommodative stimulus-response function for sinusoidal grating targets (see e.g. Charman and Tucker, 1977; 1978; Owens, 1980; Bour, 1981), although none of them appears to have systematically studied the effects on the results (if any) of the subject's refractive error.

The aim of this study was therefore to investigate the form of the monocular accommodative stimulus-response function to grating targets of different spatial frequencies and to a letter target of wider spatial bandwidth in groups of emmetropic and myopic subjects of similar age, to determine whether they show obvious differences in the form of their stimulus-response functions. The hypothesis was that myopes would show a lower gradient than emmetropes when the target was a grating of higher spatial frequency due to an increased tolerance to defocus blur.

3.2 Subjects

A priori power calculation was performed to evaluate the required number of subjects. An effect size of 0.75, α-level of 0.05 and power 0.85, gave a total sample size of 20 subjects (i.e. 10 in each group). The effect size of 0.75 equates to a 0.15 difference in stimulus-response function gradient between the groups, and a standard deviation of 0.1 in the stimulus-response function gradient within each group. Twenty adult subjects (14 female, 6 male) aged between 18 and 37 years were recruited from among the staff and students at the University of Manchester, UK. All subjects were free from ocular disease including myopic retinal degeneration. They had a visual acuity of 6/6 or better in the tested eye and no known accommodative anomalies or significant ocular history. Only one subject was an experienced observer for accommodation and psychophysical studies. Subjects with astigmatism of over 1.25D were excluded from the study, and the right eye was used for all measurements. Ten of the subjects were emmetropic (overall mean sphere +0.19D, range -0.37D to +1.37D), and 10 were myopic (overall mean sphere -2.89D, range -1.13D to -6.63D). The mean age was 25.1 years (range 19 to 37 years) for the emmetropes and 26.4 years (range 20 to 36 years) for the myopes. The myopic group included seven early-onset myopes (myopia onset at age 14 years or before) and three late-onset myopes (myopia onset at 15 years of age or older). In the early-onset myopes, three were progressing myopes (defined as an increase of 0.50D or more in the previous two years as reported by the subject) and four were stable. In the late-onset myopes one was progressing, while two were stable. The study followed the tenets of the Declaration of Helsinki and written informed consent was obtained from all participants after the nature 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.

3.3 Methods

All subjects underwent a full subjective refraction on the right eye (based on least-negative prescription with maximum achievable visual acuity). Myopic refractive error was corrected for distance viewing with thin disposable soft contact lenses to within ±0.25D (mean sphere), which was confirmed with over-refraction and visual acuity measurements. Contact lenses were worn by eight of the ten myopes, who were habitual contact lens wearers. The other two myopes had refractive errors -1.00/-0.25 x 5, and -1.00/-0.25 x 175, and did not wear contact lenses for the experiment. Instead, a -1.00D lens was added in the trial frame in addition to the lenses used to alter target vergence.

The grating targets, which were placed at a distance of 1m from the eye, consisted of vertical, sine-wave Gabor targets (Gabor, 1946). Gabor targets were used rather than true gratings to minimize any edge effects which might affect the subjects' accommodation. The target luminance was described by a function of the form:

$$\mathbf{L = L_{mean}(1 + C \sin\{2\pi Fx\}.\exp[-(x^2 + y^2)/2\sigma^2])}$$

Where:

L = Target luminance

$\mathbf{L_{mean}}$ = Mean luminance (=45 cd/m^2)

x and y = Angular Cartesian coordinates on the screen (measured from the peak of the Gaussian envelope)

C = grating contrast (=0.8 or 80%)

F = Target dominant spatial frequency

σ = Standard deviation of the Gaussian envelope (constant at 1.2 degrees)

All targets subtended a total of 6 degrees of visual angle. There were four grating targets (spatial frequencies, F = 1, 4, 8, and 16 cyc/deg) and one 80% contrast optotype “E” target. Note that, because the Gaussian envelope was the same for all the Gabor targets, their relative bandwidth decreased with the nominal centre frequency F. The octave bandwidths were 0.453 (1 cyc/deg), 0.112 (4 cyc/deg), 0.056 (8 cyc/deg) and 0.028 (16 cyc/deg): there was negligible content at higher harmonics of the fundamental frequencies.

The optotype subtended a visual angle of 25 minutes of arc (equating to a 6/30 Snellen letter), with the horizontal bars crudely approximating to a 6 cyc/deg square-wave grating. The letter was sufficiently large to be recognizable with reasonably large errors of focus, so that any subject who habitually minimized their accommodative effort could recognize the letter in the presence of substantial accommodative lag. In contrast, to produce accurate retinal focus subjects ideally needed to accommodate to produce maximal edge sharpness rather than to simply ensure letter recognition. All the targets were included in a PowerPoint presentation, alternately interleaved with blank screens, and presented on a CRT monitor having a green phosphor (chromaticity coordinates x=0.290, y=0.611, peak wavelength 547nm with a bandwidth of about 30nm, Mitsubishi Diamond Pro 2070SB, Cambridge Research Systems, UK).

Stimulus-response functions were measured by altering the target vergence with lenses. The subjects viewed the targets presented on the monitor at a fixed 1m distance (vergence –1.00D) with a natural pupil through an open-field Shin-Nippon SRW-5000 auto-refractor (Ajinomoto Trading Inc, Tokyo, Japan, see Mallen *et al.*, 2001). The auto-refractor incorporated a circular aperture that allowed a 6 degree field at 1m. This aperture served to black out the surround and remove other possible accommodative stimuli. As the aperture was positioned at 19cm (vergence – 5.26D) from the eye, it represented a much higher and more peripheral stimulus than the main targets and was not expected to have any effect on the responses. The left eye was occluded and the targets were observed monocularly through the aperture using the right eye, with the room lights off. The subjects wore a trial frame, at a vertex distance of 12mm, into which lenses (+1.00D, -0.50D, -2.00D, -3.50D, and -5.00D) were placed to alter the vergence of the targets and create accommodative stimuli covering the range 0-6D in 1.5D steps (nominally 0D, 1.5D, 3D, 4.5D and 6D). The size and spatial frequency of each set of targets was adjusted to compensate for magnification produced by the different trial lenses used and target vergences were corrected for the vertex distance of the trial lenses. Note that both the target and the field aperture were seen through the lenses, so that the vergence of the latter always remained about -5D greater than that of the target. The grating targets were presented in a randomized order to each subject, followed by the optotype. The target sequences were selected randomly from a list of all possible target sequences using a random number generation program in Excel (Microsoft Corp., 2003).

Subjects were asked to view the targets "*keeping them as clear as possible at all times*". Although the subjects were familiarized with the requirements of their task, no attempt was made to systematically train them through practice or feedback to produce maximal responses, since it was hoped that they would produce "natural" responses which reflected their accommodative performance in normal life. When the subject reported that each stimulus was clear, three readings were taken with the auto-refractor. Each target was interleaved with a blank screen and the target was presented for the minimum duration (i.e. just long enough for the subject to be able to report the target to be clear and to take the readings), to avoid grating adaptation effects. Accommodation responses, expressed in vector form (Thibos *et al*., 1997), were calculated from the means of each triplet of auto-refractor readings, with appropriate allowance for the power and vertex distance of the trial lenses worn. An increase in the power of the eye, corresponding to a more negative refraction, was taken as a positive accommodation response. Estimated responses for the vertical grating targets were based on measurements of refraction in the horizontal meridian of the eye and those for the optotype were based on best-sphere refractions.

3.3.1 Data analysis

Two single-figure indices were used to characterise each stimulus-response function: its gradient and the accommodative error index. The gradient was calculated for the quasi-linear part of the function by determining the regression line fit for data obtained with the 1.5D stimulus onwards. The accommodative error index was used because while the gradient values show how the response is changing with the stimulus, they give no indication of the magnitudes of the actual errors (lags or leads) of focus, which may be very high even though the gradient is close to unity. A function with a gradient of unity does not necessarily coincide with the “ideal” 1:1 or Donders’ stimulus-response line and substantial lags or leads may still be present. The accommodative error index (Chauhan and Charman, 1995) takes account of both the extent to which responses deviate from Donder's line over the chosen stimulus interval and the goodness of fit of the data points to the regression line. The index essentially involves determining the mean magnitude of the response error between the ideal line and the regression line over the stimulus interval and dividing it by the value of r^2 for the regression line (r is the Pearson's product moment correlation coefficient).

If the regression line fit is given by:

$$\mathbf{y = mx + c}$$

where y is the response, x is the stimulus, m is the gradient and c is the intercept, and the regression line does not cross the Donder's line, the accommodative error index (I) is given by the equation:

$$\mathbf{I = \left|(1-m)[(x_2 + x_1)/2] - c\right| / r^2}$$

where x_1 and x_2 are the stimulus levels defining the range over which the regression fit applies. If the two lines intersect within the chosen stimulus interval, a slightly more elaborate expression must be used (see Chauhan and Charman, 1995).

Unfortunately, evaluation of such errors with infrared auto-refractors is not straightforward, since the results of all auto-refractors include corrections for the position of the reflecting layer within the retina and for longitudinal chromatic aberration between the infra-red and visible wavelengths. In addition, they include a further correction to bring their results into line with those of clinical subjective procedures. The latter are typically carried out at a testing distance of 6m (vergence –0.17D) and involve a "least negative, most positive correction". They thus leave the "emmetropic" eye slightly myopic, relying on depth-of-focus to give clear vision of the test chart. Overall, then, it is likely that an auto-refractor measurement of perfect "emmetropia" implies an eye that, from the strictly optical point of view, is slightly myopic. For the present purposes, it was assumed that the Shin-Nippon estimates of responses were 0.25D too low. The intercept values in the regression line fits were therefore amended by this amount when the fits were used to derive the accommodative error indices.

3.4 Results

Stimulus-response functions for each target type were plotted for each subject. The functions generally showed the usual form of an initial non-linear region followed by a quasi-linear region (Ciuffreda, 1991; 1998). There were, however, considerable inter-subject variations in the form of the functions for different targets. Figure 3.1 shows some typical data. Note that emmetrope 3 (-0.25/-0.25 x 175) has reasonably consistent responses but emmetrope 4 (+0.25/-0.25 x 135), who has generally more scattered responses, has difficulty in accommodating to the gratings at zero vergence. Myope 4 (-1.00/ -0.25 x 5) has reasonably accurate responses which vary little with the target except for the highest stimuli, whereas myope 9 (-6.50/-0.25 x 20) produces erratic and inaccurate responses to almost all the stimuli.

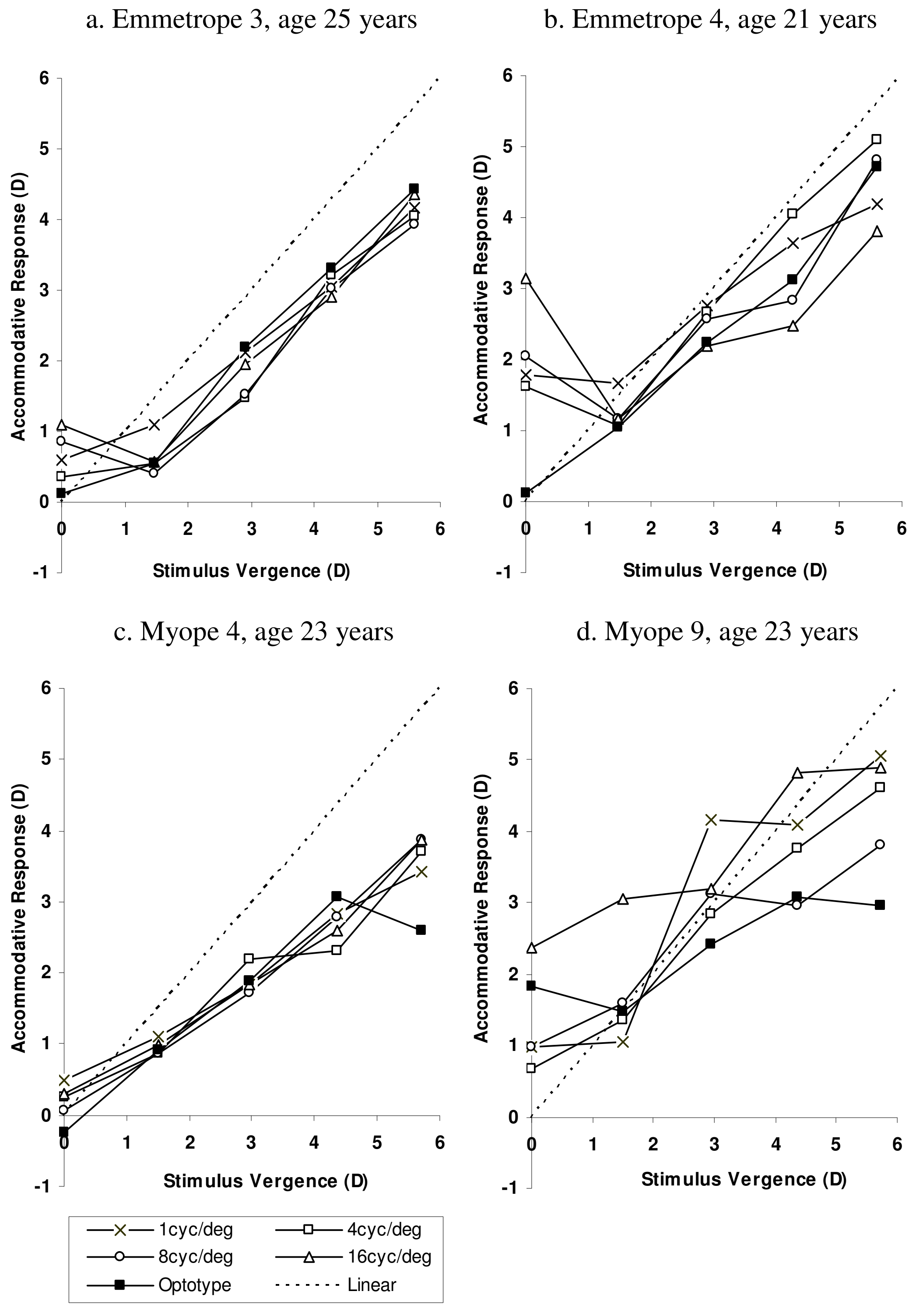


Figure 3.1: Examples of accommodation stimulus-response functions for the five targets (a) emmetrope 3, age 25 (b) emmetrope 4, age 21 (c) myope 4, -1.12D mean sphere, age 23, late-onset, stable (d) myope 9, -6.62D mean sphere, age 23, early-onset, progressing.

As a further indication of the differences between individual subjects, Figure 3.2 shows the full set of stimulus-response functions for the optotype target. Note that one emmetrope (emmetrope 7) found it difficult to relax accommodation to view the optically more-distant stimuli, and that one of the myopes (myope 5) completely failed to accommodate systematically to the target.

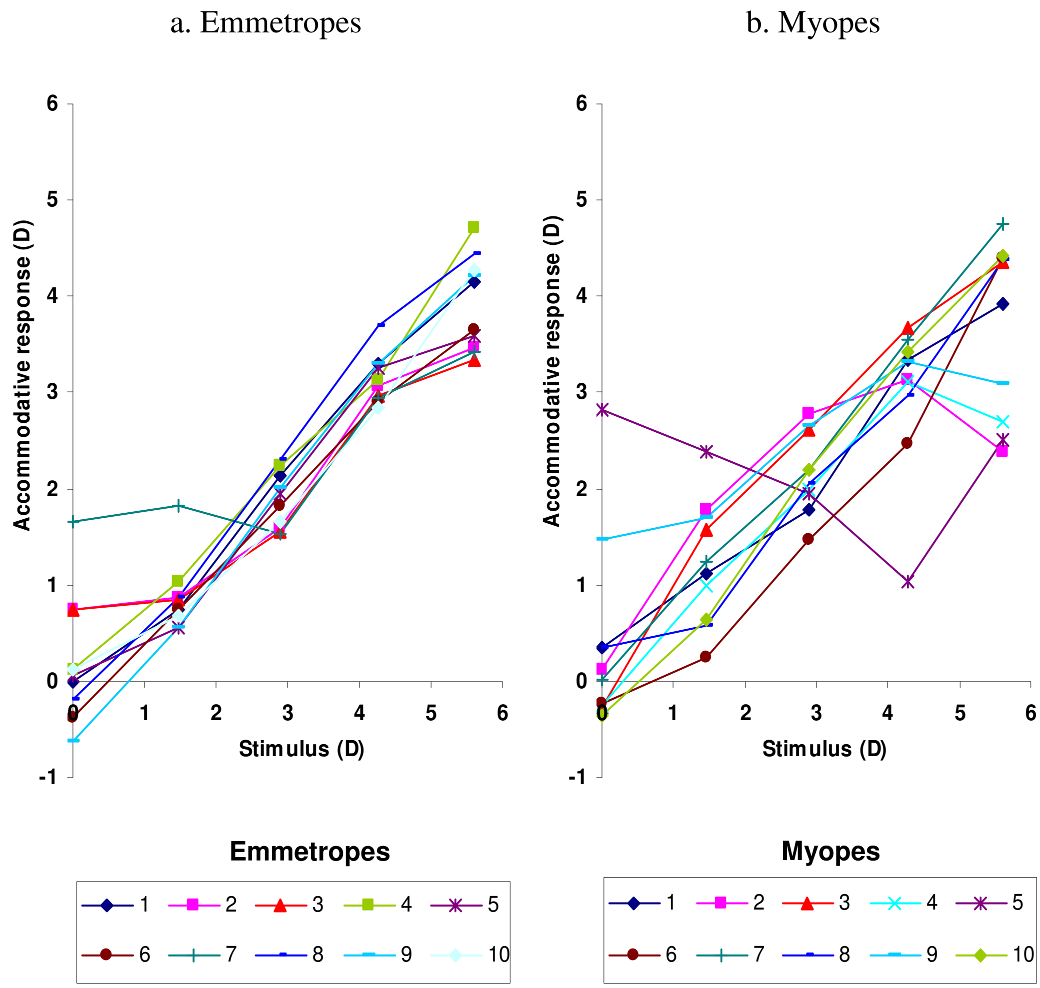


Figure 3.2: Stimulus-response functions for the high-contrast 6/30 optotype as measured with the auto-refractor for emmetropes (a) and myopes (b).

In an initial attempt to quantify possible differences between the various stimulus-response functions, the accommodative response gradient was calculated for the quasi-linear part of the accommodative response function by determining the regression line fit for data obtained with the 1.5D stimulus onwards. The results for individual subjects in the two refractive groups are shown in Figures 3.3 (a) and (b).

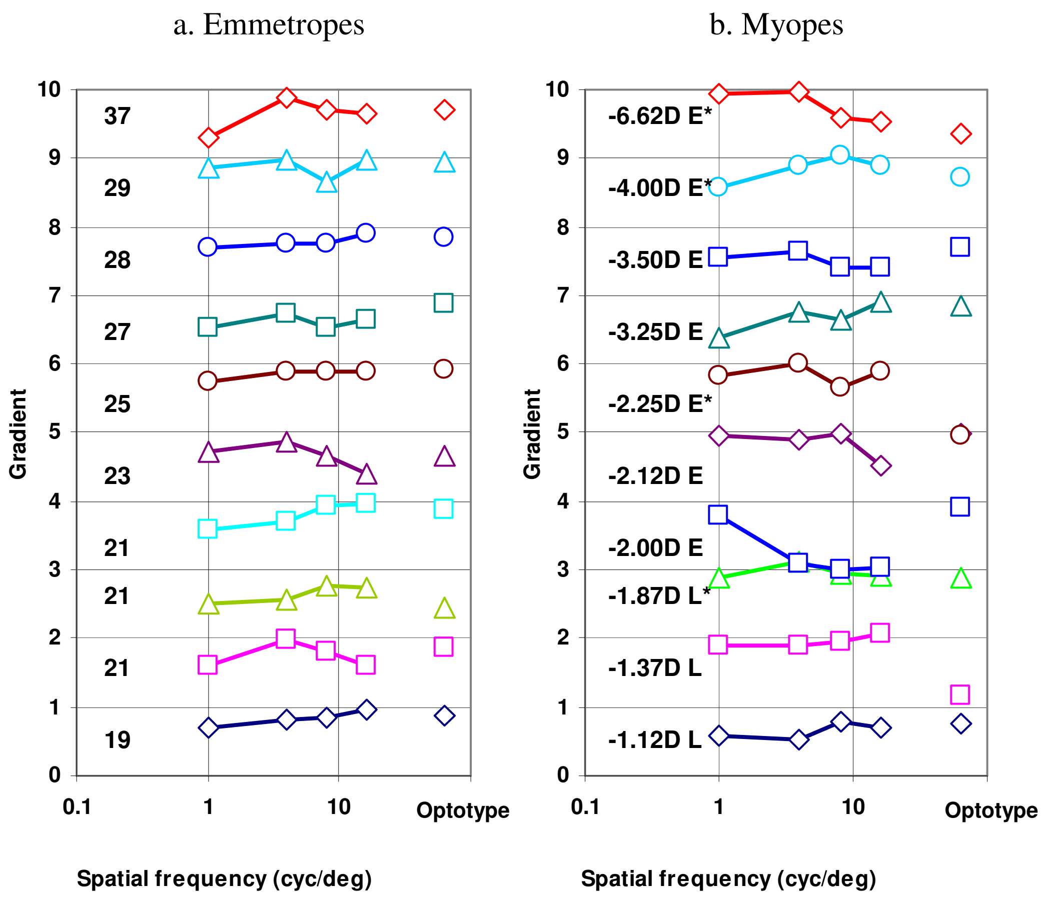


Figure 3.3: Gradients of regression-line fits to the stimulus-response function data over the stimulus interval 1.5D to 6.0D inclusive for individual subjects as a function of stimulus spatial frequency and for the optotype target. For clarity, results for each subject are successively displaced upwards by one unit for emmetropic subjects (a) arranged in order of ascending age, and for myopic subjects (b) arranged in order of increasing mean sphere error. E and L indicate early- or late-onset myopia and * indicates that the myopia is progressing.

The emmetropic group (Figure 3.3a) appears to be divided into two equal subgroups, showing (for the grating targets) different patterns of change in gradient with spatial frequency. In the first subgroup, gradients tend to increase with the spatial frequency of the target. In the second subgroup, gradients are maximal at around 4 cyc/deg and decrease at higher spatial frequencies. There appears to be no correlation between the pattern of behaviour and the age of the subjects. With the exception of one 21 year-old (emmetrope 7), who has an unusually low gradient, gradients for optotypes are generally similar to the maximal gradients for the grating targets.

Mixed performance for the grating targets is also observed among the myopic group, but it is more difficult to classify the differences involved (Figure 3.3b). There is no obvious relation between the pattern of gradient change and the magnitude, onset or progression of the myopia. It is of interest that some myopes (-1.37D, -2.25D) had very poor response gradients for the optotype, while the –2.00D myope (stable) essentially failed to accommodate to all but the lowest frequency of grating and the optotype. In general, a greater spread of accommodative behaviour is observed in the myopic group than in the emmetropic group.

The mean gradients of the subjects within the two groups are given in Table 3.1. Note that the standard deviations are larger for the myopic group. There are, however, no significant differences between the mean gradients of the two refractive groups (non-parametric Kruskal-Wallis ANOVA by ranks, $p=0.95$) and the spatial frequency of the individual targets has no significant effect on the gradient of the accommodative stimulus-response function (Kruskal-Wallis ANOVA by ranks, p=0.21). It is evident from Table 3.1 (see also Figure 3.2) that the variability found in the stimulus-response functions was greater in the myopic group for all targets.

Target	Emmetropes (n = 10)	Myopes (n = 10)
1 cyc/deg	0.62 ± 0.15	0.74 ± 0.20
4 cyc/deg	0.83 ± 0.13	0.78 ± 0.30
8 cyc/deg	0.76 ± 0.12	0.70 ± 0.32
16 cyc/deg	0.78 ± 0.20	0.68 ± 0.31
Optotype	0.81 ± 0.15	0.66 ± 0.32

Table 3.1: Mean (±SD) gradients of the accommodative stimulus-response functions, over the stimulus interval 1.5D to 6.0D inclusive, for the different targets for the emmetropic and myopic refractive groups.

The accommodative error index values for the different subjects and targets for the nominal stimulus range 1.5D to 6.0D are shown in Figure 3.4. Apart from one poorly-accommodating myopic subject (myope 10), who also had unusually low gradient values, and particular combinations of individual subjects and targets, error indices are generally of the order of 1D or less.

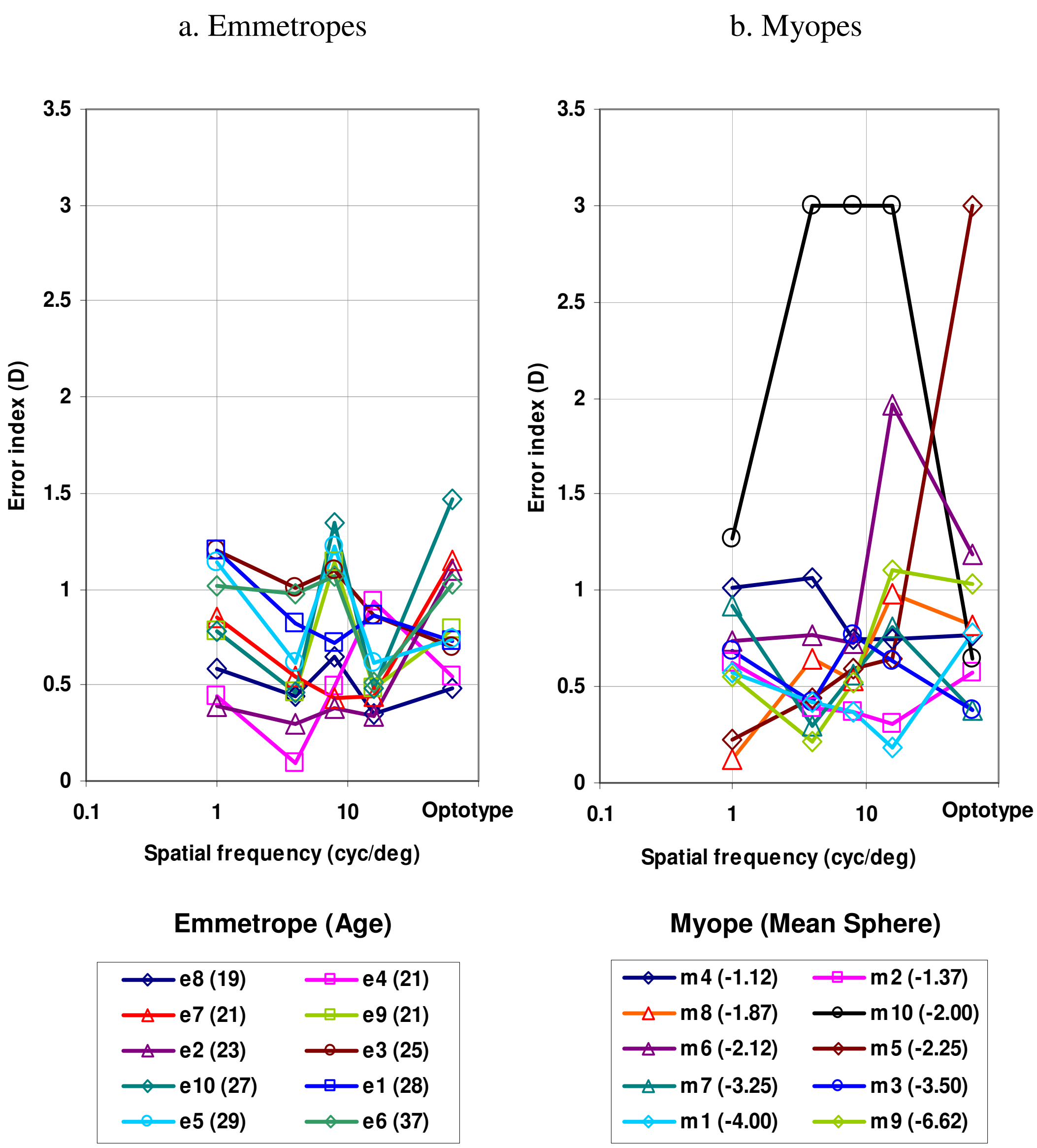


Figure 3.4: Changes in the accommodative error index as a function of the spatial frequency of the grating target and for the optotype (a) emmetropes (b) myopes. Ages (years) are given for the emmetropes and mean sphere refractive error (D) for the myopes.

The mean values of the error index are given in Table 3.2. Note that in general the indices are quite high. Since r^2 values for the stimulus-response functions generally exceeded 0.9, this implies that mean errors of accommodation were quite large (typically between 0.5D and 1.0D). However, in a few cases when gradients were very low, r^2 values were also very low, giving unrealistically high values of error index: in these cases the index was assigned a value of 3, giving the ceiling effect observable in Figure 3.4b.

Kruskal-Wallis analysis of variance by ranks shows no significant difference in the mean accommodative error indices between myopes and emmetropes (p=0.53) and between different spatial frequencies of the targets used in the study, including the optotypes (p=0.25).

Target	Mean Error Index, emmetropes (D)	Mean Error Index, myopes (D)
1 cyc/deg	0.84 ± 0.30	0.67 ± 0.34
4 cyc/deg	0.57 ± 0.29	0.77 ± 0.82
8 cyc/deg	0.85 ± 0.35	0.82 ± 0.78
16 cyc/deg	0.59 ± 0.22	1.04 ± 0.85
Optotype	0.87 ± 0.31	0.96 ± 0.76

Table 3.2: Mean (±SD) accommodative error indices (D) for the different targets for the emmetropic and myopic refractive groups.

As noted earlier, several subjects had difficulty in accommodating to stimuli at zero vergence (i.e. at optical infinity). Table 3.3 shows the mean (±SD) accommodative errors (generally leads) with these stimuli for the individual subjects within each refractive group. The problems experienced by some subjects, who include both myopes and emmetropes, are obvious.

Target	Mean response (D) (Emmetropes)	Mean response (D) (Myopes)
1 cyc/deg	0.60 ± 0.48	0.48 ± 0.78
4 cyc/deg	0.40 ± 0.91	0.40 ± 0.84
8 cyc/deg	0.62 ± 0.92	0.56 ± 1.30
16 cyc/deg	0.97 ± 1.33	1.45 ± 1.64
Optotype	0.16 ± 0.64	0.40 ± 1.00

Table 3.3: Mean (±SD) responses (D) to targets at optical infinity (zero vergence) based directly on the auto-refractor readings.

3.5 Discussion

This study found no systematic differences between the stimulus-response functions of emmetropic and myopic refractive groups and, in particular, found that changing the spatial frequency of the grating target did not produce any significant differences in the accommodation responses of the two refractive groups. Therefore it is not possible to confirm the hypothesis that myopes normally make less use of high spatial frequency information to guide their accommodation response. However, under the conditions used, where only a limited subset of the components of accommodation may be active, the striking feature of the results is that they are heavily dependant on the individuals involved. It is possible that differences in monochromatic aberrations between individuals, and the mixed nature of the myopes (early onset, late onset, progressing and stable) contributed to the inter-subject variation found in this study.

Charman and Tucker (1977; 1978) found that the stimulus-response function gradient tended to be maintained or increase at higher spatial frequencies. In contrast, other authors have suggested that accommodative response accuracy is optimal at spatial frequencies of 3-5 cyc/deg, around the peak of the contrast sensitivity function, with stimulus-response function gradients decreasing at lower and higher spatial frequencies (Owens, 1980; Bour, 1981). Examination of Figure 3.3 suggests that half of the emmetropes had gradients that increased with spatial frequency while the other half showed responses that peaked at around 4 cyc/deg or showed ambiguous changes. Thus the emmetropes showed mixed behaviour similar to that found by Ciuffreda and Hokoda (1985). The myopes' behaviour was broadly similar with the exception that one subject showed little response to any grating except 1 cyc/deg. While there were minor differences between the refractive groups in the mean gradient for each grating (see Table 3.1), the differences did not reach statistical significance. Thus the mean gradient data showed that altering target spatial frequency did not cause significant differences between the two refractive groups. The same result was found for accommodative error indices. Although the differences in the responses between the two refractive groups were not found to be statistically significant, the variability of the accommodative responses was found to be larger in the myopic group. A post-hoc power analysis was conducted in light of the lack of significant difference found between the two refractive groups. Due to the high variability found in the accommodation responses of the myopic group (especially to the high spatial frequency target) the effective power reduced to approximately 0.50. It should therefore be acknowledged that a significant difference between the groups may have been found at high spatial frequencies if a larger sample size had been used.

When individual subjects are considered, however, substantial between-subject differences in both gradient and error indices were found. It is possible that these differences are due to variations in the reliance that individuals place on the different components of accommodation. Since in the stimulus conditions used, convergence and proximity cues were lacking, the subject may have to rely more on voluntary accommodation to bring the grating target in to approximately correct focus. Hence those subjects who habitually rely on proximity and binocular cues are likely to accommodate poorly to the high spatial frequency gratings. It appears that both refractive groups contained such subjects, leading to a reduction in gradient and an increase in error index (Figures 3.3 and 3.4).

The 6/30 letter “E” target presents a slightly different challenge to the accommodation system. It is a broad-band-frequency target which can be resolved with relatively large errors of focus (around 1.5D, see e.g. Rabbetts, 1998). More precise accommodation simply improves edge sharpness, as higher spatial frequency components come in to better focus. In principle it should be much easier to achieve an accurate focus than with sinusoidal grating targets (Heath, 1956; Ciuffreda *et al.*, 1987; Tucker and Charman, 1987). However, it is of interest that, although most subjects accommodated reasonably well to the optotype, except perhaps at the highest stimulus level (5.72D), their errors of focus and error indices were quite substantial (Figure 3.4), suggesting that the subjects were using a criterion which depended more on a tolerance to defocus based on a “troublesome” or “bothersome blur” criterion rather than on “just noticeable blur” (Atchison *et al.*, 2005; Ciuffreda *et al.*, 2006). One of the myopes completely failed to accommodate systematically as the stimulus vergence varied, giving a gradient of effectively zero (Figure 3.2): others have also found that young, clinically normal, adult subjects may fail to accommodate when presented with static or dynamic stimuli (e.g. Heron *et al.*, 1999; Chen *et al.*, 2006). In general, for the optotype, variations between the stimulus-response functions of subjects were larger within the myopic group. Another possible reason for the low accommodative responses found in some of the subjects could be the lack of chromatic cues in the targets used in the present study (Fincham, 1951; Kruger *et al.*, 1997). Since all the targets were presented using the green phosphor of the CRT monitor, the accommodative response of at least some of the subjects is likely to be lower than the response found under more natural polychromatic conditions.

For all targets, it is of interest that many of the subjects experienced considerable difficulty in relaxing their accommodation to view the targets at zero vergence (optical infinity, see Table 3.3). In this case, subjects are required to reduce their accommodation below its tonic level in the face of significant opposing proximal cues, a task that proved particularly difficult for several subjects when the target was a 16 cyc/deg grating.

One further factor that deserves consideration when comparing the responses of individual subjects is the possible effect of their pupil size and aberrations on depth-of-focus and hence, possibly, on the accuracy of their responses. Individual depths-of-focus were not measured in the present study. Pupil diameters in the experiment were generally in the range of 4-6mm, in which depth-of-focus varies only weakly with pupil diameter (e.g. Atchison and Smith, 2000). Related studies (Charman and

Radhakrishnan, 2009) have found no systematic differences in the pupil diameters or accommodative miosis (mm/dioptre of accommodation response) between emmetropes and myopes. Some previous studies have shown that monochromatic aberrations can play an important role in driving accommodation (Wilson *et al*., 2002; Fernandez and Artal, 2005; Chen *et al*., 2006). Monochromatic aberrations show a large degree of variability between individuals (Porter *et al*., 2001; Paquin *et al*., 2002; Castejon-Mochon *et al*., 2002) and also change as a function of accommodation (Cheng *et al*., 2004; Radhakrishnan and Charman, 2007a). With this in mind, it is possible that differences in monochromatic aberrations between individuals may account for some of the variability observed in the present study.

Finally, it should be noted that a mixture of early, late, stable and progressing myopes was included in the myopic subject group and it remains possible that significant differences from emmetropes might have been found had the myopic group been more homogeneous. However, examination of the data for individual subjects as shown in Figures 3.3b and 3.4b gives no obvious indication that this is likely to be the case.

In conclusion, the present study fails to establish the existence of any systematic difference in the responses of emmetropes and myopes to sinusoidal grating targets. The dominant feature of the data in both refractive groups is inter-subject variation. It is possible that this is due to variations in the reliance that different individuals place on particular accommodative components. See supporting publication, Taylor *et al*. (2009) for a full account of this work.

CHAPTER 4
TREATMENT OUTCOMES OF REFRACTIVE SURGERY

4.1 Introduction

A number of ways have been suggested to report surgical outcome (Waring, 1992; Koch *et al.*, 1998; Waring, 2000; Koch, 2001). These methods are based on measures of efficacy, safety and stability of treatment. In addition to these methods, questionnaires are increasingly being used to assess health intervention. Questionnaires provide subjective information that supplements the more objective measures conventionally used. In combination this provides a more detailed description of surgical outcome.

A number of vision-specific questionnaires have been developed, validated and used to assess treatment outcome following refractive surgery. The three most recognized are the Refractive Status and Vision Profile (RSVP) (Schein, 2000; Vitale *et al.*, 2000), the National Eye Institute Refractive Error Quality of Life Instrument (NEI-RQL) (Berry *et al.*, 2003), and more recently the Quality of Life Impact of Refractive Correction (QIRC) (Pesudovs *et al.*, 2004; Garamendi *et al.*, 2005; Pesudovs *et al.*, 2006). Of these three questionnaires, the QIRC is the only one that has been specifically designed for use in the pre-presbyopic population.

The aim of this chapter is to investigate the surgical outcome of the patients that took part in the studies of accommodation. Outcome will principally be measured using refractive and visual outcome data. In addition, a validated questionnaire (QIRC) will be used to give a more comprehensive evaluation of surgical outcome.

Should any alterations in the accommodative response be found, it is important to know whether or not these were as a result of something going wrong with the surgery. Additionally, specifying the study population in detail helps obtain information on how applicable the study results may be to other populations.

4.2 Subjects

4.2.1 Research approval

Healthy adult patients were recruited from the refractive surgery clinics at Manchester Royal Eye Hospital, Manchester, UK. The project protocol received National Research Ethics Service (NRES) approval by Wrightington, Wigan and Leigh NHS Research Ethics Committee on behalf of the Central Manchester and Manchester Children's University (CMMU) Hospitals NHS Trust. The project protocol was also approved by the CMMU Trust Research and Development Office, and the University of Manchester Research Ethics Committee. The research was conducted in accordance with the tenets of the Declaration of Helsinki.

4.2.2 Recruitment

Patients interested in having refractive surgery attend an initial assessment clinic to evaluate their suitability for surgery. Those subsequently electing to have surgery usually undergo the procedure within a few months of the assessment. A member of the research team discussed the study with the patient at their initial assessment appointment and the nature and purpose of the research was explained. The patient was also given an information leaflet to read (see copy of information leaflet in appendix 4a). Approximately one week after the assessment appointment, the patient was contacted to see if they were interested in volunteering or had any questions about the study. An initial study appointment was then scheduled prior to the patient undergoing refractive surgery. At this initial study appointment the nature of the research was explained again and the patient had the opportunity to ask any questions. Written, informed consent for taking part in the study was taken from the patient at this visit (see copy of consent form in appendix 4b) and the patient was recruited on to the study.

4.2.3 Inclusion and exclusion criteria

Only patients who had elected to undergo LASIK or LASEK in at least one eye were recruited. Principal inclusion criteria were pre-presbyopia, age between 18 and 45 years, pre-operative corrected Snellen visual acuity of 6/18 (approximately 0.5 LogMAR equivalent) or better in both eyes, astigmatism below -1.50D in at least one eye (undergoing surgery), able to give informed consent and capable of returning for follow-up visits. Any level of spherical error (myopia or hyperopia) was permitted. Pre-presbyopia was defined as having no reading addition in the patient's optical prescription and measured monocular subjective amplitude of accommodation of at least 4D in each eye (using an N5 target and the "push-up" method of measurement). Exclusion criteria included any active ocular or systemic disease, any medication that could affect visual function, and an inability to read and understand written English.

4.2.4 Details of surgery

Laser refractive surgery procedures were performed by an ophthalmic surgeon at Manchester Royal Eye Hospital. LASIK was performed under topical anesthesia using Benoxinate 0.4%. A flap was created (9.0mm diameter, 135µm thickness, superior hinge) using an automated Meric M2 microkeratome. The ablation was carried out using a Wavelight Allegretto (Wavelight Laser Technologies AG, Erlanger, Germany) scanning-spot excimer laser system with a 1.0mm spot-size. In the LASEK procedures the corneal surface epithelium was loosened using a 20% dilute alcohol solution applied in a well for 20-30 seconds (Camellin, 2003). The epithelium was then peeled away and the laser ablation applied using the same methods as for LASIK. Following the laser ablation procedure the epithelium was returned to its original location and a bandage contact lens was applied.

4.3 Methods

The patients were required to attend three study visits in total. The first visit was to obtain pre-operative baseline measurements, and then two further visits occurred at one and three months post-operatively. Where possible the post-operative study visits coincided with the patient's check-up appointments. This was more convenient for the patient and helped to minimise discontinuation.

At each visit the patients underwent a subjective refraction using standard clinical techniques (based on least negative prescription with maximum achievable acuity). Uncorrected visual acuity (UCVA) and best spectacle corrected visual acuity (BSCVA) were recorded monocularly in each eye using high contrast Bailey-Lovie

LogMAR visual acuity charts. All patients filled in a Quality of Life Impact of Refractive Correction (QIRC) questionnaire at each of the three study visits. The QIRC questionnaire has been shown to be a valid and reliable way to assess quality of life in pre-presbyopes that undergo refractive surgery (Pesudovs *et al*., 2004). The QIRC questionnaire consists of 20 questions that cover a variety of vision specific quality of life issues. The questions cover issues relating to visual function (n=1, question 1), symptoms (n=1, question 2), convenience (n=5, questions 3 to 7), cost (n=2, questions 8 and 9), health concerns (n=4, questions 10 to 13) and well-being (n=7, questions 14 to 20). An example of the questionnaire is given in appendix 4c. Patients were required to answer all the questions using the five-point scaled descriptors given in the questionnaire. Instructions on how to complete the questionnaire were included. The patient was encouraged to read the instructions carefully to ensure that the answers given were as accurate as possible. Patients were also informed that the results of the questionnaire would remain anonymous to the clinical team providing the surgical care. Patients were therefore encouraged to answer as honestly as possible. Overall QIRC scores for each patient at each visit were calculated from the questionnaire responses in accordance with published scoring methods (Pesudovs *et al*., 2004). Scores are allocated for each question according to the response category selected. The sum of the scores for each question divided by the number of questions answered gives the overall QIRC score. The overall QIRC score represents a quality of life measure with higher values representing better quality of life. Pre-operative and post-operative QIRC scores were compared for the whole study population and for each question individually and each patient individually. The patients were asked to fill in the questionnaire for each type of refractive correction they wore by annotating the answers with “S” for spectacles, “C” for contact lenses or “N” for none (neither spectacles nor contact lenses). This meant that multiple answers were possible for those patients with more than one type of refractive correction or who only wore refractive correction on a part-time basis. The QIRC scores were calculated for the mode of refractive correction that the patient used most frequently.

A series of accommodation measurements were also taken at each study visit. The results of these accommodation measurements are presented and discussed in subsequent chapters of the thesis.

4.3.1 Statistical analysis

The surgical outcome results for refractive error and visual acuity are presented based on the methods suggested by Waring (2000). For the questionnaire data the main outcome measure was the QIRC score for the study population. Means for the overall score at the three time intervals (pre-operatively, one and three months post-operatively) were compared using one-way repeated measures ANOVA with Bonferroni post-hoc testing. Time was used as the categorical independent variable and QIRC score was used as the dependent variable. The results were considered significant at $p<0.05$. The statistical analysis was performed using SPSS for Windows (SPSS Version 16.0, SPSS Inc, Chicago, Ill).

4.4 Results

Thirty six healthy pre-presbyopic adults that had chosen to undergo refractive surgery for myopia and myopic astigmatism were recruited from the refractive surgery clinics at Manchester Royal Eye Hospital (Manchester, UK). The demographic characteristics of the patients recruited to the study are presented in Table 4.1, and Figures 4.1 and 4.2. The volunteers (n=36) included 14 (39%) men and 22 (61%) women and had a mean (± SD) age of 32.5 ± 6.1 years (range 19 years to 45 years) at the point of recruitment to the study. Prior to refractive surgery 53% of patients (n=19) wore contact lenses as their principal mode of refractive correction, and 44% of patients (n=16) used spectacles as their principal mode of refractive correction. The remainder (3%, one patient) predominantly wore no correction due to having an optical prescription in one eye only and being emmetropic in the other eye. Of the 36 patients recruited to the study, 34 patients had bilateral surgery (n=68 eyes) and two patients had surgery on one eye only (n=2 eyes). The total number of refractive surgery procedures was therefore 70 (eyes). The 70 procedures consisted of 16 LASIK, 53 LASEK and one clear lens extraction. Of the 16 LASIK procedures 12 (75%) were wavefront-guided procedures and of the 53 LASEK procedures 29 (55%) were wavefront-guided procedures. The remaining procedures in both surgical groups were conventional (non-wavefront-guided) procedures. One individual (age 42 years) had clear lens extraction in the right eye (-14.50/-1.50x30) and non-wave-front-guided LASEK in the left eye (-9.50/-0.50x140).

Number of patients (Number of eyes having surgery)	36 (70)
Age (years) at recruitment, Mean ± SD (range)	32.5 ± 6.1 (19 to 45)
Gender, Number (%) Female	22 (61)
Principal pre-operative mode of optical correction, Number (%)	
Contact lenses *Spectacles* *Neither spectacles or contact lenses (Rx 1 eye only)*	19 (53) 16 (44) 1 (3)
Surgery type (No. of patients), No. of eyes (No., % eyes wavefront-guided)	
LASEK *LASIK* *Clear lens extraction*	(28), 53 (29, 55) (8), 16 (12, 75) (1), 1 (N/A, N/A)
Pre-operative refractive error, Number (% of eyes)	
Low Myopia (mean sphere, -0.50D to < -3.00D) *Astigmatism in this group Mean ± SD (range)* *Moderate Myopia (mean sphere, -3.00D to -6.00D)* *Astigmatism in this group Mean ± SD (range)* *High Myopia (over -6.00D)* *Astigmatism in this group Mean ± SD (range)*	23 (33) -0.40D ± 0.39 (0.00 to -1.50) 27 (38) -0.77D ± 0.62 (0.00 to -2.25) 20 (29) -0.60D ± 0.55 (0.00 to -1.75)
Pre-operative distance best corrected visual acuity (LogMAR)	
Right eye (n=36 eyes), Mean ± SD (range) *Left eye (n=34 eyes), Mean ± SD (range)*	-0.08 ± 0.09 (-0.20 to +0.10) -0.07 ± 0.10 (-0.20 to +0.30)
Ethnic group, Number (%)	
White British Asian	35 (97) 1 (3)

Table 4.1: Demographic characteristics of the study population.

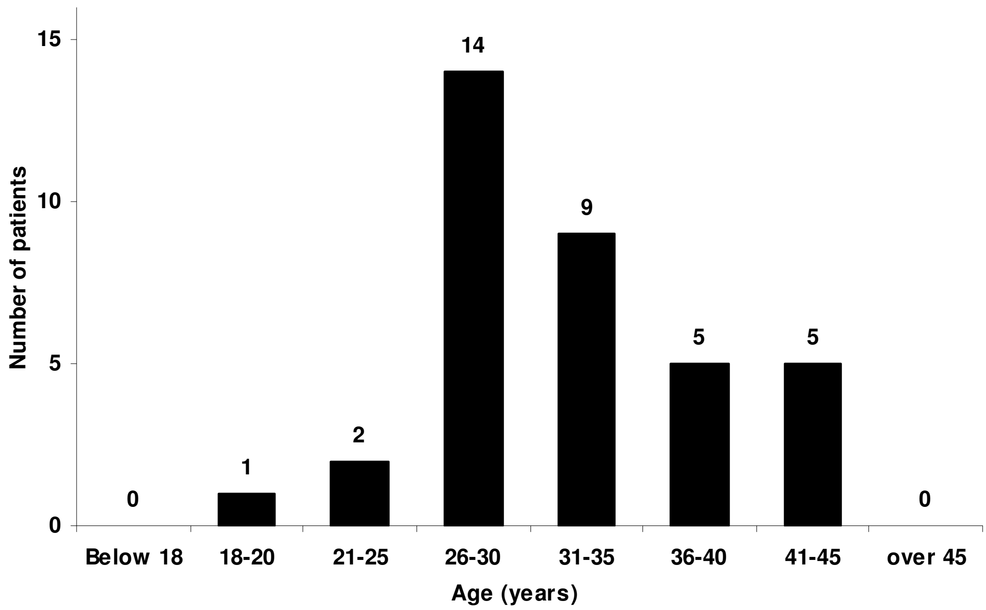


Figure 4.1: Age distribution of the study population (n=36 patients).

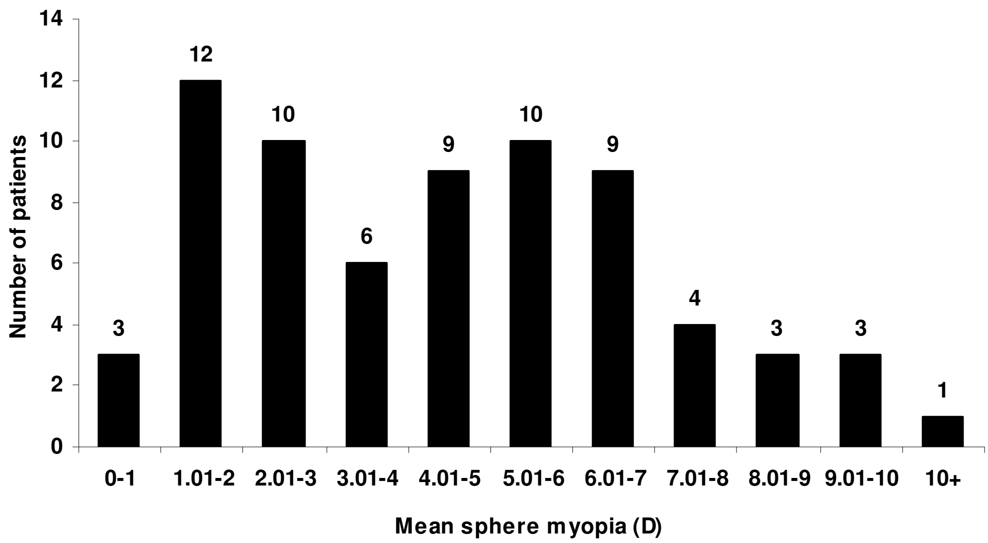


Figure 4.2: Distribution of the levels of myopia within the study population (n=70 eyes).

One of the patients was undergoing a bilateral re-treatment procedure for low myopia (Right eye: -2.00/-0.75x160, Left eye: -1.75/-0.50x180) after having undergone refractive surgery (PRK) elsewhere 10 years previously for (self reported) myopia of approximately -6.00DS in both eyes.

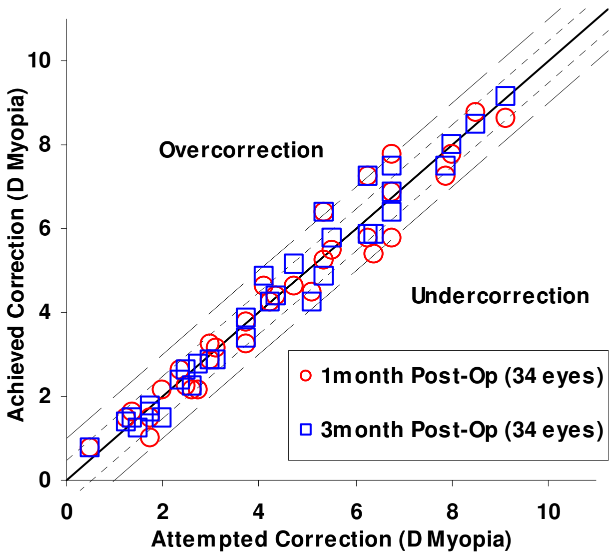
The patients attended for three study visits in total. The first study visit took place before the patient underwent refractive surgery. This visit was scheduled within one month before surgery. The visit typically took place on a day during the same week of surgery, prior to the patient undergoing the procedure (mean (± SD) = 2.75 ± 6.69 days, range 0 to 29 days prior to surgery). The second and third visits occurred at one month (mean (± SD) = 28.26 ± 5.72 days, range 21 to 48 days) and three months (mean (± SD) = 92.21 ± 13.46 days, range 71 to 131 days) post-operatively.

The mean (± SD) pre-operative mean sphere refractive error was -4.68 ± 2.89D (range -0.50D to -15.25D) in the right eye (n=36) and -4.59 ± 2.59D (range -0.50D to -9.75D) in the left eye (n=34). The mean (±SD) pre-operative BSCVA (LogMAR) was -0.08 ± 0.09 (range -0.20 to +0.10) in the right eye (n=36) and -0.07 ± 0.10 (range -0.20 to +0.30) in the left eye (n=34).

Anyone failing to attend a follow-up study appointment was contacted up to three times by phone and/or e-mail to re-arrange the appointment. Following surgery, one patient (female, age 40 years, undergoing bilateral non-wavefront-guided LASEK for myopia of: right eye: -4.00/-1.75 x 120 (V/A = -0.08 LogMAR) and left eye: -4.25/-0.75 x 25 (V/A = -0.08 LogMAR)) did not attend any of the post-operative study visits therefore only pre-operative data were available for this patient. The patient gave no reason for discontinuing from the study. This represented a discontinuation rate of 2.8%. Of the remaining 35 patients that completed the study, one patient failed to attend the one month post-operative visit but did attend the three month post-operative visit and another patient attended the one month post-operative visit but failed to attend the three month post-operative visit. All other patients attended all three study appointments. This represented a completion rate of 96.3% (104/108 study visits).

The results for the surgical outcome of the patients that were recruited to take part in the study are presented in Figures 4.3-4.7. To avoid the problem of inter-eye correlation the graphs of surgical outcome present data for right and left eyes separately. Figure 4.3 shows the refractive outcome results for right and left eyes as a function of pre-operative (myopic) refractive error for each individual patient. One outlying result for the right eye that underwent clear lens extraction was not included in Figure 4.3a. This result was excluded because the pre-operative refractive error for this eye (-14.50/-1.50 x 30) fell outside the 95% confidence interval for pre-operative refractive error. Omission of this result also allowed the graphs for right and left eyes to be plotted on the same scale. A Figure 4.3a with the excluded data is shown in appendix 4d for reference. For the omitted result the refraction was subsequently +1.50/-0.75 x 20 and +1.25/-0.50 x 25 at the one and three month post-operative visits respectively. Figure 4.3 shows that the refractive surgery was accurate throughout the entire range of pre-operative refractive error and more specifically that there was no obvious systematic over or under-correction for high levels of pre-operative refractive error.

a. Right eye data



b. Left eye data

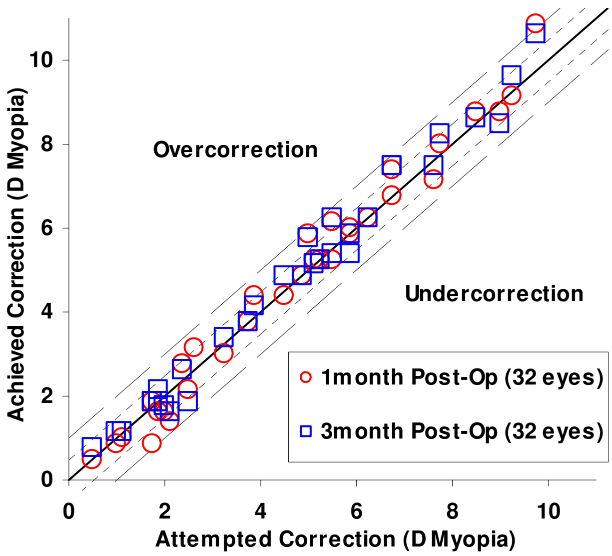
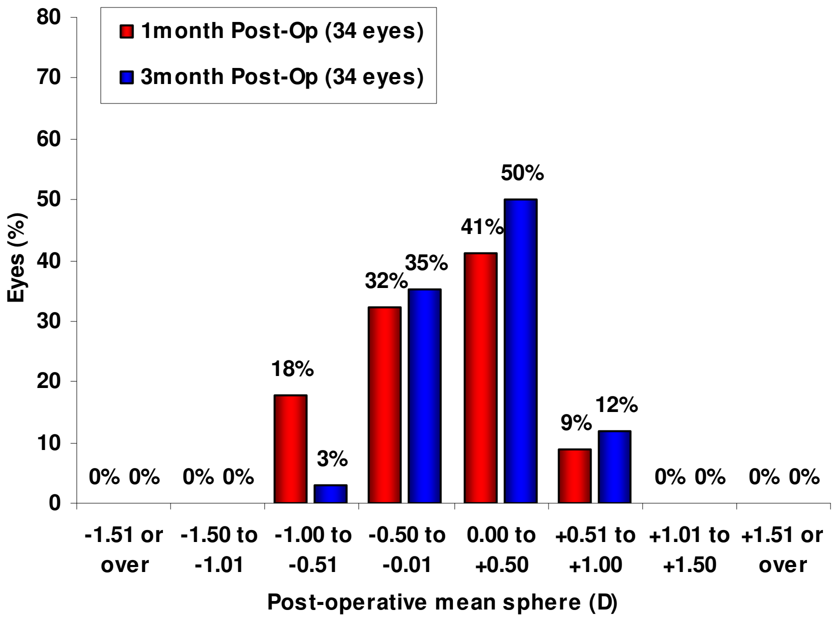


Figure 4.3: Achieved refractive correction (mean sphere) for right eyes (a) and left eyes (b) as a function of attempted refractive correction (mean sphere) for patients (n=35) undergoing refractive surgery for pre-operative myopia and myopic astigmatism. Results are presented for one month (red circles) and three month (blue squares) post-operative visits. The solid line represents 1:1 ratio and emmetropic mean sphere correction. Reference lines represent ± 0.50D from the 1:1 reference line (short dashes) and ± 1.00D from the 1:1 reference line (long dashes). Note that one outlying result (eye) is missing from the top graph (a) (see text).

Figure 4.4 shows the post-operative mean sphere refraction for right and left eyes. At the one month post-operative visit 73% of right eyes (n=25) and 81% of left eyes (n=26) were equal to or within ± 0.50D of emmetropic mean sphere correction, and 100% of right eyes (n=34) and 97% of left eyes (n=31) were equal to or within ± 1.00D of emmetropic mean sphere correction. At the three month post-operative visit 85% of right eyes (n=29) and 84% of left eyes (n=27) were equal to or within ± 0.50D of emmetropic mean sphere correction, and 100% of right eyes (n=34) and left eyes (n=32) were equal to or within ± 1.00D of emmetropic mean sphere correction.

The mean (± SD) residual astigmatism at one month post-operatively was -0.35 ± 0.46DC and -0.35 ± 0.36DC in the right and left eyes respectively. At three months post-operatively the residual astigmatism had decreased to -0.29 ± 0.35DC and -0.22 ± 0.31DC in the right and left eyes respectively. The low level of post-operative residual astigmatism indicates that the use of mean sphere refraction in Figure 4.4 accurately reflects the refractive outcome.

a. Right eye data



b. Left eye data

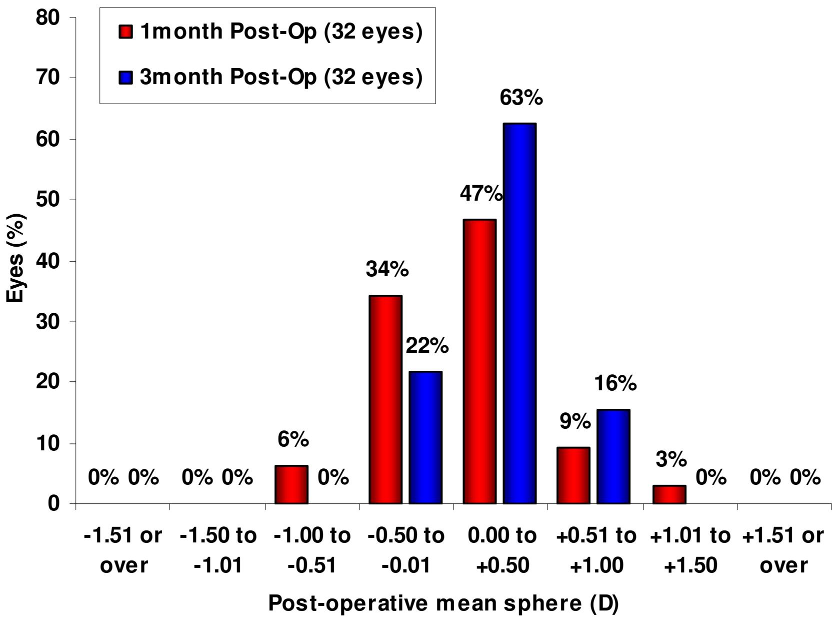
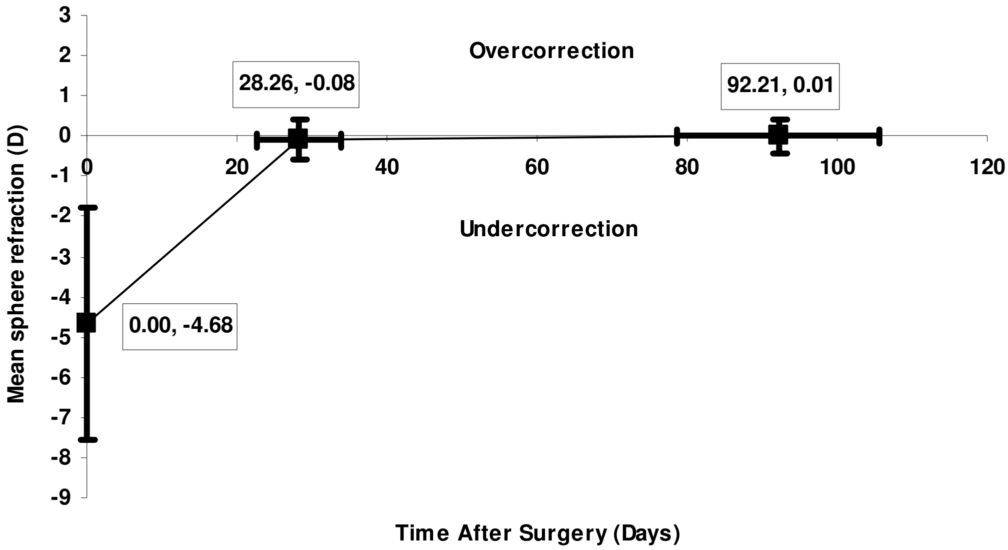


Figure 4.4: Post-operative refractive error (mean sphere) for right eyes (a) and left eyes (b) for patients (n=35) undergoing refractive surgery for pre-operative myopia and myopic astigmatism. Results are presented for one month (red bars) and three month (blue bars) post-operative visits. Note that in graph (b) the percentages do not add up to 100% due to rounding errors.

Figure 4.5 shows the refractive outcome results for right and left eyes as a function of time following refractive surgery. The mean (± SD) pre-operative mean sphere was -4.68 ± 2.89D (range -0.50D to -15.25D) in the right eye (n=36) and -4.59 ± 2.59D (range -0.50D to -9.75D) in the left eye (n=34). At the one month post-operative visit the mean sphere had decreased to -0.08 ± 0.51D (range -1.00D to +1.00D) in the right eye and +0.04 ± 0.43D (range -0.87D to +1.12D) in the left eye. This represents a small mean under-correction in the right eye and a small mean over-correction in the left eye. At the three month post-operative visit the mean sphere was +0.01 ± 0.42D (range -0.87D to +1.00D) in the right eye and +0.13 ± 0.38D (range -0.62D to +0.87D) in the left eye, representing a small mean over correction in both eyes.

Estimates of refractive stability can be made by comparing the refraction data at the one month and three month post-operative visits. The results show that the average mean sphere changed by less than 0.10D between the two post-operative visits for left and right eyes. The vast majority of right eyes (88%, n=29) and left eyes (90%, n=28) showed a change in mean sphere of 0.50D or less between the two post-operative visits and no eye showed a change of more than 1.00D. Taken collectively these results suggest that the refractive outcome remained stable between one and three months post-operatively.

a. Right eye data



b. Left eye data

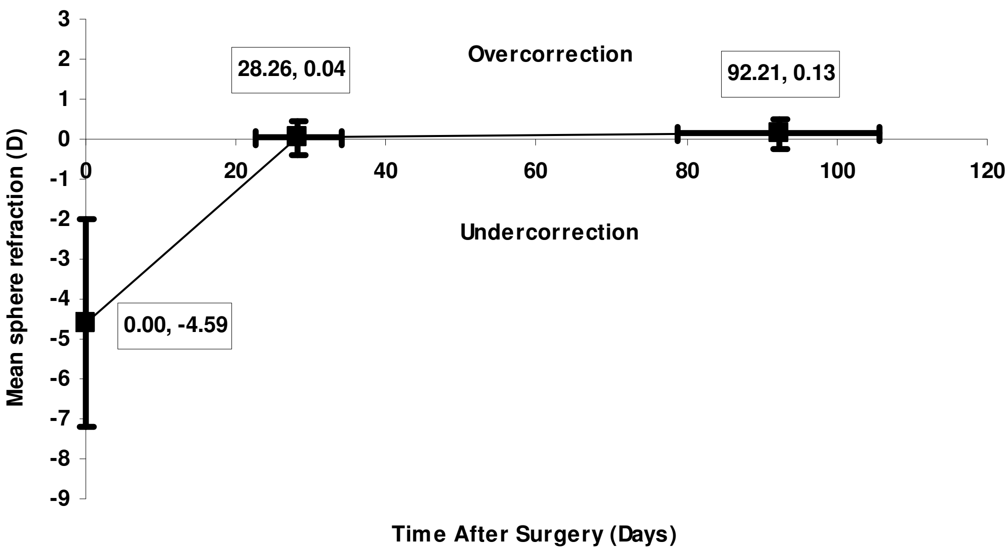
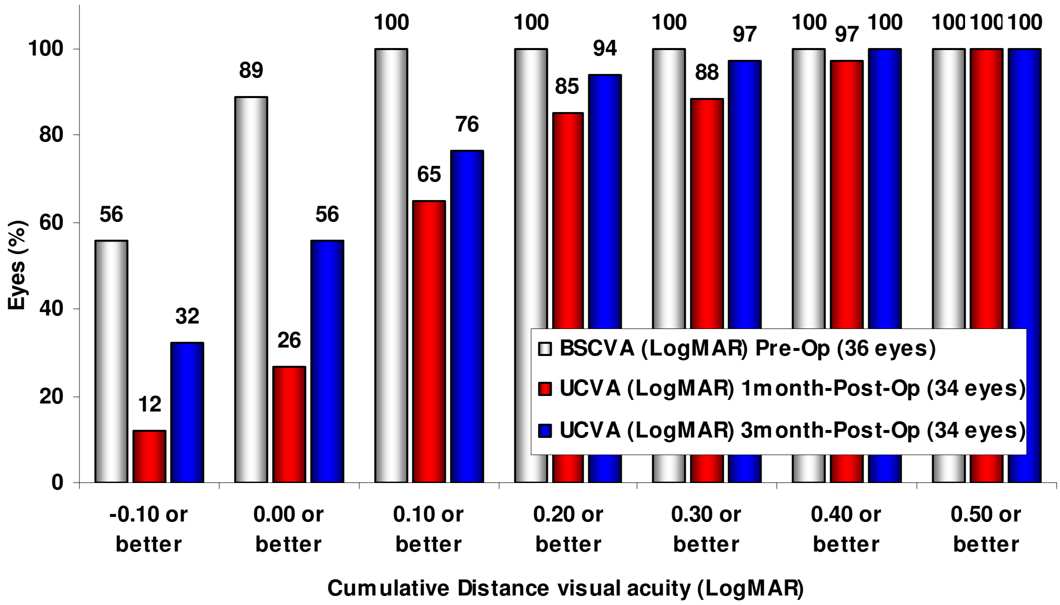


Figure 4.5: Mean (± SD) refraction (mean sphere) for right eyes (a) and left eyes (b) as a function of time (mean ± SD days) after refractive surgery. Results are pre-operatively (time=0 days, n=36 patients, 36 right eyes, 34 left eyes), and for the one month (time=28.26 days, n=34 patients, 34 right eyes, 32 left eyes) and three month (time=92.21 days, n=34 patients, 34 right eyes, 32 left eyes) post-operative study visits. The values of the data points are given in boxes.

Figure 4.6 shows the distance UCVA (LogMAR) for right and left eyes following refractive surgery. The pre-operative BSCVA is also shown on the chart (grey bars) for reference as a measure of the visual potential of the population post-operatively. Pre-operatively 89% of right eyes (n=32) and 88% of left eyes (n=30) achieved BSCVA of 0.00 (LogMAR) (6/6 Snellen equivalent) or better and 100% of both right and left eyes achieved BSCVA of +0.30 (LogMAR) (6/12 Snellen equivalent) or better. At the one month post-operative study visit 26% of right eyes (n=9) and 53% of left eyes (n=17) achieved UCVA of 0.00 (LogMAR) or better and 88% of right eyes (n=30) and 97% of left eyes (n=31) achieved UCVA of +0.30 (LogMAR) or better. At the three month post-operative study visit 56% of right eyes (n=19) and 69% of left eyes (n=22) achieved UCVA of 0.00 (LogMAR) or better and 97% of right eyes (n=33) and 97% of left eyes (n=31) achieved UCVA of +0.30 (LogMAR) or better. Efficacy indices were calculated for each eye at each post-operative visit (efficacy index = post-operative UCVA/pre-operative BSCVA) (Autrata and Rehurek, 2003; Aizawa *et al.*, 2003; Tobaigy *et al.*, 2006; Teus *et al.*, 2007). The mean (± SD) efficacy index at the one month visit was 0.69 ± 0.21 and 0.83 ± 0.20 for the right and left eyes respectively. At the three month visit this had improved to 0.87 ± 0.25 and 0.93 ± 0.16 for right and left eyes respectively.

a. Right eye data



b. Left eye data

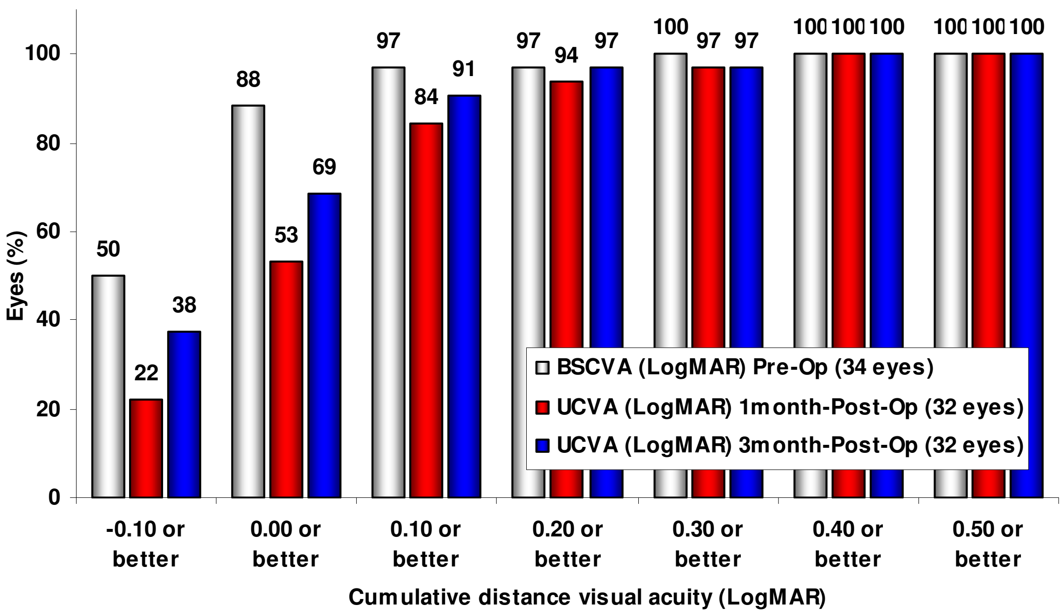
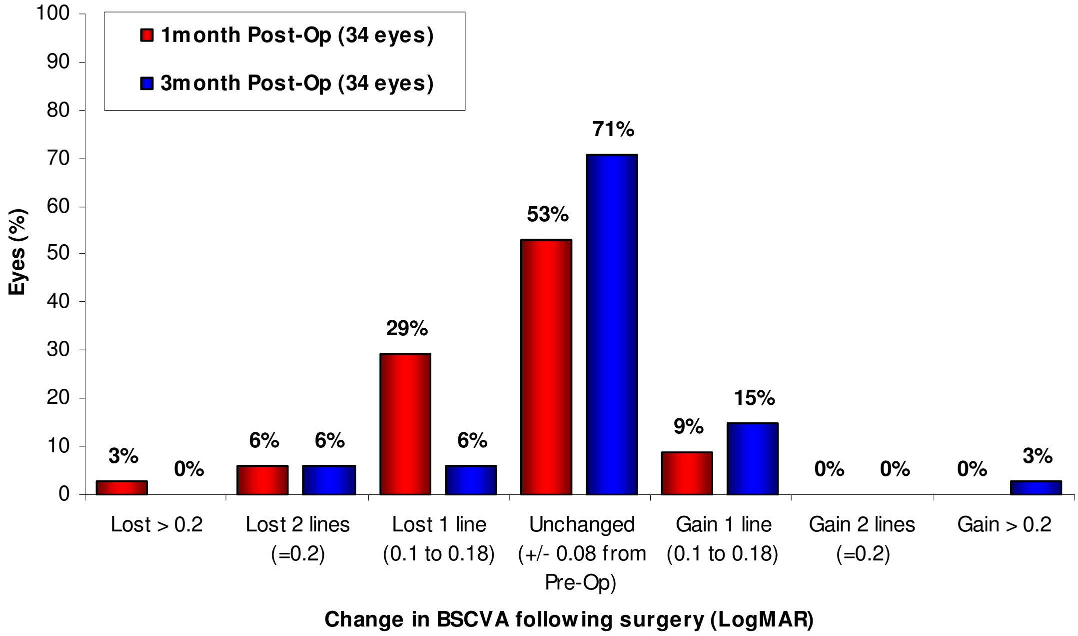


Figure 4.6: Post-operative uncorrected visual acuity (UCVA) for right eyes (a) and left eyes (b) for patients (n=36) undergoing refractive surgery. Results are presented for one month (red bars) and three month (blue bars) post-operative visits. Pre-operative BSCVA (grey bars) is also given for reference.

Figure 4.7 shows the change in BSCVA (LogMAR) from pre-operative baseline for right and left eyes following refractive surgery. The majority of patients maintained the same BSCVA following refractive surgery. At the one month post-operative visit 53% of right eyes (n=18) and 75% of left eyes (n=24) showed unchanged BSCVA post-operatively in comparison to pre-operative BSCVA. At the three month visit 71% of right eyes (n=24) and 81% of left eyes (n=26) showed unchanged post-operative BSCVA in comparison to pre-operative BSCVA. At the one month post-operative visit 3% of right eyes (n=1) lost over two lines of BSCVA. This was a 0.30 LogMAR loss from -0.10 to +0.20 (approximately 6/4.8 to 6/9.5 Snellen) due to a minor corneal defect which resolved to 0.00 LogMAR at the three month post-operative visit. At the three month post-operative visit no eyes had lost more than two lines of BSCVA.

Safety indices were calculated for each eye at each post-operative visit (safety index = post-operative BSCVA/pre-operative BSCVA) (Autrata and Rehurek, 2003; Aizawa *et al.*, 2003; Tobaigy *et al.*, 2006; Teus *et al.*, 2007). The mean (± SD) safety index at the one month visit was 0.90 ± 0.22 and 0.94 ± 0.14 for the right and left eyes respectively. At the three month visit this had improved to 1.04 ± 0.22 and 1.02 ± 0.14 for the right and left eyes respectively.

a. Right eye data



b. Left eye data

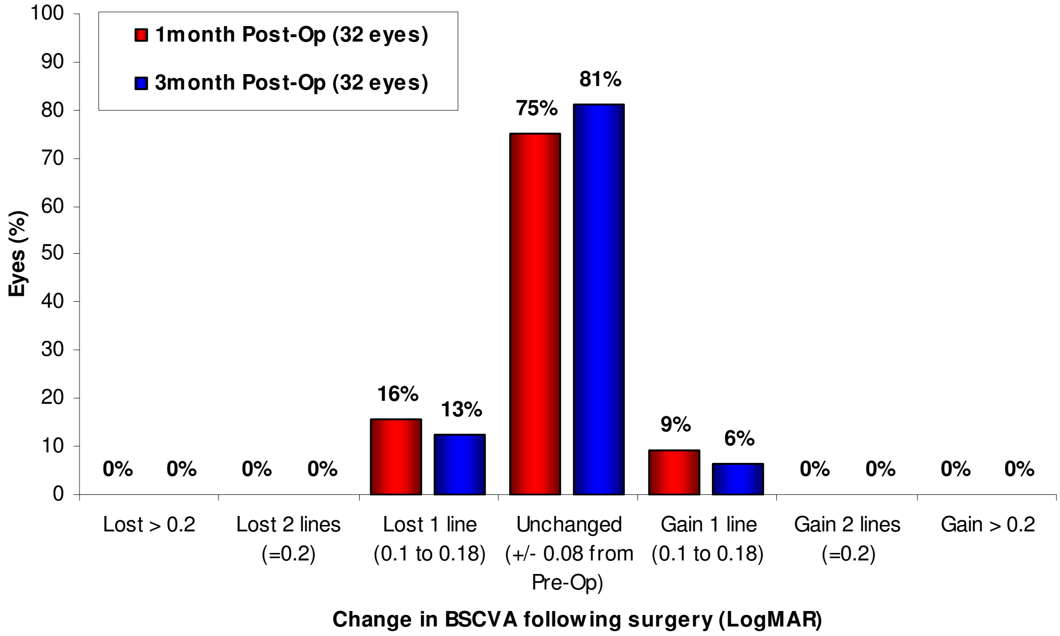


Figure 4.7: Change from pre-operative baseline in BSCVA (LogMAR) for right eyes (a) and left eyes (b) for patients (n=35) at one month (red bars) and three months (blue bars) following refractive surgery for pre-operative myopia and myopic astigmatism.

Figures 4.8-4.10 show the results for the QIRC questionnaire data. Figure 4.8 shows the QIRC scores for the study population as a function of time following refractive surgery. The pre-operative mean (± SD) QIRC score for the study group was 43.05 ± 4.89. This increased to 51.28 ± 5.54 and 55.16 ± 4.30 at the one month and three month post-operative visits respectively. One-way repeated measures ANOVA showed that the QIRC score altered significantly over time ($F_{2,\ 31} = 59.577$, $p<0.0005$). Bonferroni post-hoc pair-wise comparisons showed that the mean QIRC score altered significantly at one month ($p<0.0005$) and three months ($p<0.0005$) post-operatively in comparison to pre-operative QIRC scores. There was also a statistically significant difference in QIRC score from one month to three months post-operatively ($p<0.0005$). This suggests that the improvement in the QIRC score is apparent at one month post-operatively but that the QIRC score continues to improve between one and three months post-operatively.

The pre-operative QIRC scores were based on the mode of refractive correction used for the majority of the time. "*Spectacle wearers*" tended to wear spectacles almost all of the time and only used contact lenses (if any) occasionally for sport or social use, typically once a week for a maximum of 5-6 hours. "*Contact lens wearers*" tended to wear contact lenses all day every day and had a back-up pair of spectacles (if any) for occasional use. A small number of patients (n=2) wore spectacles and contact lenses equally (3-4 days a week for each). For these patients, the pre-operative QIRC scores were based on the mode of refractive correction giving the highest QIRC score. This was spectacles for one patient and contact lenses for the other patient.

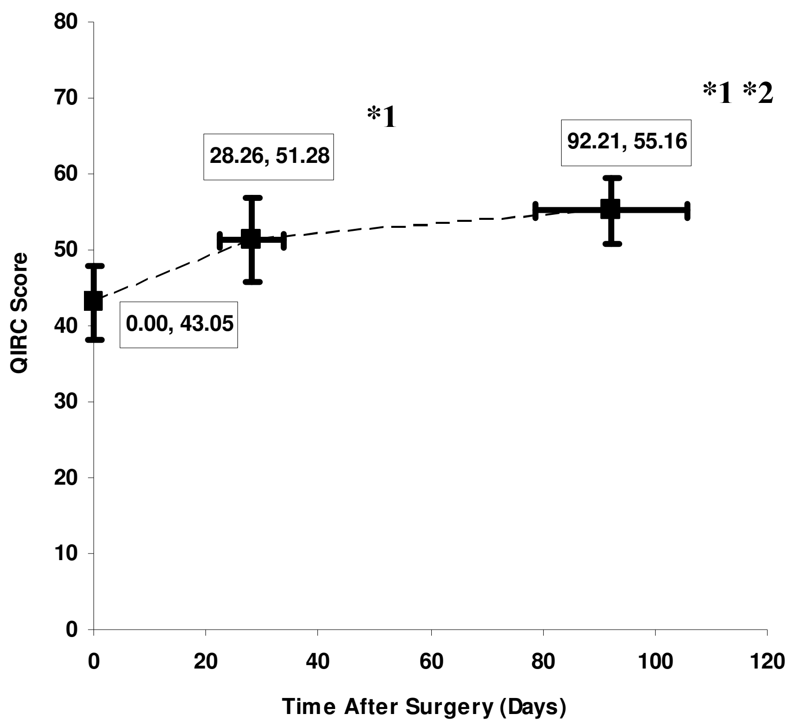


Figure 4.8: Mean (± SD) QIRC score as a function of time (Days ± SD) after refractive surgery. Results are presented pre-operatively (time=0 days, n=36 patients) and for the one month (time=28.26 days, n=34 patients) and three month (time =92.21 days, n=34 patients) post-operative study visits. The value of the data points is given in boxes.
***1 = QIRC score significantly different from pre-op QIRC score (p<0.001)**
***2 = QIRC score significantly different from one month visit QIRC score (p<0.001)**

Figure 4.9 shows the QIRC results for each individual patient at each of the three study visits. Patient 15 did not attend for the one month post-operative study visit, patient 18 did not attend for any post-operative visits and patient 35 did not attend the three month post-operative study visit. The majority of patients (91%, n=31) showed a measurable improvement in QIRC score at one month post-operatively. At the three month post-operative visit all patients showed a measurable improvement in QIRC score in comparison to the pre-operative results.

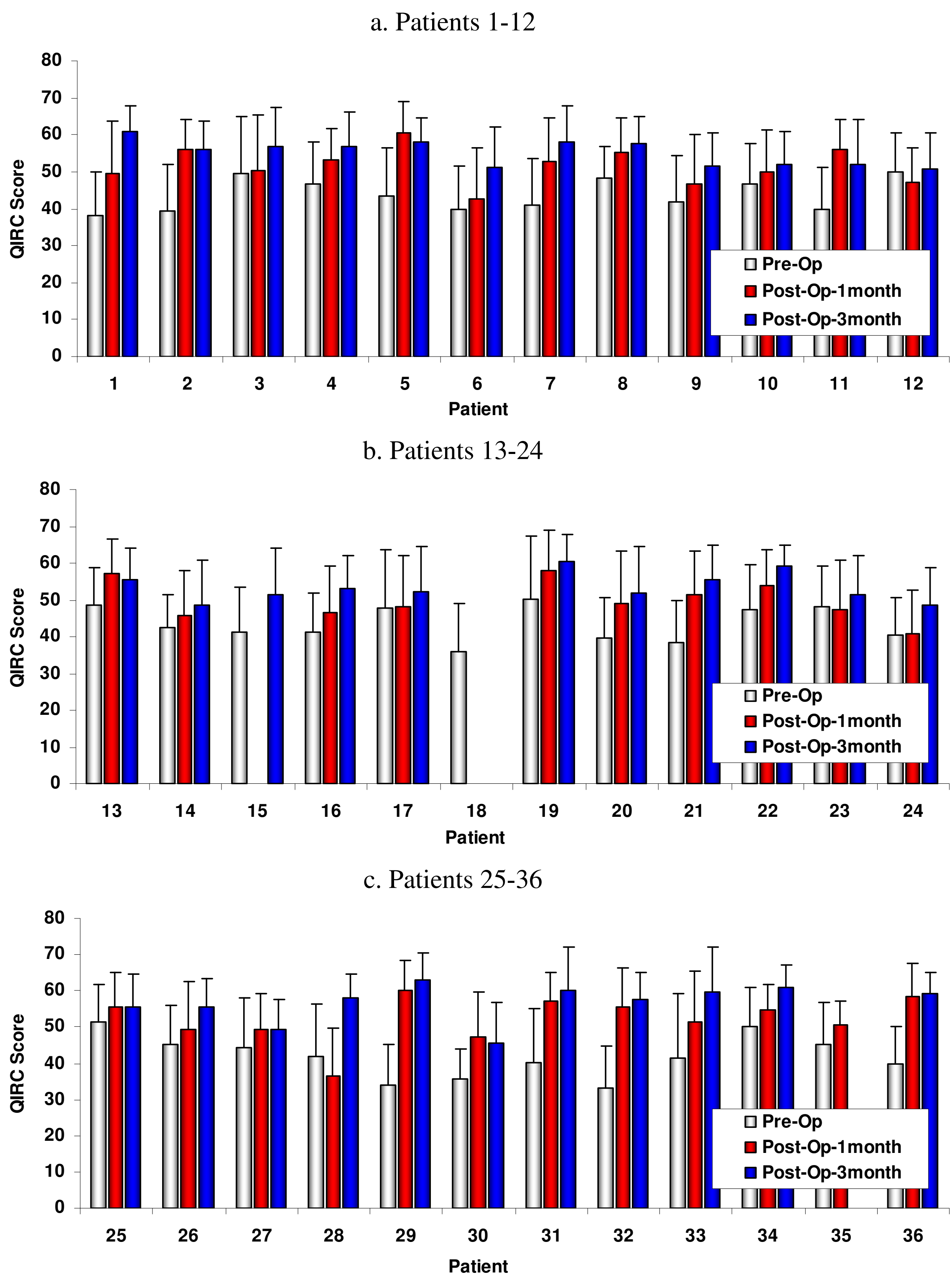


Figure 4.9: Mean (± SD) QIRC scores for patients 1-12 (graph a, top), 13-24 (graph b, middle) and 25-36 (graph c, bottom) at each study visit.

Figure 4.10 shows the mean QIRC score for each of the 20 QIRC questions for each study visit. In comparison to pre-operative scores, the majority of questions (85%, n=17/20) showed a measurable improvement in QIRC score at one month post-operatively. The only three questions that showed a decrease in QIRC score at the one month visit were questions 1, 2 and 19. These questions are from subscales representing questions about visual function (question 1, "*How much difficulty do you have driving in glare conditions?*"), symptoms (question 2, "*During the past month, how often have you experienced your eyes feeling tired or strained?*") and well-being (question 19, "*During the past month, how much of the time have you felt able to do the things you want to do?*"). The results for these questions showed that patients tended to have more difficulty driving in glare conditions, felt more eye strain/tiredness and felt less able to do the things they wanted to do in the first post-operative month. The reasons patients gave for feeling less able to do the things they wanted to do were typically that they didn't feel too confident with driving and/or that they had been advised by the surgeon to avoid certain activities (for example swimming) during the early post-operative recovery period. The scores for these three questions subsequently improved and at the three month post-operative visit all 20 questions showed a measurable improvement in overall QIRC score in comparison to pre-operative scores, indicating that the issues described were temporary and related to the early post-operative recovery phase. Overall the largest improvements in QIRC score occurred for questions 3-7, 10 and 11. Questions 3-7 cover the subscale relating to questions about convenience issues and questions 10 and 11 are both in the subscale relating to questions about health concerns.

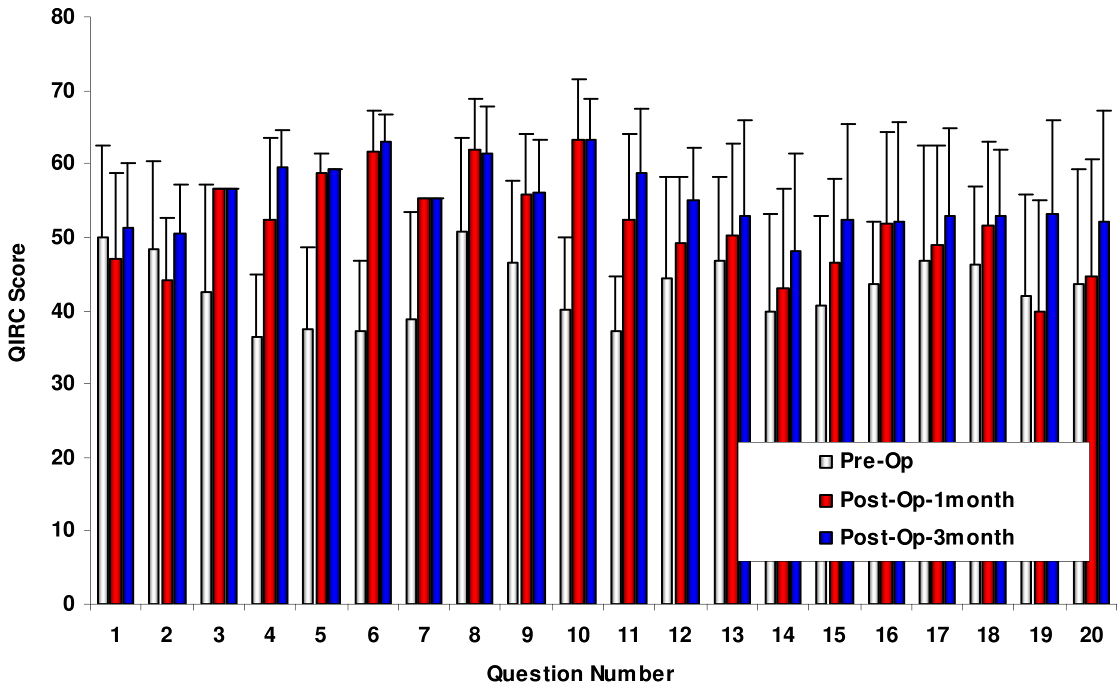


Figure 4.10: Mean (± SD) QIRC scores for each question (n=20) at each study visit. Values are calculated using data from all patients (n=36).

4.5 Discussion

The surgical outcome results show that when considered as a group, the patients recruited to the study underwent highly successful surgery. At the final (three month) post-operative study visit all eyes achieved a residual mean sphere within ± 1.00D of emmetropic correction, with the vast majority being within ± 0.50D of emmetropic correction. The refraction results showed a high level of post-operative stability between the two post-operative visits, with no eye changing by more than 1.00D, and the vast majority of eyes changing by 0.50D or less. Almost all eyes achieved UCVA of +0.30 LogMAR (6/12 Snellen) or better, with the majority of these achieving UCVA of 0.00 LogMAR (6/6 Snellen) or better, and no eyes lost more than two lines of BSCVA at the final study visit. Considered collectively, the results at the one month visit were broadly similar to those found at the three month visit, although most statistics showed small improvements with increasing post-operative time. The outcome results of this study are consistent with published studies that report the outcomes of similar populations undergoing comparable surgical techniques (Pop and Payette, 2000; Scerrati, 2001; Claringbold, 2002; Shahinian, 2002; Aizawa *et al.*, 2003; Kaya *et al.*, 2004; Kim *et al.*, 2004; Partal *et al.*, 2004; Taneri *et al.*, 2004a; 2004b; O'Doherty *et al.*, 2006; Tobaigy *et al.*, 2006; Bailey and Zadnik, 2007; Teus *et al.*, 2007; Schallhorn *et al.*, 2008).

As expected the QIRC scores showed a significant improvement following refractive surgery. In comparison to pre-operative QIRC scores, all patients showed an increase in QIRC score at the three month post-operative visit. The questions that contributed most to this increase were questions 3-7, 10 and 11. These questions relate to convenience issues (questions 3-7) and health concerns (questions 10 and 11). The QIRC outcome results found here are consistent with previously published work (Garamendi *et al.*, 2005). Garamendi *et al.* (2005) used the QIRC questionnaire to assess quality of life changes in a group of patients (n=66) undergoing LASIK for myopia. Patients were pre-presbyopic adults (mean age 30.2 years, range 21-39 years) with mean pre-operative refraction of -3.34 ± 1.86D (range -0.75D to -10.50D). They found that mean (± SD) QIRC score improved significantly from 40.07 ± 4.30 pre-operatively to 53.09 ± 5.25 post-operatively. The profile of questions exhibiting the largest increases in QIRC score were very similar to those found in the current study.

The present study showed that the QIRC scores improved after surgery at the one month post-operative visit, but it was interesting to find that they then showed a further significant increase between the one and three month post-operative visits. Given that the refractive and visual outcome results were relatively stable over this period, they provide no obvious reason for the improvements in QIRC score. Review of the literature revealed no studies that measured QIRC scores at a series of well defined time periods following surgery. Indeed, many of the studies examining changes to quality of life as a result of refractive surgery only administer questionnaires twice: once pre-operatively and once post-operatively. In a given study, the time at which the post-operative questionnaire is administered can vary dramatically between individual patients. For example in the study by Garamendi *et al*. (2005) the questionnaire was administered pre-operatively and then between 3 and 8 months post-operatively. Other studies have measured quality of life scores with questionnaires pre-operatively, and then at 2-6 months post-operatively (Schein 2000; Schein *et al*., 2001) or 2-15 months post-operatively (McDonnell *et al*., 2003). It seems reasonable to assume that quality of life measures will vary with time following refractive surgery. Patients experiencing early post-operative complications in the first few weeks following surgery may show reduced quality of life scores that later improve as the surgical complications subside. Conversely, those who experience highly successful surgery may show an initial large improvement in quality of life scores that later decrease as the novelty of not needing refractive correction wears off or they encounter late post-operative complications such as regression. The results presented here suggest the possibility that the broad post-operative time-frames used by previous studies may have masked important time dependant changes in quality of life measures following refractive surgery. More specific definition of the time period for the post-operative administration of the questionnaire also allows accurate normative data to be established for the expected improvement of quality of life score at a specific time period following surgery. It is interesting to look more closely at the reasons for the subsequent further improvement in QIRC score between post-operative visits. The questions that showed the greatest increase between the one and three month post-operative visit are listed below.

Question 1: *How much difficulty do you have driving in glare conditions?*
Question 2: *During the past month, how often have you experienced your eyes feeling tired or strained?*
Question 4: *How much trouble is having to think about your eyes (after refractive surgery) before doing things; e.g. traveling, sport, going swimming?*
Question 11: *How concerned are you about your vision not being as good as it could be?*
Question 12: *How concerned are you about medical complications from your choice of optical correction (refractive surgery)?*
Question 19: *During the past month, how much of the time have you felt able to do the things you want to do?*
Question 20: *During the past month, how much of the time have you felt eager to try new things?*

These questions covered a broad range of the questionnaires subscales, with at least one question from five of the six questionnaire subscales (visual function, symptoms, convenience, health concerns, and well being). The only subscale that did not appear to contain changes in score between one and three months post-operatively was the subscale relating to cost: patients did not appear to be more/less concerned about the cost of surgery between the two post-operative visits. The improvements seen in the answers given to the above questions suggest that, with increasing time following surgery the patients had less difficulty driving in glare conditions, less eyestrain/tiredness, fewer concerns, and were more able to do the things that they wanted to do. In combination, these factors led to the improved quality of life scores found between the two post-operative visits. It is clear that many of these factors are not revealed by refractive or visual outcome statistics.

In conclusion, the patients recruited for the accommodation studies underwent successful surgery. The results show good efficacy, safety and stability outcomes that were consistent with published literature. The study provides evidence that questionnaires can provide useful additional information in the assessment of health intervention which is not readily available from more traditional measures of refractive surgery outcomes. The results show that QIRC scores can vary with time post-operatively. This suggests that to obtain accurate data on the expected improvement in quality of life scores following refractive surgery, the timing of post-operative questionnaire administration should be well defined.

CHAPTER 5
AMPLITUDE OF ACCOMMODATION

5.1 Introduction

With increasing numbers of people undergoing refractive surgery to correct their refractive error, it is becoming increasingly important to understand more about the effects of refractive surgery on the eye. It is well known that refractive surgery is capable of introducing considerable changes to an individual's ocular aberrations (e.g. Applegate *et al.*, 1996; 1998; Oshika *et al.*, 1999; Seiler *et al.*, 2000; Mrochen *et al.*, 2001a; Marcos *et al.*, 2001; Marcos, 2001; Moreno-Barriuso *et al.*, 2001; Straub and Schwiegerling, 2003; Yamane *et al.*, 2004; Buzzonetti *et al.*, 2004; Kohnen *et al.*, 2005; Porter *et al.*, 2006; Kirwan and O'Keefe, 2009). In particular, the surgical alteration to anterior corneal asphericity is thought to contribute to alterations in the levels of spherical aberration present in the eye (Yoon *et al.*, 2005). An increase in the level of spherical aberration would be expected to cause an increase in the depth of focus of the eye. This could be potentially beneficial to those approaching presbyopia by counteracting the effects of the age-related decrease in accommodative amplitude, and hence delaying the onset of presbyopic symptoms.

Relatively little has been published regarding the effects of refractive surgery on the amplitude of accommodation. Artola *et al.* (2006) examined the monocular range of accommodation for left and right eyes in a group of 10 patients that had undergone refractive surgery and compared the results with 10 normal, emmetropic, age-matched control subjects. The refractive surgery patients had a mean age of 46.3 years and had all undergone PRK for myopia at least 10 years previously. They found that the mean amplitude of accommodation was approximately 3.3D in the refractive surgery group, compared to approximately 2.3D in the control group ($p<0.05$). Nieto-Bona *et al.* (2007) evaluated the monocular amplitude of accommodation of 36 eyes that had undergone refractive surgery. Patients (aged 25 to 45 years) had undergone LASIK for myopia of up to -8.00D between 6 and 36 months previously. Their results showed that the amplitudes of accommodation in those having undergone refractive surgery were lower than normal values, although no specific details were provided of the control group used for comparison purposes. These previous studies compare amplitudes of accommodation in a group of patients that have undergone refractive surgery with a normal (emmetropic) control group. However, evidence suggests that myopes and emmetropes exhibit different accommodative amplitudes (Fledelius, 1981; Maddock *et al.*, 1981; McBrien and Millodot, 1986a; Fisher *et al.*, 1987). Therefore, there could be differences in the amplitude of accommodation related to refractive error group between post-refractive surgery patients and emmetropic controls. These differences could mask important changes in amplitude of accommodation due to refractive surgery.

The aim of the present study was to investigate changes in the amplitude of accommodation in eyes that have undergone refractive surgery. The assumption was that the refractive surgery would increase the levels of spherical aberration, which would in turn increase the ocular depth of focus and lead to an increase in the amplitude of accommodation measured.

5.2 Subjects

The patients that took part in the measurements of amplitude of accommodation described here were a subgroup from the patients described in Chapter 4 (for recruitment methods see section 4.2.2, for inclusion/exclusion criteria see section 4.2.3, and for details of surgical procedures used see section 4.2.4). The measurements in this (and subsequent) chapters were monocular measurements taken from a selection of right and left eyes from the population described in Chapter 4 (section 4.4). If only one eye met the inclusion criteria then that eye was used for the amplitude measurements. If both eyes met the inclusion criteria then one eye was selected at random for the amplitude measurements. The demographic characteristics of the patients recruited to take part in the amplitude measurements are presented in Table 5.1 (details are given for the tested eye only). A total of 31 eyes (20 right eyes and 11 left eyes) of 31 healthy pre-presbyopic adults were selected. Of the 31 patients, one patient failed to attend for the one month post-operative visit but did attend for the three month post-operative visit. All other patients (n=30) attended all three study visits.

One of the patients was undergoing a bilateral re-treatment procedure for low myopia (Right eye: -2.00/-0.75x160, Left eye: -1.75/-0.50x180) after having undergone refractive surgery (PRK) elsewhere 10 years previously for (self reported) myopia of approximately -6.00DS in both eyes.

VARIABLE	RESULT
Number of patients (total number of eyes) Number right eyes, Number left eyes	31 (31) 20, 11
Age (years) at recruitment, Mean ± SD (range)	32.0 ± 6.2 (19 to 45)
Gender, Number (%) Female	18 (58)
Surgery type (Number of patients), Number of eyes, (Number, % eyes wavefront-guided procedures)	
LASIK *LASEK*	(6), 6 (5, 83.3) (25), 25 (14, 56.0)
Pre-operative refractive error, Mean sphere ± SD (range)	-4.63 ± 2.46D (-1.25D to -9.75D)
Pre-operative refractive error (Number, % eyes)	
Low Myopia (Mean sphere -0.50D to <3.00D) *Astigmatism in this group, Mean ± SD (range)* *Moderate Myopia (Mean sphere -3.00D to -6.00D)* *Astigmatism in this group, Mean ± SD (range)* *High Myopia (Mean sphere over -6.00D)* *Astigmatism in this group, Mean ± SD (range)*	10 (32) -0.28 ± 0.32D (0.00D to -0.75D) 12 (39) -0.63 ± 0.39D (0.00D to -1.25D) 9 (29) -0.47 ± 0.42D (0.00D to -1.25D)
Post-operative refractive error, Mean sphere ± SD (range)	
1 month Post-Op visit *3 month Post-Op visit*	-0.03 ± 0.51D (-1.00D to +1.12D) +0.12 ± 0.40D (-0.50D to +1.00D)
Pre-operative distance corrected visual acuity (LogMAR) Mean ± SD (range)	-0.09 ± 0.08 (-0.20 to +0.10)
Post-operative distance corrected visual acuity (LogMAR) Mean ± SD (range)	
1 month Post-Op visit *3 month Post-Op visit*	-0.04 ± 0.08 (-0.24 to +0.10) -0.10 ± 0.07 (-0.20 to +0.02)

Table 5.1: Characteristics of the study population taking part in the amplitude of accommodation measurements.

5.3 Methods

The patients attended for three visits in total. The first visit was conducted prior to refractive surgery to obtain baseline measurements. The two further visits occurred at one and three months post-operatively. At each visit the patient's monocular amplitude of accommodation was measured using three different methods. The amplitude was measured using two subjective methods based on the "push-up" technique and also measured objectively using a Shin-Nippon SRW-5000 auto-refractor. A single clinician (JT) collected all data to avoid operator errors. Due to the study design and use of a single clinician, the clinician was unmasked (with regard to which visit the patients were attending for). However, the clinician did not view the results of previous visits until after the study was complete, and care was taken to adhere to strict measurement protocols. In addition, one of the reasons for introducing the objective measurements was in an attempt to limit operator bias. The order of the three methods of measurement was randomized to avoid any possible fatigue effects. The method sequences were selected randomly from a list of all possible method sequences using a random number generation program in Excel (Microsoft Corp., 2003). During the measurements the patients wore their distance spectacle prescription (if applicable) in a trial frame at a vertex distance of 10mm and the non-tested eye was occluded. All measurements took place in the same clinical consulting room with the same level of ambient lighting maintained throughout.

5.3.1 N5 blur method

A line of black N5 letters on a white background was initially positioned directly in front of the viewing eye (along line of sight) along a horizontal plane at a distance of 40cm (2.5D). A horizontal plane was chosen to allow direct comparison with the objective measurement of amplitude which was also measured along a horizontal plane. The patient was instructed to keep looking at the line of print and to make every effort to keep the words on the line appearing clear and to report whether or not this was possible as the target was brought towards them. A ruler was used as a guide, with markings corresponding to the required distances (for each accommodative level) from the corneal plane in 0.50D steps. The target was moved towards the subject in discrete 0.50D increments and amplitude of accommodation was taken as the first dioptric position at which the subject was unable to keep the words clear. Three readings were obtained and averaged.

5.3.2 Critical blur method

For the critical blur method, a near vision chart was reproduced as described by Atchison *et al*. (1994a). A copy of the chart appears in appendix 5a. The chart consisted of 14 lines of non-sequential words in black print on a white background. The first line contained three words of 4, 7 and 10 letters. The second line contained five words which consisted of: two words of 4 letters, two words of 7 letters and one word of 10 letters. The subsequent 12 lines each contained six words and each had two words that were 4, 7 and 10 letters in length. The lines of text were written using lower case “Times Roman” typeface in Word 2003 (Microsoft Corp., 2003). Each line of text was then re-scaled to the appropriate size and the chart created using PhotoShop CS3 (Adobe Systems Inc, 2007). The separation between the small letters of any two adjacent lines was the same as the size of the small letters in the lower line. The key feature of this chart is its use of a dioptric scale in 0.50D steps to keep the angular subtense of the target constant over a 7.5D range. The top line of the chart is designed to be read at a distance of 1m (1D). If the chart is then moved to 67cm (1.5D) the second line now subtends the same angle as the first line did at 1m, and so on in 0.50D steps up to the 14th line which is designed to be read at 13.3cm (7.5D) and subtends the same angle as the first line did at 1m.

The measurement of amplitude of accommodation using this chart was based on the method described by Atchison *et al*. (1994a). The chart was initially positioned directly in front of the patient along a horizontal plane at a distance of 40cm (2.5D). The patient was instructed to initially look at the words on the fourth line down from the top. The patient was instructed to make every effort to keep the words on the line appearing clear and to report whether or not this was possible as the target was brought towards them. The target was moved towards the patient in discrete half-dioptre increments and the patient was instructed to look at the next smaller line of letters each time the target was moved closer, keeping the angular subtense of the target constant. The amplitude was taken as the first dioptric position at which the patient was unable to keep the words clear. Three readings were taken and averaged. If the target was still clear at the last stimulus level (7.5D) the patient was instructed to keep looking at the bottom line while it continued to be moved toward the patient in 0.50D steps and the amplitude was taken as the first dioptric position at which the patient was unable to keep the words clear.

5.3.3 Objective method

The targets consisted of a horizontal row of six black capital letters of constant size and spacing on a white background. The six optotypes used (D, E, V, N, P, and H) were selected randomly from the 10 British letters of similar legibility (British Standard 4274, 1968). These letters are constructed on a 5 x 4 grid (height x width), with a stroke width of 1/5th of the letter height and (as far as possible) the space between adjacent strokes is equal to the stroke width. The letter height was equivalent to that of a 6/9 Snellen letter and the space between each letter was equal to the letter width. Four of these targets were made, one for each of the presentation distances 1.00m, 0.50m, 0.33m and 0.25m, corresponding to 1-4D nominal stimulus levels in 1D steps. The size of the targets was scaled to compensate for the effects of angular magnification due to altering the target distance. The order of the six letters at each presentation distance was randomized to prevent the subjects simply remembering the letter sequences. The targets were created using “Helvetica” bold sans-serif type-face in Word 2003 (Microsoft Corp., 2003), and then modified and scaled down using Photoshop CS3 (Adobe Systems Inc, 2007). They were printed at 4800dpi on photographic quality white A4 paper. By altering the target size for angular magnification effects, keeping the number of letters at each stimulus level constant, keeping the optotype spacing proportional to the letter size, and using optotypes of equal (or similar) average legibility, the visual task became essentially the same at each stimulus level. Thus viewing distance became the only significant variable when changing from one target to another.

The patients viewed the targets through an open-field Shin-Nippon SRW-5000 auto-refractor (Ajinomoto Trading Inc, Tokyo, Japan, see Mallen *et al.*, 2001). The non-tested eye was occluded with a Kodak Wratten 88a filter and the target was viewed monocularly through the patient's distance spectacle prescription (if applicable) in a trial frame at a vertex distance of 10mm. Initially a -3.00DS lens was added to the spectacle prescription in the trial frame and the target was positioned directly in front of the patient's tested eye along a horizontal plane and viewed at a distance of 1m from the patient. This created a nominal 4D accommodative stimulus (which was the minimum inclusion criteria for the study). The target was then moved towards the patient from 1m to 0.25m in 1D steps (1m, 0.50m, 0.33m, 0.25m). This increased the accommodative stimulus over the nominal range 4D to 7D. Evidence suggests that the objective amplitude is typically 1D to 3D less than the subjective amplitude of accommodation (Hofstetter, 1965; Ramsdale and Charman, 1989; Kasthurirangan and Glasser, 2006). It was therefore thought that the 7D range would cover the amplitude of the majority of patients in the age range tested. Patients were instructed to make every effort to keep the words on the line appearing clear and to report whether or not this was possible as the target was brought towards them. The patient was given one practice run prior to the actual measurement so that they understood the test but no specific training was given. When the patient reported that the target was as clear as possible five readings were taken through the filter with the auto-refractor at each of the four viewing distances. The filter transmits infrared light but not visible light. This allowed measurements with the auto-refractor to be taken through the filter while at the same time the filter acted as an occluder to ensure that the patients were still viewing the targets monocularly. It has been shown that the accommodation response is binocular, with the same response occurring in both eyes (Campbell, 1960). Accommodation measurements taken through the non-viewing eye should therefore accurately reflect the responses in the viewing eye. Mean accommodation responses were calculated from the means of the five auto-refractor readings. Appropriate allowance was made for the power and the vertex distance of the trial lenses worn using equation 5.1.

Equation 5.1 $$\mathbf{F_x = F/(1\text{-}dF)}$$ (Tunnacliffe, 1993)

Where:

$\mathbf{F_x}$ = Effective power (D)

F = Lens power (D)

d = Vertex distance (m)

An increase in the power of the eye, corresponding to a more negative refraction, was taken as a positive response. Accommodative response was plotted against accommodative stimulus and the objective amplitude of accommodation was taken as the level at which the accommodative response function reached a plateau.

5.3.4 Measurement of aberrations

Distance resting aberrations with a natural pupil were measured for all subjects on the same day as the amplitude measurements were taken. The aberrations were measured using the Allegretto Wave Analyzer aberrometer (Wavelight, Erlangen, Germany). In each case the measurements were taken monocularly in the same eye used for the amplitude measurements with the non-tested eye occluded. All measurements were taken in the same clinical room with the room lights turned off. For each patient the aberration measurement was taken as the mean of five readings for a 5.00mm pupil diameter.

5.3.5 Statistical analysis

The main outcome measure of the study was amplitude of accommodation. For each measurement technique, the mean amplitude at the three time intervals (pre-operatively, one and three months post-operatively) were compared using one-way repeated measures ANOVA with Bonferroni post-hoc analysis. Pearson's product-moment correlation (r) was used to calculate the significance of correlations between the change in amplitude and the change in spherical aberration and total higher order RMS aberration (3^{rd}-5^{th} order) for the one month and three month post-operative visits. Results were considered significant at $p<0.05$. Statistical tests were performed using SPSS for Windows (SPSS Version 16.0, SPSS Inc, Chicago, Ill).

5.4 Results

Figure 5.1 shows the results for the pre-operative ocular amplitude of accommodation as a function of age for the three different measurement techniques. Using the N5 target the mean amplitude was approximately 9.4D at 20 years of age, decreasing linearly to around 5.3D at 45 years of age. Using the critical target the mean pre-operative ocular amplitude of accommodation was approximately 6.9D at 20 years of age, decreasing linearly to around 4.4D at 45 years of age. The use of the critical target produced consistently lower amplitudes than when using the N5 target but the difference between the two techniques decreased with increasing age. Measurements taken objectively showed the lowest estimates of amplitude. The results for the objective amplitude also showed a decrease in amplitude with increasing age although data were only available for a subgroup of patients (approximately 25%, n=8). The reason for this is that the range of accommodative stimuli used to measure the objective amplitude was insufficient to elicit a maximum response for most patients. Figure 5.2 shows examples of the typical results obtained when measuring objective amplitude. For the majority (approximately 75%) of patients, the level at which the accommodative response plateaus (reaches maximum) was not achieved (e.g. Figure 5.2a-c). The maximum accommodative stimulus was achieved by focusing through a -3D lens at a target placed at 0.25m, creating a stimulus of approximately 7D. Despite this relatively large stimulus, the accommodative response to this stimulus tended to be in the range 3-5D. For most patients this proved to be lower than their objective amplitude and therefore the maximum amplitude was not reached. However, for a small group of patients (n=8) the response function did plateau (e.g. Figure 5.2d). For one patient (age 29 years) the maximum response was observed because the patient responded particularly well to the accommodative stimulus, but more commonly the maximum response was observed in patients with the lowest amplitudes, hence the objective amplitudes were clustered towards the upper end of the age range tested. The results for this subgroup have been added to Figure 5.1 for completeness but were not analyzed further due to the relatively small sample size.

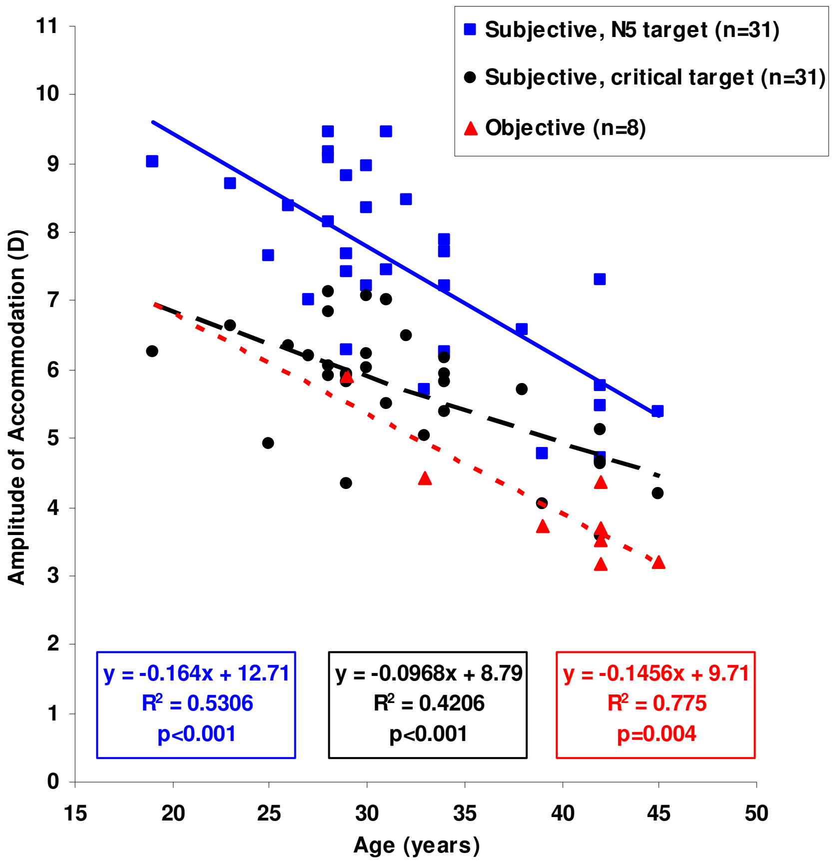


Figure 5.1: Pre-operative ocular amplitude of accommodation (D) as a function of age (years). Results are shown with linear regression line, equation and R^2 value for results using the N5 target (blue squares, blue line, blue box), critical target (black circles, black dashed line, black box) and for results obtained objectively (red triangles, red dashed line, red box).

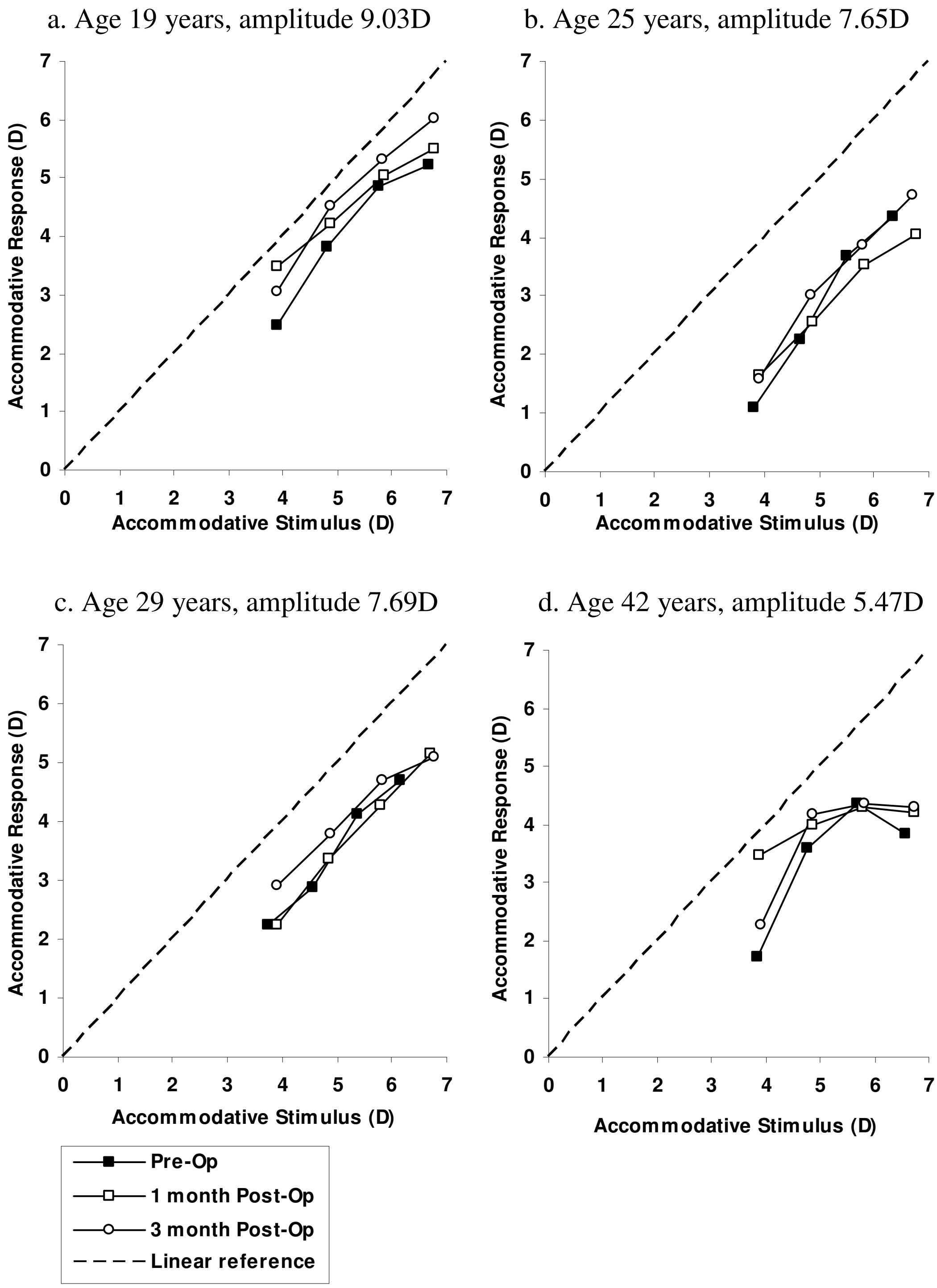
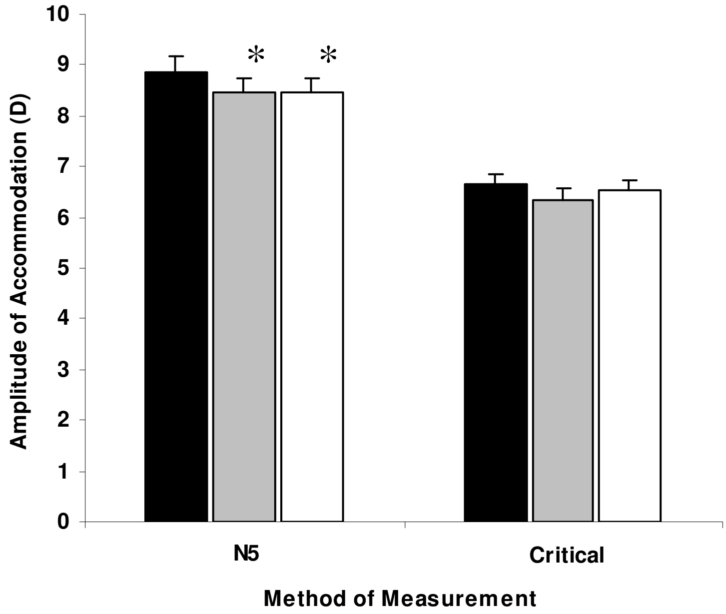


Figure 5.2: Examples of typical results of measurements taken to obtain objective amplitude of accommodation. Results are shown for four different patients (a-d). The patient's age and pre-operative subjective N5 ocular amplitude of accommodation given above each graph. Results are shown for measurements taken pre-operatively (black squares) and at one month (open squares) and three months (open circles) post-operatively.

Figure 5.3 shows the results for the spectacle and ocular amplitude of accommodation at each of the three study visits using the N5 and critical targets. Figure 5.3a shows the spectacle amplitude of accommodation results. The mean (± SD) pre-operative N5 spectacle amplitude was 8.87 ± 1.66D. This decreased to 8.46 ± 1.61D and 8.45 ± 1.59D at the one month and three month post-operative visits respectively. One-way repeated measures ANOVA showed that the N5 spectacle amplitude altered significantly over time ($F_{2, 28}$ = 7.157, p=0.003). Post-hoc testing using Bonferroni pair-wise comparisons showed a significant difference in the mean amplitude at one month (p=0.002) and three months (p=0.017) post-operatively in comparison to pre-operative levels. The difference between the one month and three month post-operative mean N5 amplitudes was not significant (p=1.000). The mean (± SD) pre-operative critical spectacle amplitude was 6.64 ± 1.09D. This showed a small decrease to 6.34 ± 1.21D and 6.52 ± 1.21D at the one month and three month post-operative visits respectively. One-way repeated measures ANOVA showed that these variations in critical spectacle amplitude over time were not statistically significant ($F_{2, 28}$ = 2.427, p=0.107).

Figure 5.3b shows the ocular amplitude of accommodation results. The mean (± SD) pre-operative N5 ocular amplitude was 7.47 ± 1.39D. This increased to 7.94 ± 1.41D and 7.97 ± 1.44D at the one month and three month post-operative visits respectively. One-way repeated measures ANOVA showed that the amplitude altered significantly over time ($F_{2, 28}$ =5.694, p=0.008). Post-hoc testing using Bonferroni pair-wise comparisons showed a significant difference in the mean amplitude at one month post-operatively (p=0.041) and three months post-operatively (p=0.006) in comparison to pre-operative amplitude levels. There was no significant difference between the one month and three month post-operative N5 amplitudes ($p=0.894$). The mean pre-operative critical ocular amplitude was $5.70 \pm 0.92D$. This increased to $6.05 \pm 1.13D$ and $6.24 \pm 1.14D$ at the one month and three month post-operative visits respectively. One-way repeated measures ANOVA showed that the amplitude altered significantly over time ($F_{2, 28} = 12.496$, $p<0.0005$). Post-hoc testing using Bonferroni pair-wise comparisons showed that the mean amplitude did not alter significantly at one month post-operatively ($p=0.167$) but did show a significant difference at three months post-operatively ($p<0.0005$) in comparison to pre-operative amplitude levels. There was no significant difference between the one month and three month post-operative critical amplitudes ($p=0.253$).

a. Spectacle amplitude of accommodation



b. Ocular amplitude of accommodation

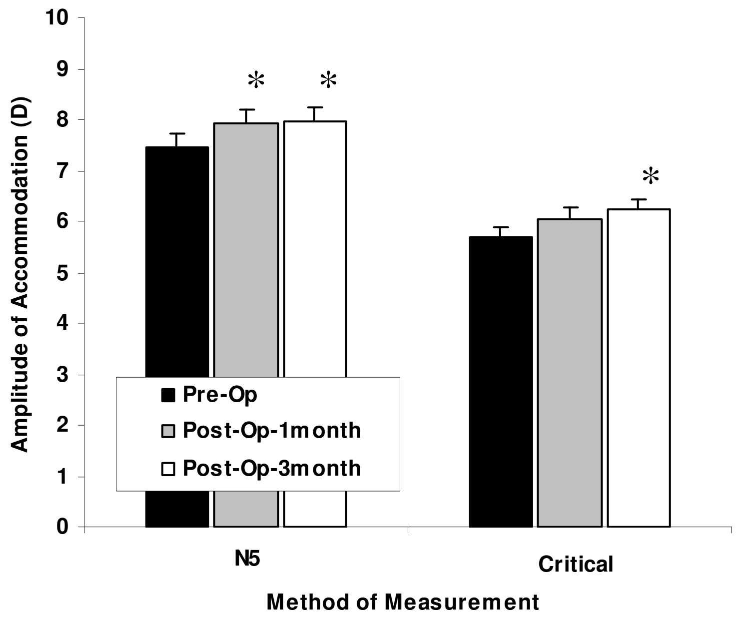
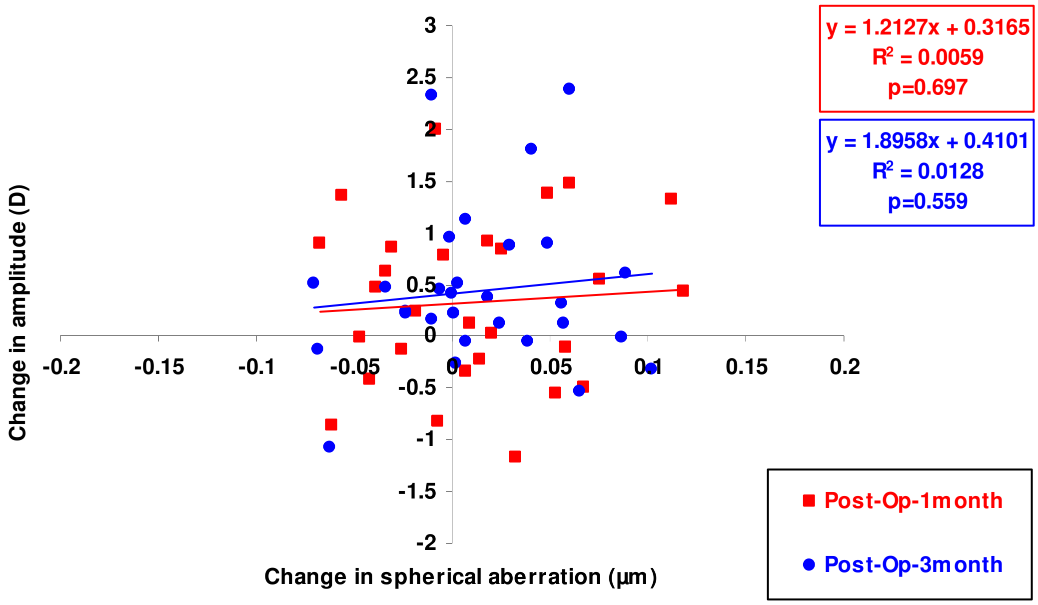


Figure 5.3: Mean (±SEM) spectacle amplitude of accommodation (a) and ocular amplitude of accommodation (b) measured monocularly for patients undergoing refractive surgery for pre-operative myopia and myopic astigmatism. Results are shown for measurements taken pre-operatively (black bars, n=31 eyes) and at one month (grey bars, n=30 eyes) and three months (white bars, n=31 eyes) post-operatively for measurements using N5 and critical targets. *Significantly different to pre-operative measurement, p<0.05.

Figures 5.4 and 5.5 show the results for the correlation between the ocular amplitude of accommodation and higher order aberrations. More specifically, they investigate whether the changes occurring between pre-operative and post-operative ocular amplitude measurements are correlated with the changes in the levels of higher order aberration following refractive surgery. Change in ocular amplitude is plotted against the change in spherical aberration (Figure 5.4) and change in total higher order RMS aberration (Figure 5.5) for a 5.00mm natural pupil diameter. Total higher order aberration was analyzed as it was thought that an overall higher level of aberrations may reduce the quality of the retinal image and hence increase the depth of focus. The change in N5 ocular and critical ocular amplitude of accommodation both showed no statistically significant correlation with the change in spherical aberration or the change in total higher order RMS aberration at either of the post-operative visits ($p>0.05$).

a. N5 ocular amplitude



b. Critical ocular amplitude

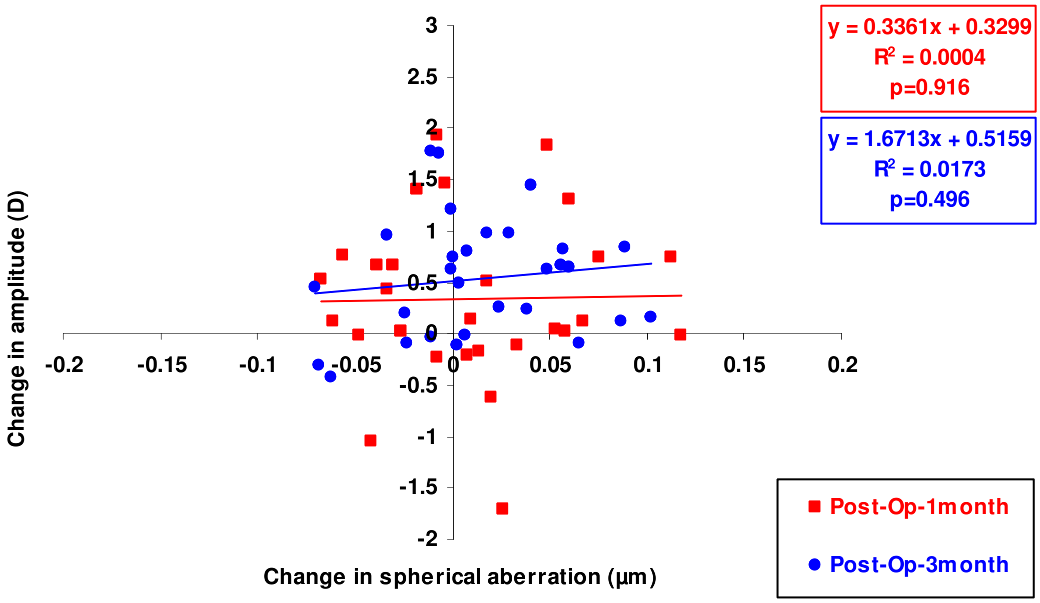


Figure 5.4: Change in N5 ocular amplitude of accommodation (graph a) and critical ocular amplitude of accommodation (graph b) plotted against the change in spherical aberration (µm) after refractive surgery. Both graphs show results at one month (red squares) and three months (blue circles) post-operatively in comparison to pre-operative measurements. All the aberration measurements represent distance resting aberrations for a 5.00mm natural pupil diameter. Results are shown with linear best fit lines, equation, R^2 and p-value.

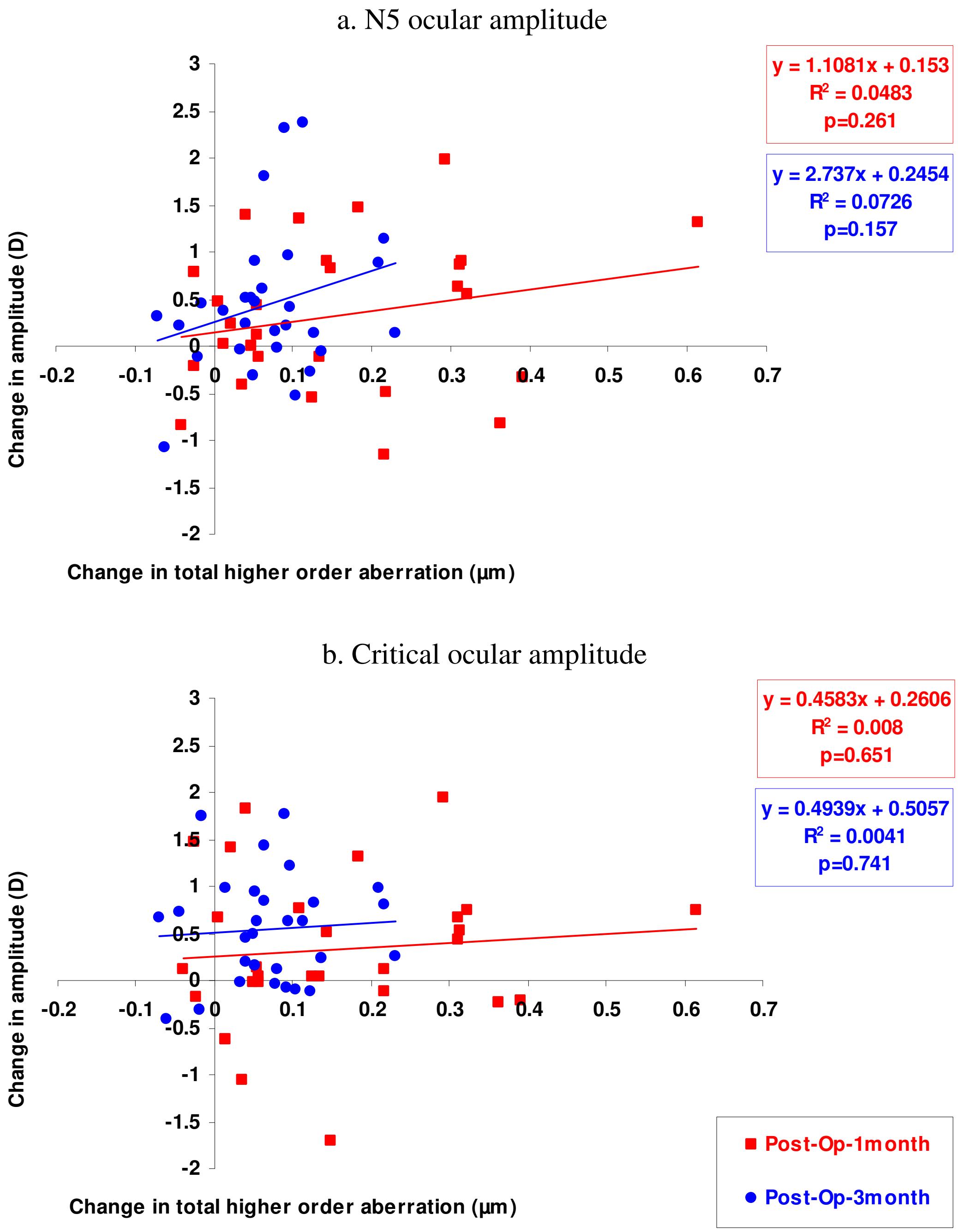


Figure 5.5: Change in N5 ocular amplitude of accommodation (graph a) and critical ocular amplitude of accommodation (graph b) plotted against the change in total higher order aberration (RMS 3rd-5th order, µm) after refractive surgery. Both graphs show results at one month (red squares) and three months (blue circles) post-operatively in comparison to pre-operative measurements. All the aberration measurements represent distance resting aberrations for a 5.00mm natural pupil diameter. Results are shown with linear best fit lines, equation, R^2 and p-value.

5.5 Discussion

It has been extensively reported and is well known that amplitude of accommodation decreases with age, leading to the onset of presbyopia during the fifth decade of life (see Atchison, 1995; Charman, 2008 for reviews). Figure 5.1 shows the decline in amplitude of accommodation (obtained pre-operatively) for the patients recruited to the present study. As expected, each of the three measurement techniques showed a linear decrease in amplitude with increasing age. The results obtained using the N5 letter targets are in broad agreement with the results of previous studies that have measured amplitude of accommodation (Schapero and Nadell, 1957; Turner, 1958; Fitch, 1971; Mordi and Ciuffreda, 1998). Perhaps the only difference in comparison to previous literature is the relatively high amplitudes of patients aged 40-45 years found in this study. This reflects the fact that only pre-presbyopic patients with subjective amplitudes of at least 4D were recruited on to the study. The "push-up" technique using N5 letter targets is the most common standard procedure used to measure amplitude of accommodation. It was therefore included here because of its obvious clinical relevance. However, letters of fixed size will increase in angular magnification as they are moved towards the eye, leading to an alteration in the effective target size used to measure amplitudes of different magnitude. Depth of focus is known to increase (and hence subjective amplitude increase) as the angular magnification of the target increases (Tucker and Charman, 1975; Rosenfield and Cohen, 1995; Atchison *et al*., 1997). The use of the critical target (Atchison *et al*., 1994a) was therefore included in the study in an attempt to provide more accurate estimates of amplitude. In their design and trial of the critical target used in this study, Atchison *et al*. (1994a) showed that "push-up" amplitudes measured using the critical target are considerably lower than amplitudes measured using an N5 target. They found differences between the techniques of around 1.8-2.2D for those aged 25-29 years, and around 0.7-0.8D for those aged 40-45 years. The results of the present study confirm those of Atchison *et al*. (1994a) showing that consistently lower amplitudes were achieved with the critical target in comparison to measurements taken with the N5 target, with the difference between the two techniques decreasing with increasing age. This occurs due to the variation in angular magnification that occurs when using a target of fixed size to measure amplitudes of different magnitude.

In the present study the objective measures produced the lowest estimates of amplitude of accommodation. Over the age range for which data were available the objective amplitudes were generally about 1D to 2D lower than those measured subjectively. These results agree well with previous literature (Hofstetter, 1965; Ramsdale and Charman, 1989; Kasthurirangan and Glasser, 2006) and occur because the objective method is free from depth of focus effects. However, results were only available for a subgroup of the patients. This was because the range of accommodative stimuli used to measure the objective amplitude was insufficient to elicit a maximum response for the majority of patients. The range of distances over which the objective measurements were taken (1m to 0.25m) was limited by the physical size of the auto-refractor (i.e. targets could not be placed closer than 0.25m from the eye). However, the accommodative stimulus range could have been extended with the use of additional negative lenses which would have allowed the objective measurement to be recorded for all patients. From visual inspection of the limited data available (n=8 patients), the objective amplitude did not appear to be affected by refractive surgery (see e.g. Figure 5.2d). Due to the small sample size (n=8) the objective data were not included in the overall analysis. The difficulty found when measuring the objective amplitudes is likely to have been caused as a result of using negative lenses to stimulate accommodation. The use of negative lenses has been shown to be a relatively poor accommodative stimulus in comparison to altering target distance (see e.g. Gwiazda *et al.*, 1993; Abbott *et al.*, 1998). While it would have been possible to extend the accommodation stimulus range with the use of increasing negative lenses, with hindsight it should be acknowledged that a better approach may have been to use a beam-splitter and test over a larger range of distances (i.e. use beam-splitter to allow closer distances to be tested). This would have allowed objective data to be obtained for each patient.

A single clinician collected all data to avoid operator errors. However, as a single clinician collected all data, they knew whether the patient was attending for the first visit (pre-operatively) or for one of the post-operative visits. It should be acknowledged that this absence of masking may introduce operator bias, particularly in a subjective test. Objective measurements were introduced in an attempt to limit operator bias. However, given that the methodology used only allowed limited objective data to be collected, in hindsight it would have been better to introduce masking for the subjective measurements. Despite the lack of masking, the subjective results are still likely to be valid due to strict adherence to the measurement protocol.

Many people undergo refractive surgery with the aim of achieving freedom from spectacles and/or contact lenses. However, even after successful correction of distance refractive error, patients still require refractive correction for near work following the onset of presbyopia. It has been suggested that alterations to spherical aberration following refractive surgery can increase the ocular depth of focus and hence delay the onset of presbyopic symptoms (Artola *et al*., 2006). In contrast, other studies have reported a decrease in amplitude of accommodation in those having undergone refractive surgery (Nieto-Bona *et al*., 2007). The main aim of the present study was to investigate the changes in the amplitude of accommodation in eyes that have undergone refractive surgery. In the study, the patients acted as their own control (pre-operatively versus post-operatively), allowing control of the influence of age and refractive error group effects which may have been confounding factors in previous studies which compared amplitudes after surgery with a control group. The main findings of the present study are highlighted in Figure 5.3. This shows that the spectacle amplitude of accommodation measurements decreased after refractive surgery, and the ocular amplitude of accommodation measurements increased after refractive surgery. It is well known from basic visual optics theory that in the presence of refractive error, accommodation measured in the spectacle plane (spectacle accommodation) differs from accommodation measured in the corneal plane (ocular accommodation) due to the effects of lens effectivity. This can be used to explain the apparent incongruous finding of both an increase and decrease in amplitude of accommodation found in the present study. To illustrate this, a typical patient recruited to the study is considered. A myope corrected (pre-operatively) with a -4.50D spectacle lens at a vertex distance of 10mm from the eye, has a spectacle amplitude of accommodation of 8.75D and, following surgery, they are emmetropic.

Equation 5.2: $$\mathbf{OA = [\ 1/((1/L_1)\text{-}d)\ ] - [\ 1/((1/L_2)\text{-}d)\ ]}$$

(Douthwaite, 1995)

Where:

OA = Ocular amplitude of accommodation (D)

$\mathbf{L_1}$ = Power of spectacle lens (D)

$\mathbf{L_2}$ = Vergence of object at maximum amplitude (D)

$\mathbf{L_2}$ is calculated as: (spectacle lens power) – (amplitude of accommodation)

d = Vertex distance (m)

Using equation 5.2, the actual amplitude of accommodation exerted at the eye pre-operatively is 7.4D. The patient is left emmetropic after surgery, therefore even if no change occurred to the amplitude following surgery, an apparent reduction of 1.35D would be recorded post-operatively simply due to the alteration that had occurred in the refractive error. The results for the change in ocular amplitude show an increase of approximately 0.50D following surgery. Even allowing for an increase in the amplitude of accommodation of this magnitude, the spectacle amplitude would still record an apparent decrease of approximately 0.85D (i.e. 1.35D – 0.50D). The apparent decrease in spectacle amplitude due to the change in refractive error therefore masks the true increase in ocular amplitude measured following refractive surgery. The practical implications of these results are that a spectacle corrected myope undergoing successful refractive surgery is unlikely to experience significant benefit from the modest increase in subjective amplitude of accommodation (approximately 0.50D) following surgery, due to the greater decrease in amplitude found due to the reduction in refractive error. However, it is possible that a myope corrected pre-operatively with contact lenses may experience some benefit, with a slight delay in the onset of presbyopic symptoms.

The difference between the results for spectacle and ocular accommodation may explain the conflicting results found in previous studies (Artola *et al.*, 2006; Nieto-Bona *et al.*, 2007). It is not explicitly clear from these previous studies whether their results represent spectacle or ocular accommodation measurements. Differences in the method used to calculate amplitude could therefore be a possible reason for the conflicting findings of these studies.

An additional aim of the present study was to investigate whether alterations to the amplitude of accommodation could be explained by alterations to the levels of higher order aberrations following refractive surgery. No correlations were found between the change in amplitude of accommodation and the change in spherical aberration (Figure 5.4) or the change in total RMS aberration (Figure 5.5). The present study was therefore unable to confirm that the alterations to amplitude of accommodation were linked to the changes in ocular aberrations. There are a number of possible reasons for this. One possible reason is that only distance resting aberrations were measured. Monochromatic aberrations are known to change as a function of accommodation (Cheng *et al.*, 2004; Radhakrishnan and Charman, 2007a), therefore it is possible that the aberrations at maximum amplitude (i.e. fully accommodated state) will have greater relevance for changes to the depth of focus and hence the amplitude of accommodation. Depth of focus has been shown to vary with a variety of other factors including, luminance levels (Campbell, 1957; Oshima, 1958; Tucker and Charman, 1986), target contrast (Campbell, 1957; Atchison *et al*., 1997), target spatial frequency or target detail (Ogle and Schwartz, 1959; Tucker and Charman, 1975; 1986; Jacobs *et al*., 1989; Atchison *et al*., 1997; Marcos *et al*., 1999), visual acuity (Green *et al*., 1980), pupil size (Campbell, 1957; Oshima, 1958; Ogle and Schwartz, 1959; Tucker and Charman 1975; Charman and Whitefoot, 1977; Tucker and Charman, 1986; Atchison *et al*., 1997; Marcos *et al*., 1999), refractive group (Rosenfield and Abraham-Cohen, 1999) and age (Mordi and Ciuffreda, 1998). The experimental conditions were kept constant before and after the surgical procedure, therefore the luminance and target detail were constant. Similarly, by examining the same patient group before and after surgery the age remained constant and the pupil size is likely to have been relatively constant. Despite the refractive state changing, the refractive group of the participants also remained constant.

It is thought that a decrease in visual acuity causes an increase in depth of focus (Green *et al*., 1980). Better visual acuity results in an improved ability to detect blur and hence a smaller depth of focus. Some of the patients did show slight decreases in visual acuity after refractive surgery (see Table 5.1). Refractive surgery is also capable of causing a decrease in contrast sensitivity (Holladay *et al*., 1999; Marcos *et al*., 2001; Nakamura *et al*., 2001; Chan *et al*., 2002; Bailey *et al*., 2004). It is possible that these changes to visual function may have contributed to the observed increase in amplitude of accommodation by decreasing the patient's ability to detect blur and hence increasing the depth of focus.

In conclusion, ocular amplitude of accommodation was found to increase (by approximately 0.50D) following refractive surgery, which may be of potential benefit in delaying the onset of presbyopic symptoms. However, this increase can be masked by a greater (apparent) decrease in spectacle amplitude that occurs due to the effects of lens effectivity, implying that a spectacle wearing high myope undergoing surgery may experience presbyopic symptoms slightly earlier (then they otherwise would have done) following refractive surgery. No significant correlation was found between the change in amplitude of accommodation and the change in distance aberrations following surgery. It may be that changes in aberrations during accommodation or other changes to visual function (loss of visual acuity or contrast sensitivity) following surgery contribute to the changes in amplitude of accommodation.

CHAPTER 6
ACCOMMODATIVE STIMULUS-RESPONSE FUNCTIONS

6.1 Introduction

Numerous studies have suggested that higher order monochromatic aberrations may play an important role in controlling the accommodative mechanism (Wilson *et al*., 2002; Fernandez and Artal, 2005; Chen *et al*., 2006; Chin *et al*., 2009). One area that has received attention is the relationship between accommodative accuracy and the levels of higher order aberration present in the eye.

He *et al*. (2005) investigated the relationship between ocular aberrations and accommodative lag in normal emmetropic and myopic eyes. They compared the lags of accommodation to a near three dioptre stimulus, to the subject's natural levels of whole eye ocular aberration. Their results suggested that reduced retinal image quality (caused by higher levels of total higher order RMS aberration) was associated with higher accommodative lag. They found that this effect was specific to myopes, with emmetropes showing no significant correlation between lag and natural aberration levels. Neither group showed a significant relationship between the levels of spherical aberration and the lag of accommodation. A possible reason for this is that the small levels of naturally occurring spherical aberration may have been insufficient to highlight any effects related specifically to spherical aberration.

Theagarayan *et al*. (2009) investigated the effects of altering spherical aberration on the static accommodative stimulus-response function. They measured stimulus-response functions after the introduction of controlled amounts of spherical aberration (ranging between ± 0.20μm) via custom-made contact lenses. Their results showed that increasing negative spherical aberration decreased lag and increased stimulus-response function gradient, and increasing positive spherical aberration increased lag and decreased stimulus-response function gradient. These effects were maintained over a 30-60 minute period, suggesting that there was no short term adaptation to the levels of altered spherical aberration. A potential limitation of the study by Theagarayan *et al*. (2009) is the relatively small number and mixed nature of the subjects in the study (5 emmetropes, 5 myopes). They presented results for all 10 subjects collectively and did not compare refractive groups. It is possible that myopes may behave differently to variations in aberration levels (He *et al*., 2005), therefore grouping all subjects may have masked any effects specific to refractive group. In addition, when altering aberrations with contact lenses it is possible that lens movement may alter the level of induced aberrations (Guirao *et al*., 2001).

Gambra *et al*. (2009) have used adaptive optics to show that increasing negative spherical aberration produces a decrease in accommodative lag, and increasing positive spherical aberration produces an increase in accommodative lag. These results support the findings of Theagarayan *et al*. (2009).

Many studies have reported that patients undergoing refractive surgery tend to experience an increase in higher order aberrations (e.g. Applegate *et al.*, 1996; 1998; Oshika *et al*., 1999; Seiler *et al*., 2000; Mrochen *et al*., 2001a; Marcos *et al*., 2001; Marcos, 2001; Moreno-Barriuso *et al*., 2001; Straub and Schwiegerling, 2003; Yamane *et al*., 2004; Buzzonetti *et al*., 2004; Kohnen *et al*., 2005; Porter *et al*., 2006; Kirwan and O'Keefe, 2009), with the levels of spherical aberration often found to undergo the largest changes. This leads to the possibility that post-operative changes in aberrations, especially changes in spherical aberration may result in changes to the accommodative stimulus-response function. The aim of this study was therefore to investigate the effect of refractive surgery on the stimulus-response function. It was hypothesized that if higher order aberrations are capable of influencing the lag of accommodation found when viewing near targets (He *et al*., 2005; Theagarayan *et al*., 2009; Gambra *et al*., 2009) and patients undergoing refractive surgery experience (potentially large) changes in ocular aberrations, then it is likely that refractive surgery will cause alterations to the stimulus-response function. Despite the extensive number of studies that have examined the accommodative stimulus-response function there appears to be no studies that have investigated the effects of refractive surgery on the accommodative stimulus-response function. It was hoped that studying refractive surgery patients, who are likely to undergo considerable changes in aberrations over a short period of time, would provide further insight into how ocular aberrations influence the accommodative mechanism.

6.2 Subjects

A total of 31 eyes of 31 healthy pre-presbyopic adults that had chosen to undergo refractive surgery for myopia and myopic astigmatism took part in the study. The patients taking part in the study of accommodative stimulus-response functions described here were the same group that took part in the study described in Chapter 5 (see Table 5.1 for demographic characteristics).

6.3 Methods

The patients attended for three visits in total. The first visit was prior to refractive surgery to obtain baselines measurements. The two further visits occurred at one and three months post-operatively. All measurements took place in the same clinical consulting room with the same level of ambient lighting maintained throughout. At each visit monocular stimulus-response functions were measured by altering the target distance. The targets consisted of a row of high contrast black 6/9 (Snellen) letters on a white background which were presented at distances of 4.00m, 1.00m, 0.50m, 0.33m and 0.25m in a random order. The targets were constructed as described in Chapter 5 for the measurement of objective amplitude of accommodation (see section 5.3.3). The target size was adjusted for target distance to keep the angular subtense of the target constant. The test distances corresponded to accommodative stimuli over a range of 0.25D to 4.0D. The patients wore a trial frame, at a vertex distance of 10mm, containing the full distance refractive correction (if any) in front of the viewing eye and a Kodak Wratten 88a filter in front of the non-viewing eye. Patients viewed the targets with a natural pupil through an open-field Shin-Nippon SRW-5000 auto-refractor and were instructed to "*keep the letters as clear as possible at all times*". The head was stabilized with a chin and forehead rest. Each patient was familiarized with the requirements of the task and given one trial run to make sure they understood the test procedure. No attempt was made to systematically train them to produce maximal responses through practice or feedback since it was hoped that they would produce "natural" responses that reflected their accommodative performance in normal life. When the patient reported that the target was clear this was confirmed by asking the patient read out the first letter of the row and then five measurements were taken with the Shin-Nippon SRW-5000 auto-refractor. Measurements were taken through the filter in front of the non-viewing eye. The filter transmits infrared light but not visible light. This allowed measurements with the auto-refractor to be taken through the filter, while at the same time the filter acted as an occluder to ensure that the patients were still viewing the targets monocularly. Mean accommodation responses were calculated from the means of the five auto-refractor readings, with appropriate allowance for the power and vertex distance of the trial lenses worn (if any). An increase in power of the eye, corresponding to a more negative refraction, was taken as a positive response. Accommodative stimulus-response functions were plotted for each patient at each visit.

6.3.1 Data analysis

Two single-figure indices were used to characterise each stimulus-response function: its gradient and the accommodative error index (Chauhan and Charman, 1995). The error index was used in addition to the gradient because gradient values alone do not demonstrate whether the responses succeed in yielding precisely focused retinal images. Substantial leads or lags of accommodation are still possible even with a stimulus-response gradient of unity. This data analysis is described in Chapter 3 (see section 3.3.1). However, in the current study the indices were calculated over a nominal range of 1.0D to 4.0D as opposed to the 1.50D to 6.0D range used in Chapter 3.

6.3.2 Measurement of aberrations

Distance resting aberrations with a natural pupil were measured for all subjects on the same day as the accommodative stimulus-response functions were measured. The aberrations were measured using the Allegretto Wave Analyzer aberrometer (WaveLight, Erlangen, Germany). In each case measurements were taken monocularly in the same eye used for the stimulus-response function measurements with the non-viewing eye occluded. All measurements were taken in the same clinical room with the room lights turned off. For each participant the aberration measurement was taken as the mean of five readings for a 5.00mm pupil diameter.

6.3.3 Statistical tests

The main outcome measures of the study were accommodative stimulus-response function gradient and accommodative error index. Mean gradient and error index at the three study visits (pre-operatively and one and three months post-operatively) were compared using one-way repeated measures ANOVA. Pearson's product-moment correlation (r) was used to calculate the significance of correlations between each of the main outcome measures and age and pre-operative refractive error. Correlations were also investigated between the change in each of the main outcome measures and the change in spherical aberration and total higher order RMS (3^{rd}-5^{th} order) for the one month and three month post-operative visits. Results were considered significant at $p<0.05$. Statistical tests were performed using SPSS for Windows (SPSS Version 16.0, SPSS Inc, Chicago, Ill).

6.4 Results

Stimulus-response functions were plotted for each patient at each of the three visits. Figure 6.1 shows some typical data from individual patients with a range of different ages and pre-operative refractive errors. At each of the three visits the accommodative stimulus-response functions typically showed the usual form of an initial non-linear region followed by a quasi-linear region (Ciuffreda, 1991; 1998). Figure 6.2 shows the results for the mean accommodative stimulus-response functions for the whole group at each of the three study visits. The results for all five target presentation distances are shown with the gradients calculated for results over the linear region (nominal 1D to 4D stimulus range). The mean (± SD) pre-operative response-stimulus function gradient was 0.84 ± 0.17. The gradient decreased to 0.76 ± 0.17 and 0.75 ± 0.16 at the one month and three month post-operative visits respectively. One-way repeated measures ANOVA showed that the gradient altered significantly over time ($F_{2, 28}$ =6.532, p=0.003). Post-hoc testing using Bonferroni pair-wise comparisons showed that the mean gradient changed significantly at one month (p=0.037) and three months (p=0.027) post-operatively in comparison to the pre-operative gradient. There was no significant difference between the one month and the three month post-operative response-stimulus function gradients (p = 1.000).

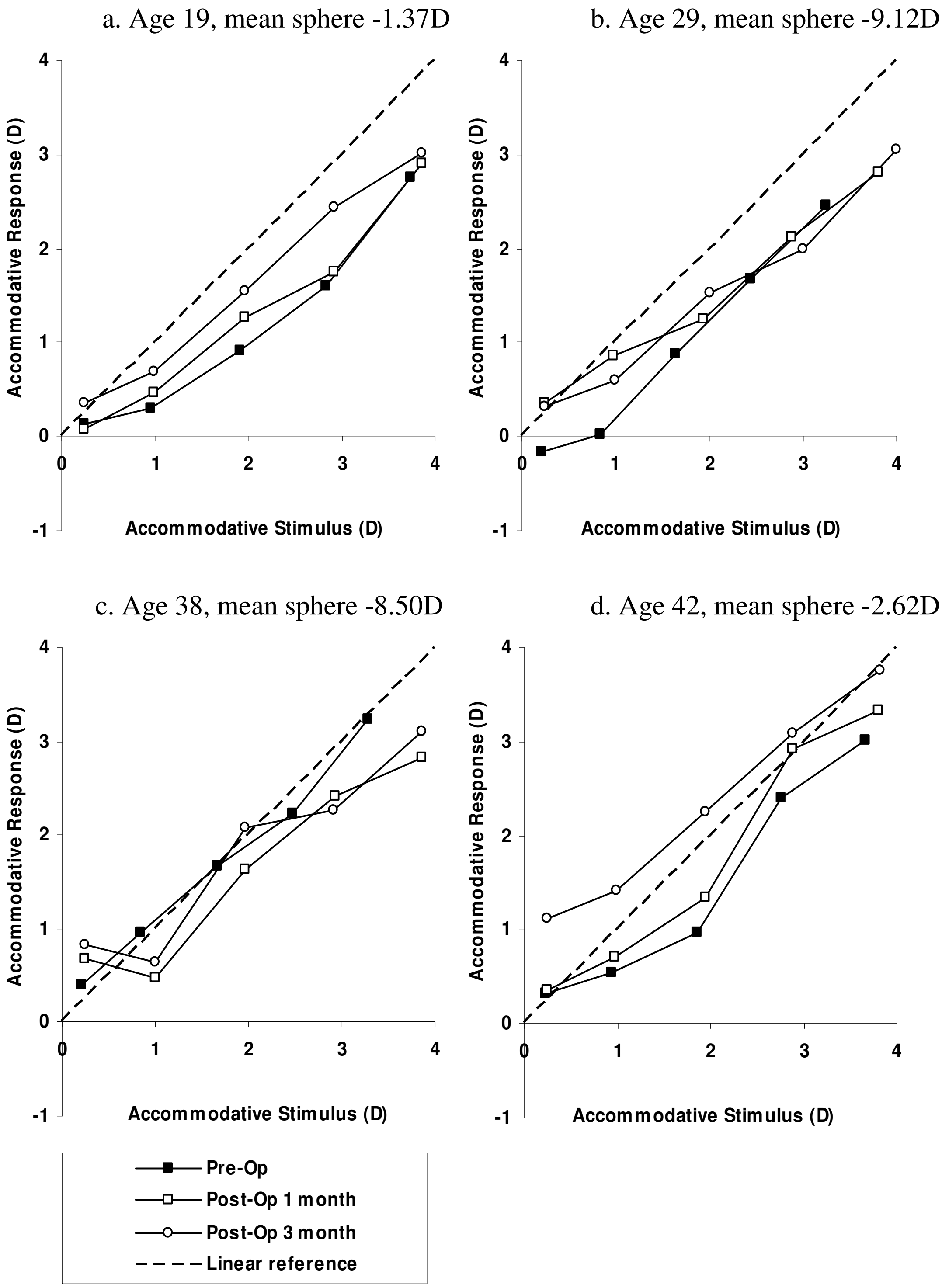


Figure 6.1: Examples of accommodative stimulus-response functions for four different patients (a-d) undergoing refractive surgery. Results are shown for measurements taken pre-operatively (solid squares) and at one month (open squares) and three months (open circles) post-operatively. The age and pre-operative mean sphere refraction are provided above each graph.

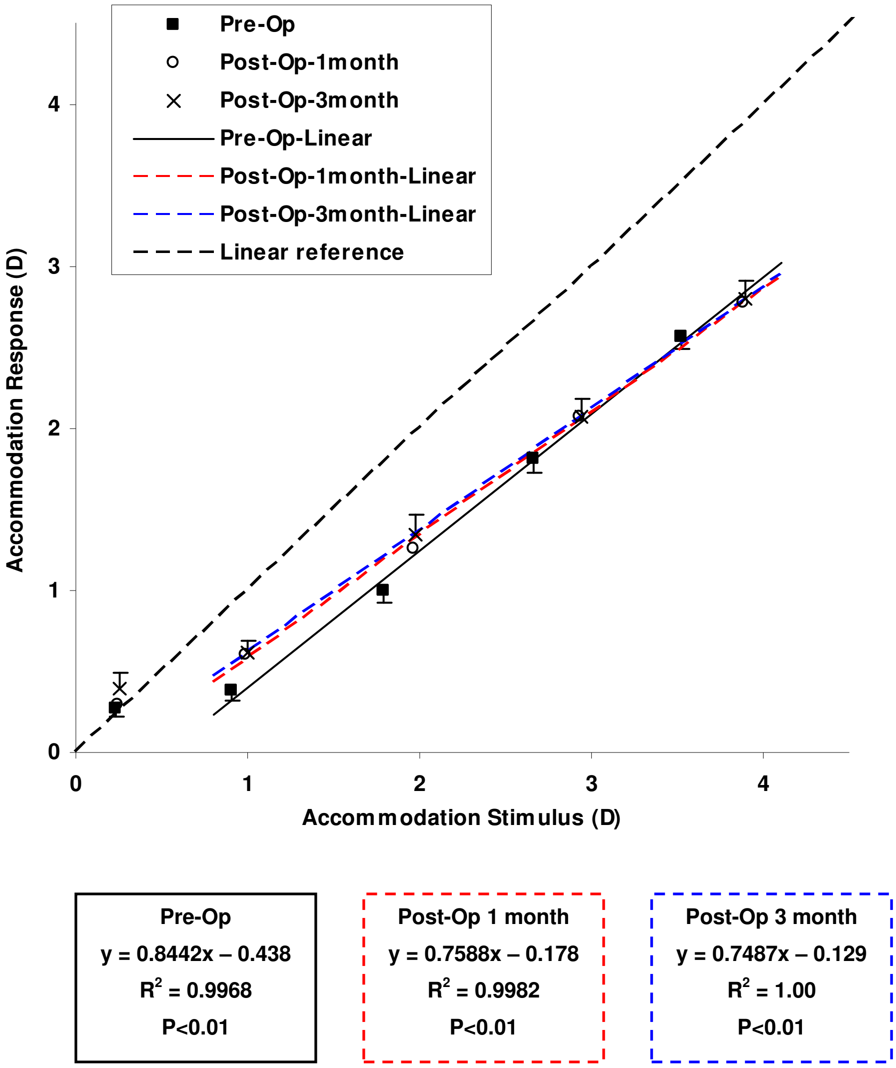


Figure 6.2: Mean accommodative response-stimulus functions using targets at varying distances for patients undergoing refractive surgery. Results are shown with linear regression lines for measurements taken pre-operatively (closed squares, solid black line, n=31 eyes) and at one month (open circles, red dashed line, n=30 eyes) and three months (crosses, blue dashed line, n=30 eyes) post-operatively. Stimuli values vary slightly between patients due to correcting lens effectivity and therefore the stimulus values are the mean values for all patients at each stimulus level. Mean stimulus values vary between visits due to the alteration in refractive error occurring following surgery and the subsequent alteration in lens effectivity correction. y-error bars indicating 1 standard error are included for two series (pre-operative and three months post-operative), for clarity they are added in one direction only.

It can be seen from Figure 6.2 that the change in mean gradient was principally caused by a decrease in lag at low accommodative response levels (below about 3D). The graph also suggests a tendency towards higher lags at higher accommodative response levels (above 3D) although the limited stimulus range makes it difficult to comment further on this.

Figure 6.3 shows the stimulus-response function gradient for each patient as a function of patient age (Figure 6.3a) and pre-operative refractive error (Figure 6.3b). No significant correlation was found between the stimulus-response function gradient and patient age pre-operatively ($r = 0.065$, $n=31$, $p=0.731$) or at one month ($r = -0.100$, $n=30$, $p=0.599$) or three months ($r = -0.239$, $n=31$, $p=0.203$) post-operatively in the present study. A possible reason for this is the limited age range of the patients taking part in the study. Pre-operatively the stimulus-response function gradient showed no significant correlation with the level of myopia present ($r = 0.212$, $n=31$, $p=0.253$). Following refractive surgery the stimulus-response function gradient showed a negative correlation with the level of pre-operative myopia. Higher levels of pre-operative myopia were associated with lower stimulus-response function gradients post-operatively. This correlation was significant at the one month post-operative visit ($r = -0.431$, $n=30$, $p=0.017$) but not at the three month post-operative visit ($r = -0.315$, $n=31$, $p=0.090$).

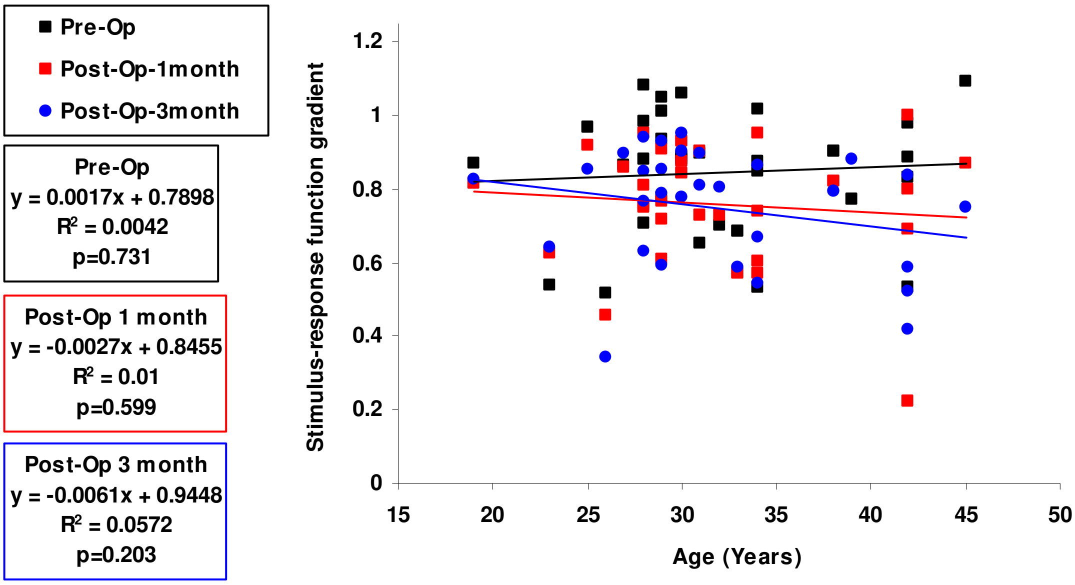
Figure 6.4 shows the change in stimulus-response function gradient as a function of the change in aberration levels that occurred after refractive surgery. Changes in gradient and aberrations that occurred at each post-operative visit were calculated relative to the pre-operative baseline. The change in gradient showed a negative correlation with the change in 4th order primary spherical aberration (Figure 6.4a). Increases in levels of change in negative spherical aberration were associated with an increase in the stimulus-response function gradient and increases in levels of change in positive spherical aberration were associated with a decrease in the change in stimulus-response function gradient. This relationship between the change in spherical aberration and change in gradient approached statistical significance at the one month post-operative visit (r = -0.327, n=30, p=0.089) and was significant at the three month post-operative visit (r = -0.558, n=31, p=0.002). This indicates that the changes in 4th order spherical aberration are likely to be linked with the decrease in stimulus-response function gradient observed following refractive surgery. The change in total higher order aberrations following surgery showed no significant correlation with the change in stimulus-response function gradient at either the one month (r = -0.004, n=30, p=0.984) or three month (r = -0.223, n=31, p=0.254) post-operative visits (Figure 6.4b). Similarly, no significant correlation was found between RMS of third or fourth order aberrations and stimulus-response function gradient at either of the post-operative study visits (data not shown).

The use of gradient alone does not necessarily succeed in demonstrating the accuracy of the accommodative response due to the fact that substantial errors of accommodation (leads or lags) are possible irrespective of the gradient. Indeed, Figure 6.1 shows that while the form of the accommodative stimulus-response functions remained similar at each visit, the results of some of the patients showed a vertical shift in the stimulus-response functions between different study visits. In Figure 6.1 this is perhaps most noticeable for patients (a) and (d). Values for accommodative error index were therefore calculated to see if this altered following refractive surgery. The mean (± SD) pre-operative error index for the group was 0.82 ± 0.38D. This showed a very slight increase to 0.85 ± 0.56D and 0.84 ± 0.56D at the one month and three month post-operative visits respectively. One-way repeated measures ANOVA showed that the mean error index did not alter significantly over time ($F_{2, 28}$ =0.096, p=0.909).

Figure 6.5 shows the error index for each patient as a function of age (Figure 6.5a) and pre-operative refractive error (Figure 6.5b) for each of the three study visits. No significant correlations were found between the error index and patient age or between the error index and pre-operative refractive error at any of the study visits.

Figure 6.6 shows the change in error index as a function of the change in aberration levels that occurred after refractive surgery. Changes in error index and aberrations that occurred at each post-operative visit were calculated relative to the pre-operative baseline. No significant correlations were found between the change in error index and the change in primary spherical aberration (Figure 6.6a) or the change in total higher order aberrations (Figure 6.6b). Similarly, no significant correlation was found between the RMS of 3^{rd} or 4^{th} order aberrations and error index at either of the post-operative study visits (data not shown).

a. Stimulus-response function gradient as a function of age



b. Stimulus-response function gradient as a function of pre-operative mean sphere

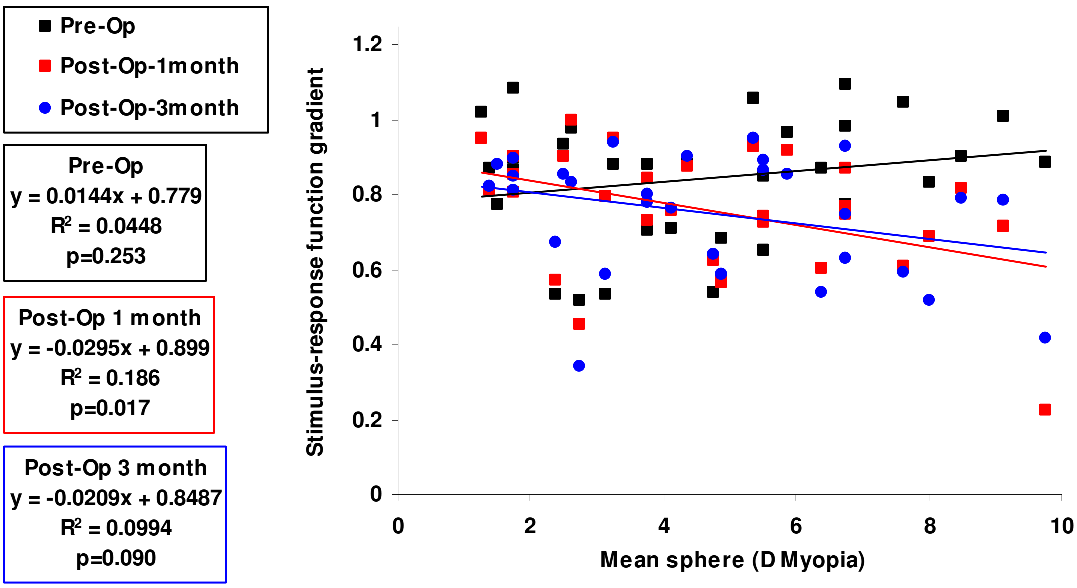
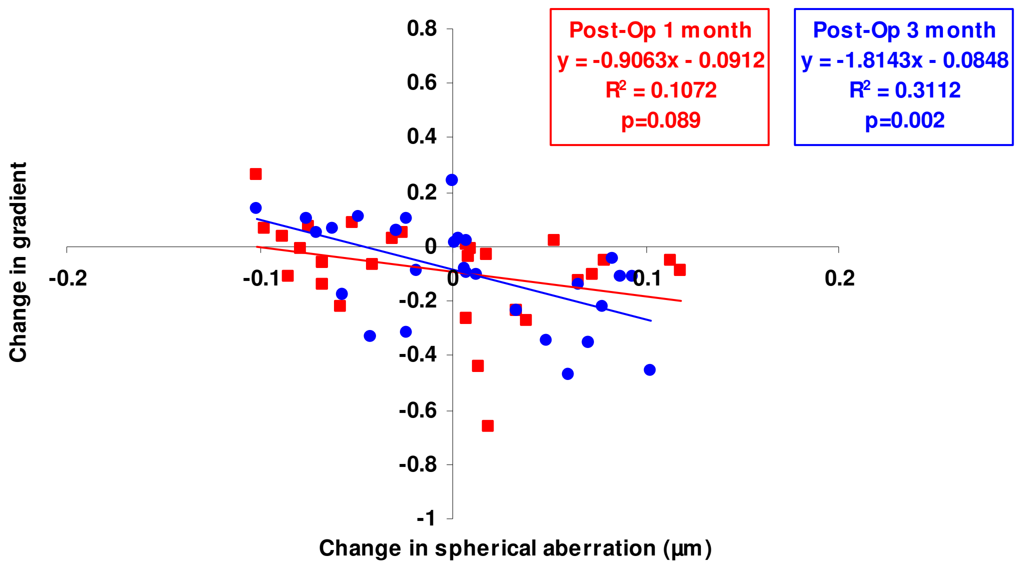


Figure 6.3: Accommodative stimulus-response function gradient as a function of age (years, graph a) and pre-operative mean sphere (D myopia, graph b) for patients undergoing refractive surgery. Results are presented with linear regression line, equation and R^2 value for measurements taken pre-operatively (closed black squares, black line, black outlined box) and post-operatively at one month (closed red squares, red line, red outlined box) and three months (closed blue circles, blue line, blue outlined box).

a. Spherical aberration



b. Total higher order aberration (RMS 3rd-5th order)

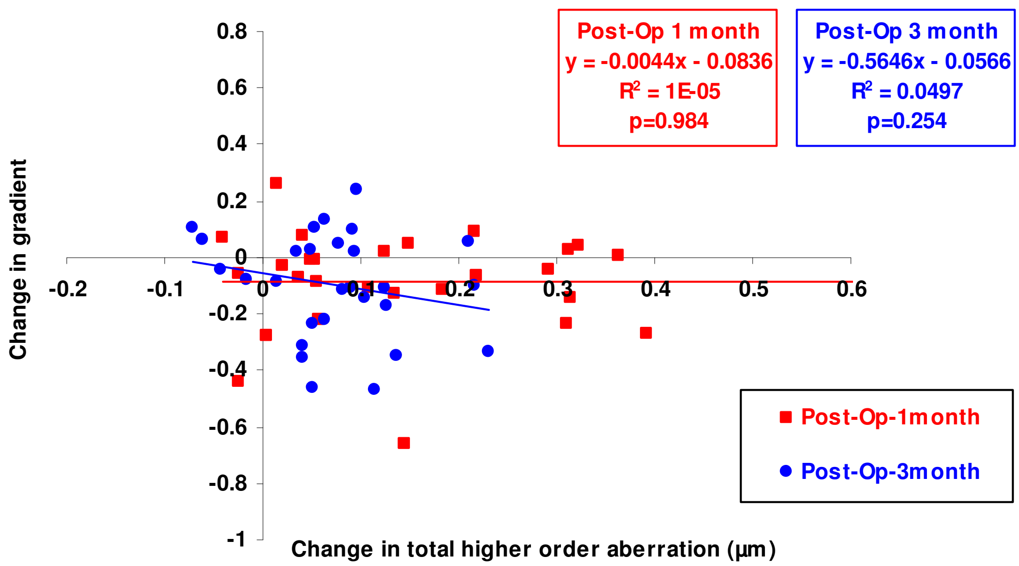
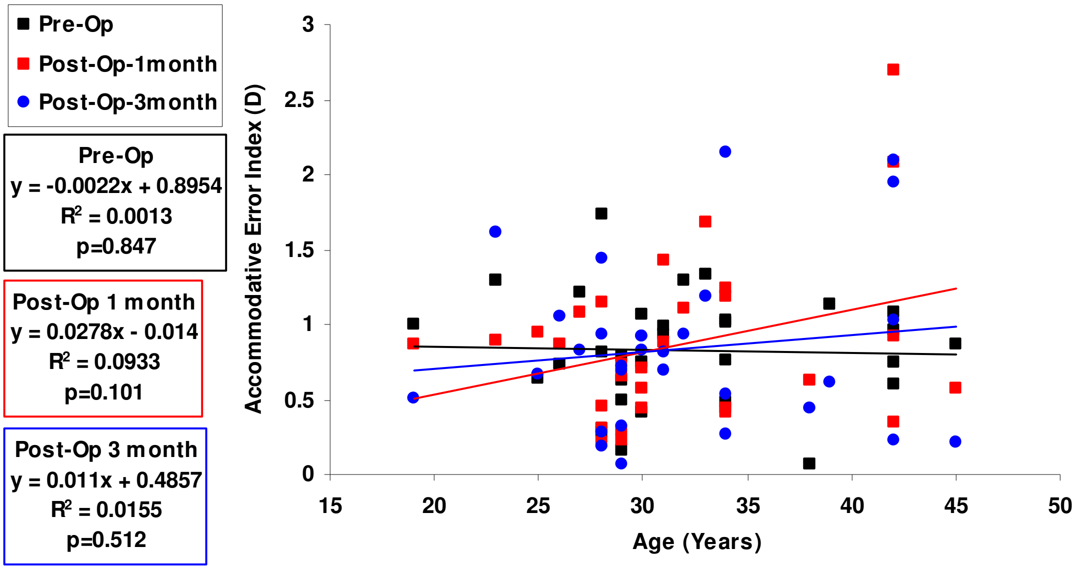


Figure 6.4: Change in accommodative stimulus-response function gradient as a function of change in aberration levels (µm) for patients undergoing refractive surgery. Results are shown with linear regression lines, equation and R^2 value for measurements at one month (red squares, red line, red outlined box) and three months (blue circles, blue line, blue outlined box) post-operatively in comparison to pre-operative measurements. Aberrations are shown for a 5.00mm natural pupil for primary spherical aberration (graph a) and total higher order aberration (RMS 3rd-5th order, graph b).

a. Accommodative error index as a function of age



b. Accommodative error index as a function of pre-operative mean sphere

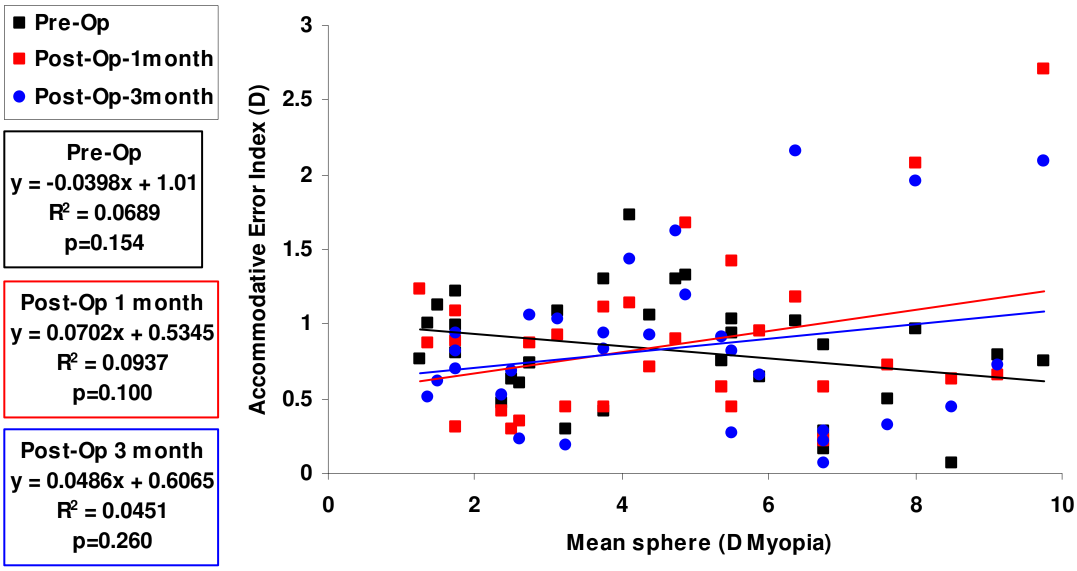
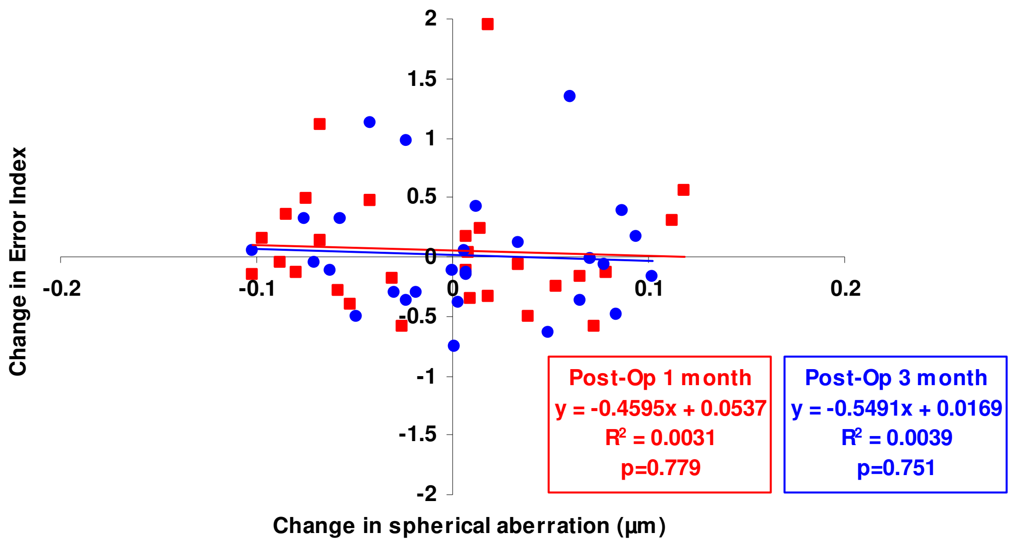


Figure 6.5: Accommodative error index (D) as a function of age (years, graph a) and pre-operative mean sphere (D myopia, graph b) for patients undergoing refractive surgery. Results are presented with linear regression line, equation and R^2 value for measurements taken pre-operatively (black squares, black line, black outlined box) and post-operatively at one month (red squares, red line, red outlined box) and three months (blue circles, blue line, blue outlined box).

a. Spherical aberration



b. Total higher order aberration (RMS 3rd-5th order)

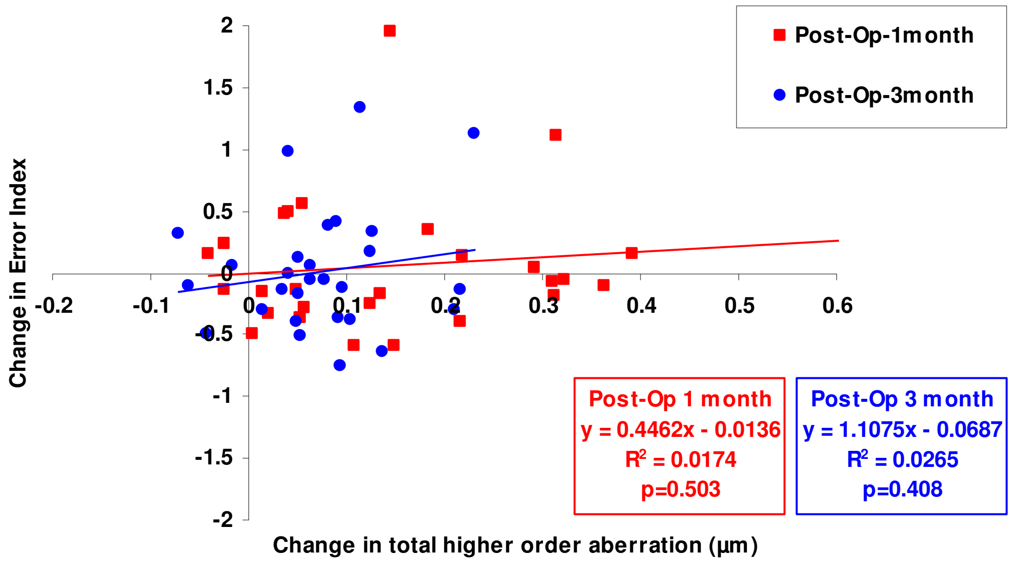


Figure 6.6: Change in accommodative error index (D) as a function of change in aberration levels (µm) for patients undergoing refractive surgery. Results are shown with linear regression lines, equation and R^2 value for measurements at one month (red squares, red line, red outlined box) and three months (blue circles, blue line, blue outlined box) post-operatively in comparison to pre-operative measurements. Aberrations are shown for a 5.00mm natural pupil for primary spherical aberration (graph a) and total higher order aberration (RMS 3rd-5th order, graph b).

6.5 Discussion

Prior to refractive surgery the patients recruited to the study typically showed stimulus-response function gradients between 0.6 and 1.0 (Figure 6.3). These gradients are consistent with the results of previous research (Ward and Charman, 1985; Gwaizda *et al*., 1993; Abbott *et al*., 1998). In agreement with previous studies, the stimulus-response function gradients were found to be relatively stable over the (pre-presbyopic) age range tested (Ramsdale and Charman, 1989; Mordi and Ciuffreda, 1998; Kalsi *et al*., 2001). Before surgery the gradients also showed little variation with the pre-operative refractive error. A possible reason for this is the homogeneous nature of the patients (all stable myopes). The patients underwent considerable changes in ocular aberration following refractive surgery. The majority of patients experienced increases in total higher order RMS, although a small number showed a decrease due to the wavefront guided nature of their refractive surgery procedure. Total higher order RMS increases typically ranged from 0.05-0.20µm, although were as high as 0.35-0.40µm for some individuals over the pupil diameter measured (see Figures 6.4 and 6.6). As expected the majority of the change in aberrations occurred for 3rd and 4th order aberrations, with changes in spherical aberration ranging between ±0.10µm (Figures 6.4 and 6.6). These changes in aberrations were broadly in line with those expected from previous studies (Oshika *et al*., 1999; Marcos, 2001; Marcos *et al*., 2001; Moreno-Barriuso *et al*., 2001; Straub and Schwiegerling, 2003; Yamane *et al*., 2004; Kohnen *et al*., 2005; Kirwan and O'Keefe, 2009). The main aim of the present study was to investigate the impact of refractive surgery on the accommodative stimulus-response function. It has been shown that variations in higher order aberrations can influence lag of accommodation (He *et al*., 2005; Theagarayan *et al*., 2009; Gambra *et al*., 2009). It was therefore hypothesized that the alteration in aberrations following refractive surgery would alter the lag of accommodation to near targets. The main finding of the present study is highlighted in Figure 6.2. Mean (± SD) stimulus-response function gradient decreased from 0.84 ± 0.17 pre-operatively, to 0.76 ± 0.17 and 0.75 ± 0.16 at the one and three month post-operative visits respectively. The decrease in stimulus-response gradient was apparent at one month post-operatively and maintained at the three month post-operative visit. Accommodative error indices were also evaluated pre-operatively and post-operatively. Error indices take in to account vertical and horizontal translations of the stimulus-response function as well as the goodness of fit of the data points to the regression line (Chauhan and Charman, 1995). Error indices were generally found to be around 1.00D or below, which were comparable to those found in the study in Chapter 3. The mean error index did not alter significantly following refractive surgery, suggesting that the alteration in accommodative function was specific to stimulus-response function gradient.

An additional aim of the present study was to investigate whether alterations to the stimulus-response function could be explained by alterations to the levels of higher order aberration following refractive surgery. Figure 6.4a shows that the change in gradient showed a significant negative correlation with the change in spherical aberration. An increase in negative spherical aberration following surgery tended to be associated with an increase in the stimulus-response function gradient, and an increase in positive spherical aberration following refractive surgery tended to be associated with a decrease in the stimulus-response function gradient. No significant correlation was found between change in stimulus-response function gradient and change in total higher order RMS aberration. The results therefore appeared to be specific to spherical aberration and sensitive to the sign of the spherical aberration (positive or negative). This finding is in agreement with previous studies that have altered spherical aberration using adaptive optics (Gambra *et al.*, 2009) and using custom-made contact lenses with different levels of spherical aberration (Allen *et al.*, 2009; Theagarayan *et al.*, 2009).

No patients in the present study reported any difficulties during the measurement of the accommodative stimulus-response functions. They all appeared able to focus clearly on the targets at each viewing distance. However, there is evidence of patients reporting symptoms related to difficulty with close work following refractive surgery (Kim *et al.*, 2009). Kim *et al.* (2009) found that in a group of 29 patients (aged 30.5 ± 7.9 years) reporting visual difficulty after refractive surgery, 72.4% of them described symptoms related to difficulty with near vision tasks (before refractive surgery all patients were asymptomatic). In approximately 30% of these patients the authors attributed these symptoms to high lags of accommodation while viewing a near target at 40cm. In the remainder the symptoms were attributed to binocular vision anomalies. It is possible that patients experiencing larger changes in aberrations (than those found in the present study) would experience greater changes in their accommodative stimulus-response functions. This suggests the prospect that alteration to higher order aberrations following surgery may be a contributory factor in those reporting post-operative difficulties with close work.

There is some evidence that manipulation of higher order aberrations (spherical aberration using contact lenses) can improve visual function (Rae *et al*., 2009). In contrast, Artal *et al*. (2004) showed that stimuli viewed with an individual's own (natural) aberrations always appeared sharper than when the stimuli were viewed through an altered (rotated) version of their natural aberrations (n=5 subjects). The authors suggested that the brain adapts to the eye's own aberrations, and somehow removes or ignores the effects of blur generated by the sensory mechanism so that image quality is maximized and images appear clear. They also speculated that optimizing the eye's optical quality through wavefront-guided refractive surgery may not be as beneficial as expected if the brain is adapted to the pre-operative levels of aberration, and that a period of adaptation to the new levels of aberration may be required. In the present study, stimulus-response functions were measured at two post-operative time intervals. It was therefore possible to investigate whether adaptation to the new levels of aberration (assuming adaptation can and does occur) might influence the accommodative response. Given that the accommodative stimulus-response gradient showed no significant change between the one month and three month post-operative visits, this study provided no evidence of adaptation of the accommodative response during the three month follow-up period. This is in general agreement with several previous studies that have shown no evidence of adaptation to monochromatic aberrations over shorter periods of up to five minutes using adaptive optics (Artal *et al*., 2004) and up to an hour using custom-made contact lenses (Theagarayan *et al*., 2009). It is therefore possible that the changes to the accommodative response may be permanent.

In conclusion, accommodative stimulus-response gradient reduced significantly following refractive surgery and the change in gradient was found to be significantly correlated with the change in spherical aberration at three months post-operatively. An increase in positive spherical aberration led to a decrease in the accommodative response and an increase in negative spherical aberration led to an improvement in the accommodative response. These results are consistent with those found by studies that have used contact lenses (Theagarayan *et al*., 2009) and adaptive optics (Gambra *et al*., 2009) to alter spherical aberration and investigate the influence on the accommodative response.

CHAPTER 7
ACCOMMODATIVE FACILITY

7.1 Introduction

Accommodative facility is frequently included as part of the assessment of the accommodative mechanism and provides a measure of the eye's ability to focus on a sequence of stimuli at various distances or vergences in a given period of time. Accommodative facility test results can be a useful indicator of accommodative dysfunction (Levine *et al*., 1985) and can be used to aid the diagnosis of accommodative insufficiency (Hennessey *et al*., 1984).

A number of studies have suggested that higher order monochromatic aberrations may play an important role in controlling the accommodative mechanism (Wilson *et al*., 2002; Chen *et al*., 2006). In particular, it has been shown that alteration of higher order aberrations may be capable of influencing the latency (Chin *et al*., 2009), velocity (Fernandez and Artal, 2005) and accuracy of the accommodative response (Theagarayan *et al*., 2009; Gambra *et al*., 2009).

Many studies have reported that patients undergoing refractive surgery tend to experience an increase in higher order aberrations. If it is the case that aberrations can influence components of the accommodation response, and patients undergoing refractive surgery undergo substantial changes in their ocular aberrations, then it is reasonable to assume that patients undergoing refractive surgery will exhibit changes in their ability to focus rapidly on objects placed at different distances or vergences from the eye. The aim of this study was therefore to investigate the effect of refractive surgery on accommodative facility. It was thought that changes in ocular higher order aberrations due to refractive surgery would alter accommodative facility. Despite the extensive number of studies that have examined accommodative facility there appears to be no studies that have specifically investigated the effects of refractive surgery on accommodative facility. It was hoped that studying refractive surgery patients, who are likely to undergo considerable changes in aberrations over a short period of time, would provide further insight into how ocular aberrations influence the accommodative mechanism.

7.2 Subjects

The patients taking part in the study were the same group that took part in the studies described in Chapters 5 and 6 (see Table 5.1 for demographic characteristics).

7.3 Methods

The patients attended for three visits in total. The first visit was prior to refractive surgery to obtain baseline measurements. The two further visits occurred at one and three months post-operatively. At each visit monocular accommodative facility was measured at distance (4.0m) and at near (0.40m) in the same clinical room with the room lights on. The subjects wore a trial frame, at a vertex distance of 10mm, containing the full distance refractive correction (if any) in front of the tested eye and an occluder placed in front of the non-tested eye. The procedures used for measuring accommodative facility in this study are very similar to methods previously described in many studies of accommodative facility (e.g. Zellers *et al*., 1984; Allen and O'Leary, 2006). Distance accommodative facility was measured using a “plano/-2.00D” lens combination mounted in a flipper (ordered from Paul Adler Optometrists, Stotfold, Herts, and confirmed by focimetry on delivery). The patients viewed a row of high contrast black 6/9 letters on a white background at a distance of 4.0m. Patients were instructed to “*look at the letters and try to keep them in focus all the time. I am going to put a lens in front of your eye which will cause the letters to blur. When this happens you will need to re-focus on the letters to keep them clear. When they are clear, please say “clear”. I will then remove the lens which will cause the letters to blur once more. You will then need to re-focus again to keep the letter clear. When they are clear, please say “clear”. I will go on repeating this procedure to see how many times you can clear the letters in 1 minute*”. Patients were given 20 seconds of practice prior to the actual test to make sure they understood the test procedure. Distance accommodative facility measurements always started with the introduction of the -2.00D lens. Near accommodative facility was measured using a “+2.00D/-2.00D” lens combination mounted in a flipper (ordered from Paul Adler, Stotfold, Herts, and confirmed by focimetry on delivery). The patients viewed a row of high contrast black 6/9 letters on a white background mounted on a stand at a viewing distance of 0.40m. The patients were given instructions very similar to those for the distance facility procedure except this time the two lenses that were interchanged were ±2.00D instead of the “plano/-2.00D” used for the distance measurements. Patients were again given 20 seconds practice prior to the actual measurements to make sure that they understood the test procedure. Near facility testing always began with the +2.00D lens. The distance and near facility responses over a one minute period were recorded for each patient at each visit using a digital voice recorder (Olympus WS-210S). These recordings were used for subsequent data analysis.

7.3.1 Measurement of aberrations

Distance resting aberrations with a natural pupil were measured for all subjects on the same day as the accommodative facility measurements. The aberrations were measured using the Allegretto Wave Analyzer aberrometer (WaveLight, Erlangen, Germany). In each case measurements were taken monocularly in the same eye used for the accommodative facility measurements with the non-tested eye occluded. All measurements were taken in the same clinical room with the room lights turned off. For each participant the aberration measurement was taken as the mean of five readings for a 5.00mm pupil diameter.

7.3.2 Data analysis

The digital voice recorder was connected to a desktop computer which saved the facility recordings as media files. This created a total of 186 media data files. Each of these recordings was then examined using a 1/100th stopwatch program on the computer. From the recordings, measurements were obtained for overall distance and near facility rates (cycles/min). One complete cycle indicates that the letter targets seen through both the "+2.00D and -2.00D" lenses or both the "plano and -2.00D" lenses were cleared. Positive response time (PRT) and negative response time (NRT) were calculated for both distance and near facility responses. The PRT describes the time taken for "distance-to-near" accommodation (i.e. through the negative lenses).

The NRT describes the time taken for the disaccommodation “near-to-far” response (i.e. time taken to relax accommodation through the positive lens at near or no lens at distance).

The main outcome measures were distance and near accommodative facility rate. PRT and NRT were calculated for each of the main outcome measures. Each of the components of accommodative facility (overall rate, PRT and NRT) were compared across the three study visits using one-way repeated measures ANOVA. Pearson’s product-moment correlation (r) was used to calculate the significance of correlations between the distance and near facility rate and patient age. Correlations were also investigated between the change in each of the components of accommodative facility and the change in higher order aberrations for the one month and three month post-operative visits. Results were considered significant at $p<0.05$. Statistical tests were performed using SPSS for Windows (SPSS Version 16.0, SPSS Inc, Chicago, Ill).

7.4 Results

Figure 7.1 shows the results for the distance and near accommodative facility rates at each of the three study visits. The mean (± SD) pre-operative distance facility rate for the group was 15.75 ± 4.85 cycles/min. This increased to 16.55 ± 5.28 cycles/min and 18.55 ± 5.04 cycles/min at the one month and three month post-operative visits respectively. One-way repeated measures ANOVA showed that the mean distance facility rate altered significantly over time ($F_{2, 28} = 6.287$, $p=0.003$). Post-hoc testing using Bonferroni pair-wise comparisons showed that the mean distance facility did not change significantly at one month post-operatively (p=1.000) but did change significantly at three months post-operatively (p=0.008) in comparison to pre-operative distance facility levels. The difference between the one and three month post-operative distance facility rates was also statistically significant (p=0.032). As expected, the near facility rate was found to be lower than the distance facility rate. The near facility rate remained relatively stable throughout the three study visits. The mean (± SD) pre-operative near facility rate for the group was 9.78 ± 4.80 cycles/min. The near facility rate was subsequently 9.83 ± 4.47 cycles/min and 9.60 ± 4.86 cycles/min at the one month and three month post-operative visits respectively. One-way repeated measures ANOVA showed that the mean near facility rate did not alter significantly over the three visits ($F_{2, 28} = 0.056$, p=0.946).

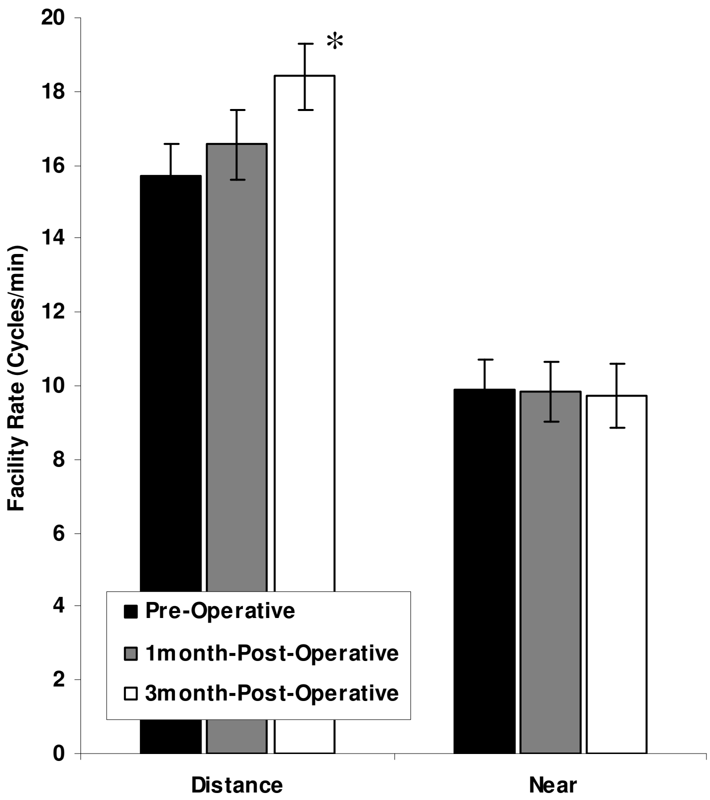


Figure 7.1: Mean (± SEM) distance and near facility rate for patients undergoing refractive surgery. Results are presented pre-operatively (black bars, n = 31 eyes) and post-operatively at one month (grey bars, n = 30 eyes) and three months (white bars, n = 31 eyes). *Significantly different to pre-operative measurement (p<0.05).

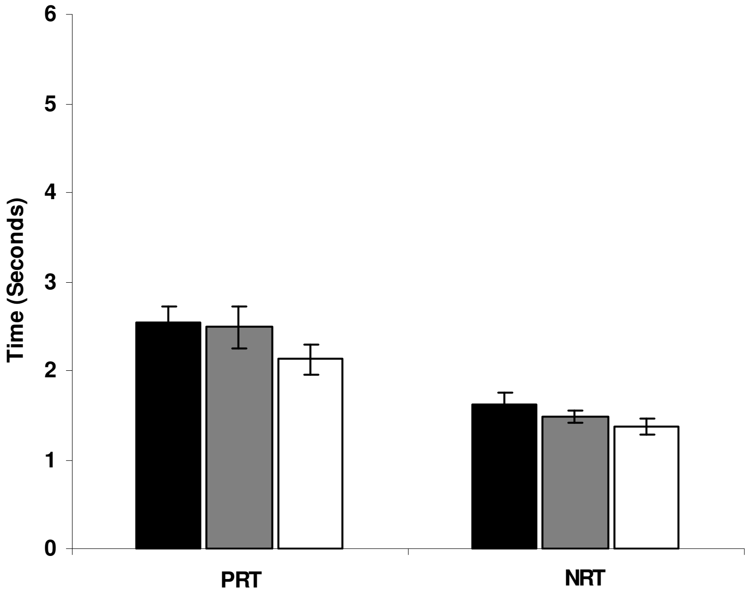
Figure 7.2 shows the results for the positive accommodation response time (PRT) and negative accommodation response time (NRT) for both distance facility (Figure 7.2a) and near facility (Figure 7.2b) at each of the three study visits. The distance facility results (Figure 7.2a) show that both the PRT and the NRT decreased with each study visit. As expected, the negative response time were more rapid than the positive response times indicating that it took patients longer to focus from distance to near, than from near to distance. The measurements of NRT were also found to be less variable than the measurements of PRT. The mean (± SD) pre-operative distance

PRT for the group was 2.53 ± 1.01 seconds. This decreased to 2.49 ± 1.26 seconds and 2.10 ± 0.92 seconds at the one month and three month post-operative visits respectively. One-way repeated measures ANOVA showed that the mean distance PRT did not alter significantly over time ($F_{2, 28}$ = 2.776, p=0.071). The mean (± SD) pre-operative distance NRT for the group was 1.64 ± 0.69 seconds. This decreased to 1.49 ± 0.37 seconds and 1.39 ± 0.49 seconds at the one month and three month post-operative visits respectively. One-way repeated measures ANOVA showed that the mean distance NRT did not alter significantly over time ($F_{2, 28}$ =2.685, p=0.077). Despite neither the distance PRT nor the distance NRT showing a statistically significant decrease between study visits, it is clear that the modest reductions in both the PRT and the NRT contributed to the significant alteration in the overall distance facility rate (see Figure 7.1). The near facility results (Figure 7.2b) show that the PRT decreased with each study visit, while the NRT increased with each study visit. The measurements of near PRT and NRT were found to be much more variable than the measurements of distance PRT and NRT. The mean (± SD) pre-operative near PRT for the group was 3.69 ± 2.39 seconds. This decreased to 3.58 ± 2.78 seconds and 2.94 ± 2.08 seconds at the one month and three month post-operative visits respectively. One-way repeated measures ANOVA showed that the mean near PRT did not alter significantly over time ($F_{2, 28}$ = 1.137, p=0.328). The mean (± SD) pre-operative near NRT for the group was 3.99 ± 2.65 seconds. This increased to 4.22 ± 3.14 seconds and 4.81 ± 3.74 seconds at the one month and three month post-operative visits respectively. One-way repeated measures ANOVA showed that the mean near NRT did not alter significantly over time ($F_{2, 28}$ = 1.221, p=0.302). It is interesting to note that the decrease in near PRT combined with the increase in near NRT contributed to an overall stable near facility rate (see Figure 7.1).

As accommodative facility rate is dependent on the patient's age, correlation between accommodative facility rate and patient age was assessed for distance and near at each study visit. The results are shown in Figure 7.3. The distance facility rate showed a negative correlation with increasing age at each study visit (Figure 7.3a). The relationship between distance facility rate and patient age was significant at the pre-operative visit (r = -0.333, n=31, p=0.034) but did not reach statistical significance at the one month (r = -0.300, n=30, p=0.054) or the three month (r = -0.236, n=31, p=0.100) post-operative visits. No significant correlation was found between near accommodative facility and patient age at any of the study visits (Figure 7.3b).

Tables 7.1 and 7.2 show the results for the correlation between the change in accommodative facility and the change in aberration levels that occurred after refractive surgery. Changes in facility rate, PRT, NRT and aberration levels at each post-operative visit were calculated relative to the pre-operative baseline. The results are shown for the components of distance facility in Table 7.1 and near facility in Table 7.2. No significant correlations were found between the change in facility rate, PRT or NRT and the change in spherical, RMS 3rd order, RMS 4th order or RMS total higher order aberrations for distance or near facility at either of the post-operative visits.

a. Distance facility



b. Near facility

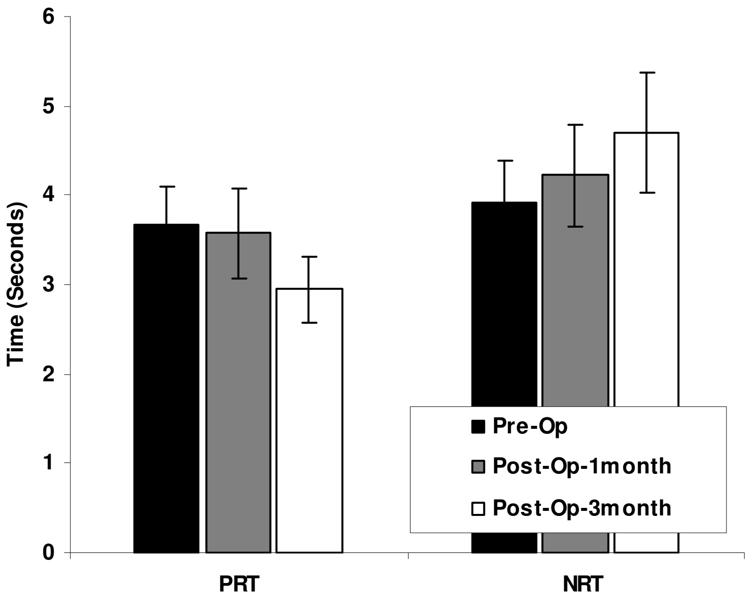
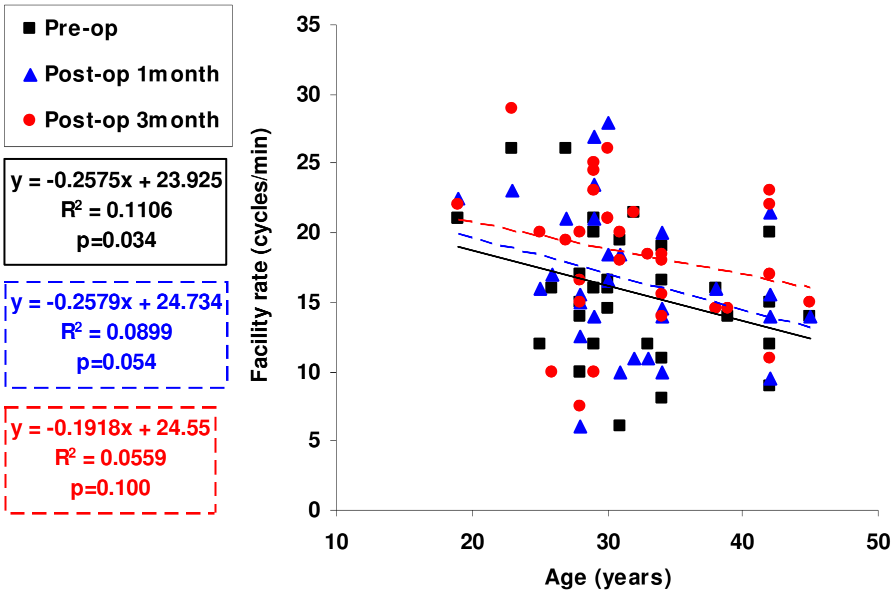


Figure 7.2: Mean (± SEM) positive accommodation response time (PRT) and negative accommodation response time (NRT) for patients undergoing refractive surgery. Results are presented pre-operatively (black bars, n = 31 eyes) and post-operatively at one month (grey bars, n = 30 eyes) and three months (white bars, n = 31 eyes) for both distance facility (graph a) and near facility (graph b).

a. Distance facility



b. Near facility

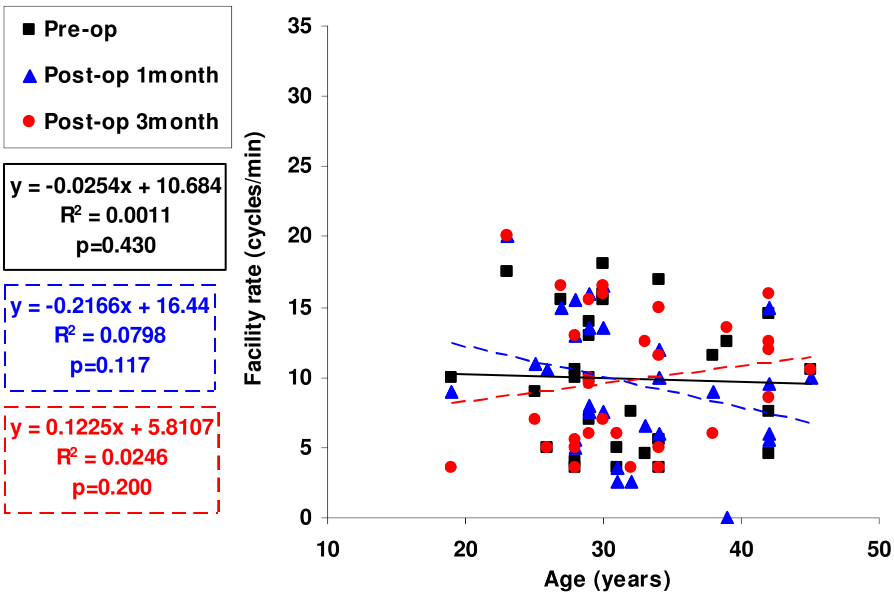


Figure 7.3: Accommodative facility rate (cycles/min) as a function of age (years) for patients undergoing refractive surgery. Results are shown for distance facility (graph a) and near facility (graph b) with linear regression line, equation and R^2 value for measurements taken pre-operatively (closed black squares, solid black line, black outlined box) and post-operatively at one month (solid blue triangles, blue dashed line, blue dashed outlined box) and three months (solid red circles, red dashed line, red dashed outlined box).

DISTANCE FACILITY	**Aberration**	**Regression equation**	**Correlation (r)**	**R^2**	**p-value**
Facility rate *1 month post-op*	Spherical	y = 10.547x + 0.7765	0.1425	0.0203	0.469
	RMS 3rd order	y = -1.1375x + 0.8341	-0.0316	0.001	0.871
	RMS 4th order	y = -0.1655x + 0.7095	-0.0032	0.00001	0.985
	RMS higher order	y = 0.1078x + 0.6793	0.0032	0.00001	0.985
Facility rate *3 month post-op*	Spherical	y = 16.167x + 2.6303	0.2045	0.0418	0.287
	RMS 3rd order	y = 12.446x + 1.9146	0.2117	0.0448	0.270
	RMS 4th order	y = -18.33x + 3.2041	-0.1892	0.0358	0.326
	RMS higher order	y = 10.183x + 1.9902	0.1649	0.0272	0.392
PRT *1 month post-op*	Spherical	y = 0.8664x – 0.0418	0.0480	0.0023	0.809
	RMS 3rd order	y = -0.7122x + 0.0378	-0.0819	0.0067	0.679
	RMS 4th order	y = -1.8095x + 0.0941	-0.1625	0.0264	0.409
	RMS higher order	y = -1.0618x + 0.1201	-0.1432	0.0205	0.467
PRT *3 month post-op*	Spherical	y = -1.5887x – 0.4338	-0.0872	0.0076	0.654
	RMS 3rd order	y = -3.1152x – 0.2431	-0.2293	0.0526	0.231
	RMS 4th order	y = 5.7196x – 0.5965	0.2553	0.0652	0.181
	RMS higher order	y = -2.2503x – 0.283	-0.1578	0.0249	0.414
NRT *1 month post-op*	Spherical	y = 0.2501x – 0.1191	0.0245	0.0006	0.899
	RMS 3rd order	y = 0.0309x – 0.1248	0.0063	0.00004	0.974
	RMS 4th order	y = 0.5431x – 0.1638	0.0889	0.0079	0.653
	RMS higher order	y = 0.1171x – 0.1396	0.0283	0.0008	0.884
NRT *3 month post-op*	Spherical	y = -0.5576x – 0.2292	-0.0447	0.002	0.820
	RMS 3rd order	y = -1.8978x – 0.1111	-0.2027	0.0411	0.292
	RMS 4th order	y = 3.7684x – 0.3341	0.2441	0.0596	0.202
	RMS higher order	y = -1.2745x – 0.1422	-0.1296	0.0168	0.502

Table 7.1: Correlation between the change in the distance facility rate, PRT, and NRT and the change in the aberration levels for patients undergoing refractive surgery. Results are shown for the linear regression equation, correlation coefficient (r), R^2 value and p-value for post-operative measurements at one month and three months in comparison to pre-operative baseline. Aberrations were measured for a 5.00mm natural pupil diameter for primary spherical aberration, RMS 3rd order, RMS 4th order and RMS total higher order aberrations (3rd-5th order).

NEAR FACILITY	Aberration	Regression equation	Correlation (r)	R^2	p-value
Facility rate	Spherical	y = -0.6772x + 0.0484	-0.0100	0.0001	0.960
1 month	RMS 3^{rd} order	y = 0.2693x + 0.021	0.0084	0.00007	0.967
post-op	RMS 4^{th} order	y = -8.0163x + 0.685	-0.1929	0.0372	0.326
	RMS higher order	y = -1.4123x + 0.2777	-0.0510	0.0026	0.796
Facility rate	Spherical	y = -18.251x – 0.0859	-0.2528	0.0639	0.186
3 month	RMS 3^{rd} order	y = 12.016x – 0.9373	0.2238	0.0501	0.243
post-op	RMS 4^{th} order	y = 2.3902x – 0.2373	0.0265	0.0007	0.889
	RMS higher order	y = 13.249x –1.1049	0.2352	0.0553	0.220
PRT	Spherical	y = -5.966x – 0.1837	-0.1323	0.0175	0.502
1 month	RMS 3^{rd} order	y = -0.2443x – 0.1088	-0.0100	0.0001	0.954
post-op	RMS 4^{th} order	y = 0.5995x – 0.1856	0.0224	0.0005	0.913
	RMS higher order	y = -0.326x – 0.0866	-0.0173	0.0003	0.929
PRT	Spherical	y = -3.9605x – 0.6455	-0.0854	0.0073	0.658
3 month	RMS 3^{rd} order	y = -9.1532x – 0.0817	-0.2663	0.0709	0.163
post-op	RMS 4^{th} order	y = 13.877x – 1.0407	0.2449	0.0600	0.200
	RMS higher order	y = -6.7918x – 0.1863	-0.1884	0.0355	0.328
NRT	Spherical	y = -3.1524x + 0.2597	-0.0678	0.0046	0.731
1 month	RMS 3^{rd} order	y = 2.3524x – 0.0012	0.1058	0.0112	0.591
post-op	RMS 4^{th} order	y = -3.0263x + 0.522	-0.1140	0.0113	0.590
	RMS higher order	y = 0.6482x + 0.1808	0.0346	0.0012	0.863
NRT	Spherical	y = 6.8479x + 0.7177	0.1175	0.0138	0.544
3 month	RMS 3^{rd} order	y = -12.803x + 1.5651	-0.2951	0.0871	0.120
post-op	RMS 4^{th} order	y = -19.629x + 1.2826	-0.2746	0.0754	0.149
	RMS higher order	y = -16.274x + 1.8955	-0.3575	0.1278	0.057

Table 7.2: Correlation between the change in the near facility rate, PRT, and NRT and the change in the aberration levels for patients undergoing refractive surgery. Results are shown for the linear regression equation, correlation coefficient (r), R^2 value and p-value for post-operative measurements at one month and three months in comparison to pre-operative baseline. Aberrations were measured for a 5.00mm natural pupil diameter for primary spherical aberration, RMS 3^{rd} order, RMS 4^{th} order and RMS total higher order aberrations (3^{rd}-5^{th} order).

7.5 Discussion

The pre-operative measurements for facility rate and the components of facility (PRT and NRT) in the present study were broadly consistent with those found in previous investigations of accommodative facility (Zellers *et al*., 1984; Allen and O'Leary, 2006; Radhakrishnan *et al*., 2007).

The main findings of the present study were that overall distance facility rate appeared to increase (improve) following surgery (significant difference at three months post-operatively relative to pre-operatively) and that the near facility rate showed no significant change following refractive surgery. The change in distance facility rate occurred due to a combination of decreases in both the positive and negative distance response times. Despite no alteration in the overall near facility rate following refractive surgery, it was found that patients tended to exhibit faster near PRT and slower near NRT after refractive surgery relative to pre-operative measurements. However, these differences did not reach statistical significance. A general observation while conducting the measurements was that the patients often commented on how difficult it was to relax accommodation to the near target (through the +2.00D lens). This was particularly true post-operatively. Similar findings were reported by Radhakrishnan *et al*. (2007), who found that myopes exhibited relatively slow disaccommodation responses during near accommodative facility testing. This is thought to occur due to the difficulty faced by the patient in focusing on a target in the presence of opposing accommodative cues. Knowledge of the target's physical distance presents a strong proximal cue, which is in conflict with the vergence cue provided by the positive lens, making it more difficult to accommodate appropriately. The somewhat unnatural nature of this task may mean that difficulty with this task has little relevance to how an individual's disaccommodation response would react in the real world, which is potentially rich in other (more realistic) accommodative cues.

It has been shown that training can improve accommodative facility rates (Allen *et al.*, 2010). None of the subjects underwent facility training during the present study. It could be argued that the improvement in distance facility rate at three months post-operatively was due to the patients having received more practice with the technique. This is unlikely as there was a gap of two months between the three month post-operative measurements and the previous facility measurements, and there was also no improvement in the near accommodative facility rate. Hence the increase in distance facility rate is more likely to be caused by changes in the eye following refractive surgery. However, the improvement in facility rate was in the order of 2-3 cycles/minute which is likely to be of limited clinical significance.

It is worth mentioning that the accommodative facility task itself will alter (slightly) between the pre-operative and post-operative measurements due to the change in refractive error caused by the surgery. Pre-operatively the facility measurements were taken through the patient's distance refraction in a trial frame at a vertex distance of 10mm. Assuming that the lens flipper was at 15mm from the eye, and the pre-operative refractive error was -5.00D, then the stimuli for distance facility would oscillate between -0.23D and -1.98D, and the stimuli for near facility would oscillate between -0.45D and -3.83D. If the patient was emmetropic post-operatively, then the facility measurements were taken through the lens flipper only. In this situation, assuming the lens flipper was still held at 15mm from the eye, then the stimuli for distance facility would oscillate between -0.25D and -2.18D, and the stimuli for near facility would oscillate between -0.50D and -4.22D. These small differences in stimuli are unlikely to make a large difference to the facility results. If anything, these differences suggest that the post-operative task was more difficult. Therefore it is unlikely that these differences in stimuli are a cause of the slight improvement found in distance facility rate. However they may have contributed to the difficulties reported by the patients when trying to relax accommodation to the near target.

No significant correlations were found between the change in aberration levels and the change in the components of facility following surgery at either of the post-operative visits (Tables 7.1 and 7.2). This suggests that the increase in facility rate was not related to the change in aberration levels. A possible reason for this is that the magnitude of the aberrations may not be the important factor. Of more significance may be the relative importance that the individual places on aberrations as an accommodative cue.

In conclusion, accommodative facility measurements appeared relatively resistant to the effects of refractive surgery. A small increase (improvement) in distance facility rate of approximately 2-3 cycles/min was observed at three months post-operatively which is likely to be of only limited clinical significance.

CHAPTER 8
DYNAMIC ACCOMMODATION RESPONSE

8.1 Introduction

There is increasing evidence that monochromatic aberrations can play a role in the control of the accommodative mechanism. More specifically, it has been suggested that even-order aberrations can combine with defocus to produce asymmetries between the images produced with positive and negative defocus, and that this creates an odd-error cue which can provide directional information to the accommodative mechanism (Wilson *et al*., 2002). Studies have shown that correction of higher order aberrations using an adaptive optics system can produce a deterioration in the dynamic accommodation response (Fernandez and Artal, 2005; Chen *et al*., 2006). Chin *et al*. (2009) recently showed that manipulation of higher order aberrations with an adaptive optics system can produce a decrease in the amplitude and an increase in the latency of the dynamic accommodation response under certain conditions.

It has been extensively documented that patients undergoing refractive surgery tend to experience an increase in higher order aberrations (e.g. Applegate *et al.*, 1996; 1998; Oshika *et al*., 1999; Seiler *et al*., 2000; Mrochen *et al*., 2001a; Marcos *et al*., 2001; Marcos, 2001; Moreno-Barriuso *et al*., 2001; Straub and Schwiegerling, 2003; Yamane *et al*., 2004; Buzzonetti *et al*., 2004; Kohnen *et al*., 2005; Porter *et al*., 2006; Kirwan and O'Keefe, 2009). It is therefore hypothesized that changes to higher order aberrations following refractive surgery will alter an individual's ability to detect blur and hence alter aspects of the dynamic accommodation response.

Accommodative dynamics have been studied extensively (see Ciuffreda and Kenyon, 1983; Ciuffreda, 1991; 1998; Hung *et al*., 2002). However, there appears to be no studies that have examined the effects of refractive surgery on dynamic aspects of accommodation. The aim of this study was to investigate the effects of refractive surgery on the dynamic accommodation response. In this study the dynamic accommodation response was compared between a group of patients that had undergone refractive surgery and an emmetropic control group. Ocular aberrations were also assessed to investigate whether they could help explain any differences in accommodative dynamics between the two groups.

8.2 Subjects

A power analysis was performed to evaluate the required number of subjects. An effect size of 0.75, α-level of 0.05 and power 0.85, gave a total sample size of 20 subjects (i.e. 10 in each group). Based on the expected differences in accommodative response between the two refractive groups, the effect size of 0.75 equates to a 0.75D difference in amplitude of response between the groups, and a standard deviation of 0.50D in the amplitude of response within each group. A total of 20 subjects took part in this study, which consisted of a group of refractive surgery patients (n=10) and an age-matched emmetropic control group (n=10). The refractive surgery patients were a subgroup of the cohort described in Chapter 4. For the refractive surgery group all dynamic accommodation measurements were taken three months post-operatively. The refractive surgery patients selected for this experimental protocol all had good post-operative visual and refractive outcome results. Both spherical and cylindrical correction were ±0.50D or less and post-operative unaided distance vision (UCVA) (LogMAR) was +0.20 (6/9 Snellen equivalent) or better in the tested eye to ensure clear visualization of the targets without refractive correction. As the experimental set up and procedures for the dynamic measurements were relatively time consuming and required a certain level of concentration, subject observational skill and ability to maintain steady and accurate fixation were used as two additional selection criteria. The refractive surgery patients had a mean (± SD) age of 28.9 ± 4.7 years (range 19 to 34 years). In the tested eye the mean (± SD) pre-operative refractive error (mean sphere) was -3.39 ± 1.84D (range -1.25D to -5.87D) and the mean (± SD) pre-operative distance best spectacle corrected visual acuity (BSCVA) (LogMAR) was -0.12 ± 0.06 (range 0.00 to -0.20). The refractive procedures consisted of eight LASEK and two LASIK. Six of the LASEK procedures and one of the LASIK procedures were wavefront-guided while the remaining three procedures were conventional (non-wavefront-guided) procedures. Post-operatively the mean (± SD) refractive error (mean sphere) in the tested eye was +0.08 ± 0.31D. The mean (± SD) post-operative UCVA (LogMAR) was -0.11 ± 0.09 (range +0.12 to -0.20) and the mean (± SD) BSCVA was -0.13 ± 0.06 (range 0.00 to -0.20).

Ten healthy emmetropic, age-matched control subjects were recruited from among the staff and students at The University of Manchester. Subjects had unaided vision (LogMAR) of 0.00 (6/6 Snellen equivalent) or better, spherical refraction ±0.50D, astigmatism of less than 0.50D, an amplitude of accommodation of over 4.0D in the tested eye, and were free from any abnormal ocular conditions. Age matching was ±

3 years from members of the refractive surgery group. The mean (± SD) age of the subjects in the emmetropic group was 28.4 ± 4.4 years (range 22 to 37 years). The mean (± SD) refractive error in the tested eye (mean sphere) was +0.09 ± 0.20D. The mean (± SD) UCVA (LogMAR) was -0.08 ± 0.05 (range 0.00 to -0.20) and the mean (± SD) BSCVA was -0.13 ± 0.05 (range -0.08 to -0.20). All experimental procedures were explained and the subjects gave their informed consent prior to participation in the study. Statistical testing (two-tailed t-test) showed no significant differences between the refractive surgery patients (post-operatively) and the emmetropes in terms of age, refractive error (mean sphere), UCVA, or BSCVA ($p>0.05$).

8.3 Methods

The apparatus set up used for the dynamic measurements is shown in Figure 8.1. The subjects alternately focused between two real targets placed at far and at near. Both targets were high contrast black Maltese crosses printed on white paper. The distance cross measured 16cm x 16cm and was presented at a distance of 4m (0.25 D stimulus). The near cross measured 1cm x 1cm and was presented at 0.25m (4 D stimulus). The angular subtense was therefore constant with each stimulus subtending an angle of approximately 2.3 degrees at the eye. The subjects viewed the targets with a natural pupil through an open-field Shin-Nippon SRW-5000 auto-refractor. The auto-refractor monitored the subject's refraction continuously at a temporal frequency of 30 Hz while the subjects viewed the stimuli. The head was stabilized with a forehead and chin rest. An increase in power of the eye, corresponding to a more negative refraction was taken as a positive accommodation response. The auto-refractor incorporated a circular aperture that allowed a 6 degree field of view and served to black out the surround and remove other possible accommodative stimuli. At any point in time the subject could therefore only see either the far or the near target alternately through the aperture and these were the only targets visible to the subject. This was achieved by having the distance target fixed at 4m and the near target attached to a sliding mechanism on an optical bench at a distance of 0.25m. The sliding mechanism allowed the near target to be moved horizontally in and out of view. Prior to the measurements the distance and near targets were manually aligned for each individual patient so that when in position both the distance and near stimuli appeared in the centre of the aperture. The far target, near target and auto-refractor were all aligned to ensure on axis measurements. All of the dynamic measurements were taken monocularly with the non-tested eye occluded with an eye patch. No refractive corrections were worn during the measurements. All measurements were taken in a clinical testing room with the room lights on.

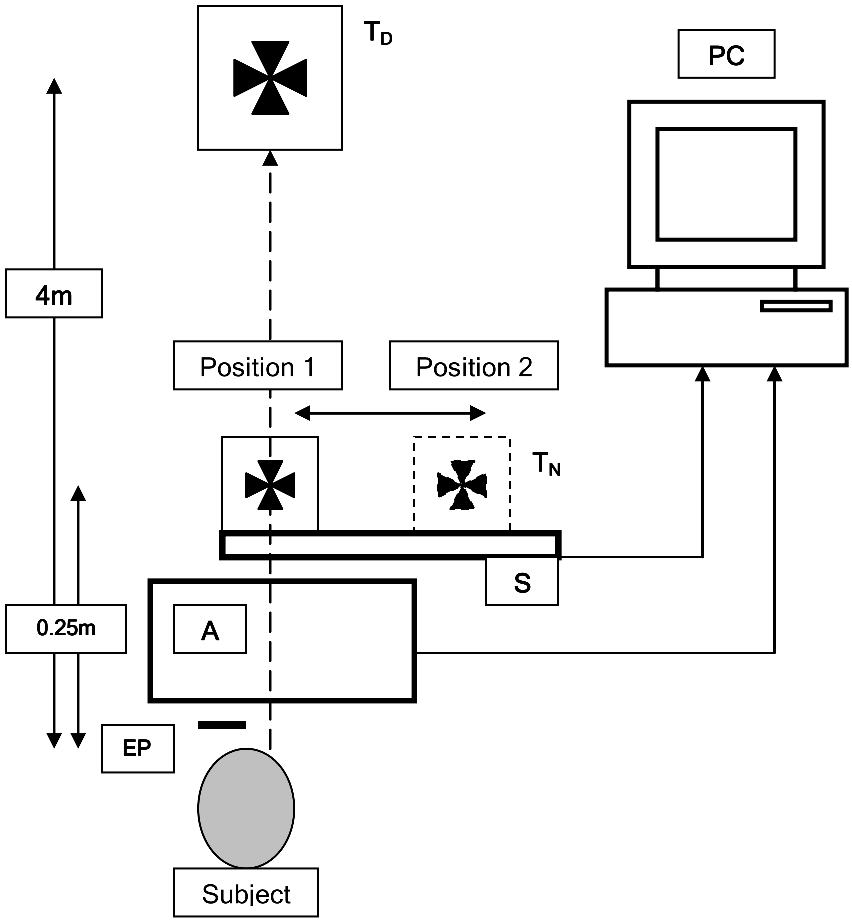


Figure 8.1: Schematic of the experimental set up. The distant target (T_D) and near target (T_N) were aligned with the subject's tested eye and the non tested eye was covered with an eye patch (EP). The subject viewed the targets monocularly through a Shin-Nippon SRW-5000 auto-refractor (A) which incorporated a 6º aperture for viewing the targets. The distant target was fixed at 4m (0.25 D stimulus) and the near target was attached to a sliding mechanism (S) at a fixed distance of 0.25m (4.0 D stimulus). The sliding mechanism allowed the near target to be moved horizontally in and out of view. When the near target was in position 1 only the near target could be seen through the aperture, and when the near target was moved to position 2 only the distance target could be seen through the aperture. The sliding mechanism was linked to a desktop computer (PC) which recorded the onset of the near and distance stimuli. The auto-refractor measured the accommodative response continuously at a temporal frequency of 30 Hz and the responses were recorded on the computer.

The sliding mechanism used for the near target presentation was attached to an electrical circuit that sent a signal to a desktop computer. The electrical circuit is shown in Figure 8.2. The electrical circuit allowed a voltage change to be registered when the near target was moved horizontally in and out of view. A position switch controlled a motor that moved the near target horizontally. When the near target was in the centre of the aperture a limit switch was depressed and when the near target was moved out of view (and the distance target came in to view) the limit switch was released and second limit switch was depressed. Each time this occurred a voltage change output from the circuit was registered on the computer. This made it possible to record the specific time of onset of both the distance and near stimuli.

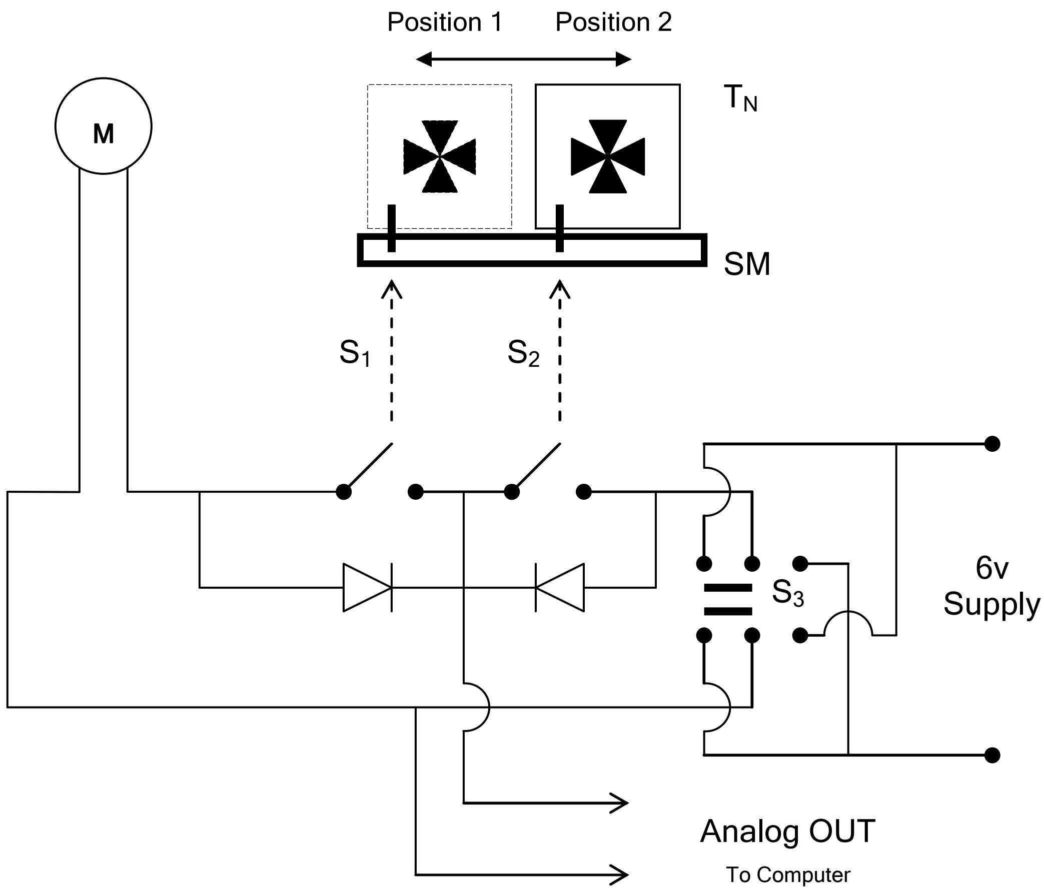


Figure 8.2: Diagram of the circuit connected to the sliding mechanism (SM) that carried the near target (T_N). A motor (M) controlled by a position switch (S_3) moved the near target horizontally between positions 1 and 2. Limit switches S_1 and S_2 were alternately depressed/released when the near target was in position 1 and 2 respectively. Each time the target position was altered a voltage change output from the circuit was recorded on the computer.

The sliding mechanism was designed and built specifically for use in this study to allow the recording of the stimulus onset. The near and far targets were alternately presented approximately every 5-10 seconds over a period of 1-2 minutes for each subject. This produced an accommodative trace for approximately 10 accommodation responses covering both far-to-near and near-to-far accommodation responses. The reason for not using a fixed time period to alternate the stimuli was to reduce the possibility of the subject anticipating the stimulus. Subjects were instructed to view the centre of the stimuli keeping them “as clear as possible at all times”. Prior to the measurements subjects were given a practice run to experience the task during which no data were collected.

The information from the Shin-Nippon auto-refractor and the near target sliding mechanism were fed into a computer. Installed on the computer was a program that could record these measurements for subsequent analysis. The computer program was designed and written by Professor James Wolffsohn (Aston University, Birmingham) in 2008 and used with his permission (see Chapter 2, section 2.1 for a description of the installed software and the specifications of the Shin-Nippon auto-refractor during the dynamic measurements).

Calibration of the set up using the automated software was performed for each patient individually prior to the recording of the measurements. This calibration involved two stages. Firstly, in the “Measurement and Automation” program menu (Figure 8.3a) an image was captured of the target on the patient’s eye and the contrast of the targets was maximized by manually altering the program’s contrast settings. This stage helped ensure accurate acquisition of bar separation measurements. The second stage was the calibration of the accommodation response. This was done in the main program menu (Figure 8.3b) under the calibration tab. The bar separation was determined while the patient viewed the distance target.

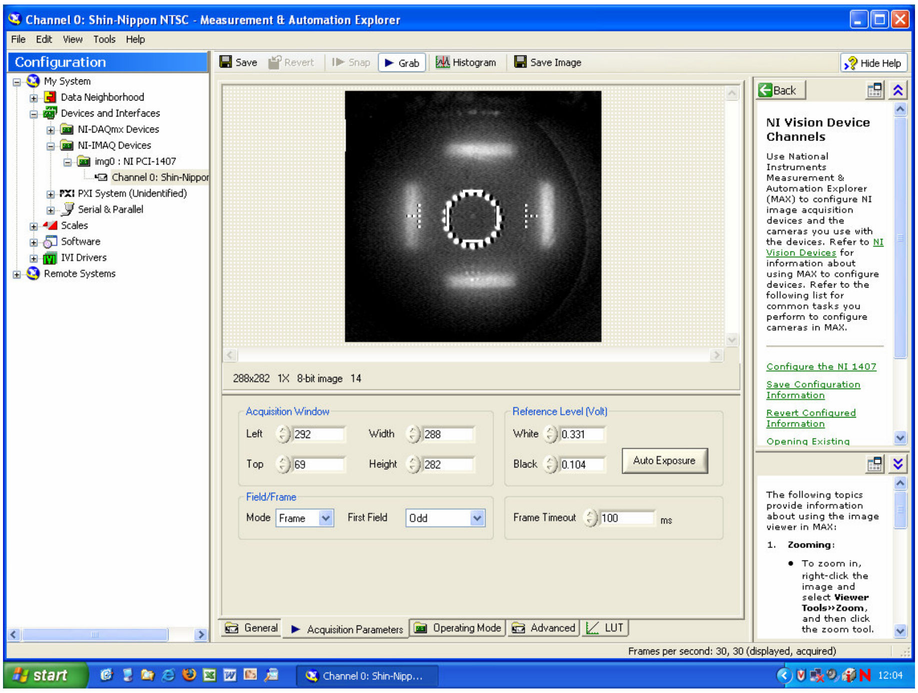


Figure 8.3a: Calibration stage. Measurement and Automation Explorer screen on the computer used for the initial calibration of the image prior to the dynamic measurements.

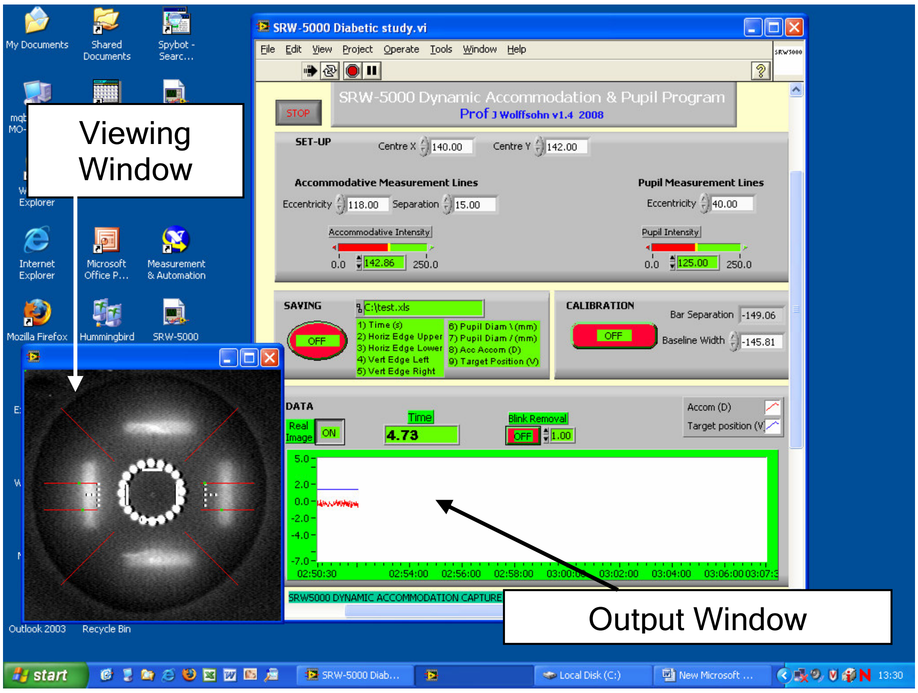


Figure 8.3b: Measurement stage. Example of the computer screen output during the dynamic measurements. A viewing window allowed continuous real-time visualization of the targets on the patient's eye to aid alignment of the targets during the measurements. An output window allowed real-time viewing of the measurements of the accommodation stimulus (Voltage change, blue trace) and the accommodation response (Dioptres, red trace).

This value was entered in the program and acted as a distance reference for the accommodation measurements. Following the initial practice run, the measurements were taken. During the measurements a magnified view of the subject's eye was observed in the viewing window on the computer (Figure 8.3b). This made it possible to observe that accurate fixation was maintained throughout the measurements. The output window on the computer monitor allowed continuous recording of the accommodation stimulus and response to be viewed simultaneously in real-time. This made it possible to view the stabilization of the accommodation response before changing the stimulus positions. The stimulus position and accommodation response data were saved into an excel spreadsheet for subsequent data analysis.

8.3.1 Data analysis

Approximately 10 accommodative (distance-to-near) and disaccommodative (near-to-distance) responses were recorded for each subject. Using the recordings of stimuli onset it was possible to isolate and extract individual accommodative and disaccommodative responses for analysis. Five accommodative and disaccommodative responses for each subject were analyzed individually to obtain values for latency, amplitude of response, time constant and peak velocity as described below. The responses included in the analysis were those for which the onset of the response could be clearly identified, a steady state level of accommodation was reached at the end of the response, and for which the exponential functions provided a good model for the data with all accommodation response measurements being within 1D of the exponential curve. Curves were excluded from the analysis if a blink occurred during the initial response phase or at the end of the response phase which made identifying the beginning or end of the accommodation response difficult. Other remaining blinks (if any) were removed prior to analysis.

8.3.2 Latency

Latency was calculated as the time interval between the onset of the stimulus and the onset of an accommodative response to that stimulus. The onset of the stimulus was given by the recorded voltage change from the near target sliding mechanism. An algorithm was used to determine the onset of the accommodation response. The algorithm chosen has been used previously in similar research and found to reliably determine the onset of accommodative and disaccommodative responses (Kasthurirangan *et al*., 2003). For accommodation the algorithm searched for three consecutive increasing data values followed by four consecutive data values in which no two consecutive decreases occurred. The inverse of the algorithm was used to determine the onset of the disaccommodation response. When these criteria were met, the first data point in the sequence was used as the onset of the response. All calculated onsets were confirmed by visual inspection.

8.3.3 Amplitude and Time Constant

Each accommodative and disaccommodative trace was fitted with an exponential function (Beers and Van Der Heijde, 1994; 1996; Yamada and Ukai, 1997; Kasthurirangan *et al*., 2003). The equations used to fit the trace were:

$$\mathbf{y = y_0 + a\,(1 - e^{-x/\tau})} \qquad \text{for accommodation}$$

and $$\mathbf{y = y_0 - a\,(1 - e^{-x/\tau})} \qquad \text{for disaccommodation}$$

Where:

$\mathbf{y}$ = Accommodation

$\mathbf{y_0}$ = Initial amplitude of accommodation at the start of the response

$\mathbf{a}$ = Total amplitude change during the response

$\mathbf{x}$ = Time in seconds

$\boldsymbol{\tau}$ = Time constant

The initial amplitude of accommodation at the start of the response ($\mathbf{y_0}$) and the final accommodation value at the end of the response were obtained from the raw data in the refractive records. From these values the total amplitude change during the response ($\mathbf{a}$) was calculated. Values were then calculated for 10% and 90% response amplitude and the refractive records were analyzed to find the corresponding times $\mathbf{t_{10}}$ and $\mathbf{t_{90}}$ when the response reached 10% and 90% of the amplitude respectively.

These values were then used to calculate the time constant using a derivation from the above equation where:

$$\tau = \frac{t_{90} - t_{10}}{\ln 9}$$ (Radhakrishnan *et al*., 2007)

Where:

τ = Time constant (seconds)

t_{90} = Time taken to reach 90% of the total amplitude response (seconds)

t_{10} = Time taken to reach 10% of the total amplitude response (seconds)

8.3.4 Peak velocity

Once values for the time constant and the total amplitude of the response were known, peak velocity was calculated using a simple formula in which:

$$v = a / \tau$$ (Radhakrishnan *et al*., 2007)

Where:

v = Peak velocity (D/s)

a = Total amplitude of response (D)

τ = Time constant (seconds)

8.3.5 Measurement of aberrations

Distance resting aberrations with a natural pupil were measured for all subjects on the same day as the dynamic accommodation measurements were taken. The aberrations of the refractive surgery patients were measured at Manchester Royal Eye Hospital using an Allegretto Wave Analyzer aberrometer (WaveLight, Erlangen, Germany). The aberrations of the emmetropic subjects were measured at the University of Manchester using a Shack-Hartmann aberrometer (IRX3, Imagine eyes, Paris). In each case measurements were taken monocularly in the same eye used for the dynamic accommodation measurements with the non-tested eye occluded. Measurements were taken in a clinical room with the room lights turned off. For each participant the aberration measurement was taken as the mean of five readings for a 5.00mm pupil diameter.

Ideally the aberrations would have been measured using the same instrument for all patients. However, this was not possible to the logistics of where/when the patients were recruited. It should therefore be acknowledged that there could be differences in the aberrations between subjects due to the different techniques used to measure the aberrations.

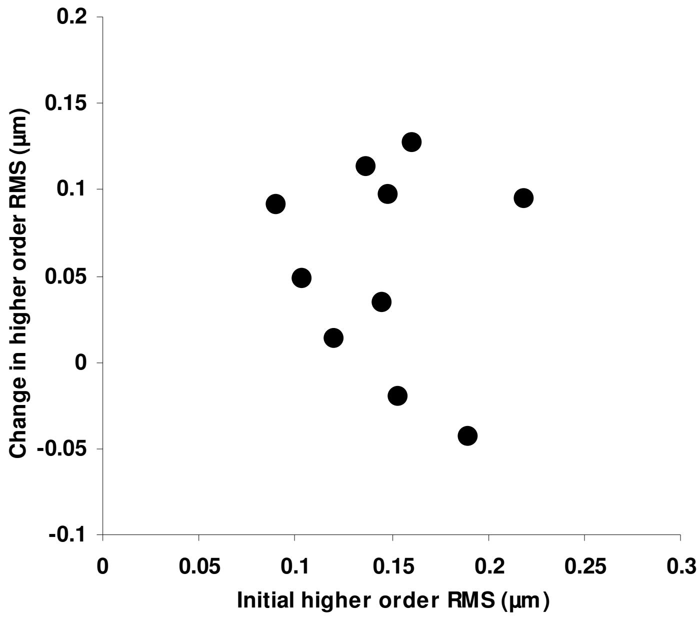
8.3.6 Statistical analysis

The main outcome measures were latency, amplitude of response, time constant and peak velocity. Each of these parameters were calculated for both accommodation and disaccommodation responses for all participants. ANOVA was used to compare the parameters for accommodation and disaccommodation to test for within-subject differences and to compare the results from the refractive surgery patients and the emmetropes to test for between-subject differences. Pearson's product-moment correlation (r) was then used to calculate the significance of correlations between each of the main outcome measures and the distance resting aberrations for spherical aberration and total higher order RMS aberration (3^{rd}-5^{th} order) for a 5.00mm pupil diameter. Results were considered significant at $p<0.05$. Statistical tests were performed using SPSS for Windows (SPSS Version 16.0, SPSS Inc, Chicago, Ill).

8.4 Results

Figure 8.4 shows the changes in aberration occurring due to surgery in the refractive surgery group. Evaluation of aberration levels showed that mean (± SD) total higher order RMS (3^{rd} to 6^{th} order) altered significantly in the refractive surgery group from pre-operative values of 0.14 ± 0.04μm to 0.21 ± 0.07μm at the three month post-operative visit (two-tailed paired t-test, $p<0.05$). Figure 8.4a shows the changes in total higher order RMS error at the three month post-operative visit as a function of the initial RMS error. It is evident from Figure 8.4a that total higher order RMS increased in the majority of participants, with a small number of participants showing a decrease in RMS error. Mean (± SD) 4^{th} order spherical aberration remained relatively stable after surgery with pre-operative values being 0.01 ± 0.05μm and altering to 0.00 ± 0.06μm at the three month post-operative visit ($p>0.05$). Figure 8.4b shows the change in 4^{th} order spherical aberration as function of initial (pre-operative) spherical aberration. It is clear from Figure 8.4b that although the mean change in spherical aberration across the group was not significant, a number of patients showed changes in spherical aberration of over 0.05μm in either a positive or a negative direction.

(a)



(b)

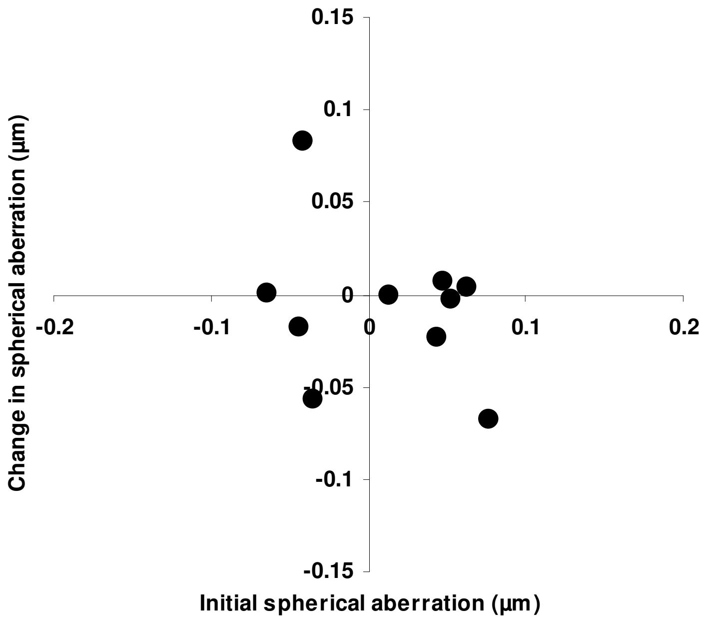


Figure 8.4: Changes in (a) higher order aberrations and (b) 4th order spherical aberration at three months post-operatively as a function of initial (pre-operative) aberration levels for the refractive surgery group.

Comparisons were also made between the aberration data of the two groups (post-operative refractive surgery patients and emmetropes). Mean (± SD) total higher order RMS (3^{rd} to 6^{th} order) in the emmetropic group was 0.15 ± 0.05µm, which was significantly different from the post-operative refractive surgery group (two-tailed t-test, p=0.03). Mean (± SD) 4^{th} order spherical aberration in the emmetropic group was 0.05 ± 0.03µm, which was significantly different from the post-operative refractive surgery group (two-tailed t-test, p=0.04).

The experiment was performed successfully by all 20 participants. Figure 8.5 shows examples of the typical dynamic measurement data traces obtained during the experiment for the refractive surgery patients (Figure 8.5a) and the emmetropic control group (Figure 8.5b). A continuous one-minute section of each trace is shown for each participant. The results showed that while viewing the distance target the accommodative response closely matched the distance stimulus. Following the onset of the near target there was a short latency after which the accommodative effort increased rapidly and then leveled off to a steady state with a lag of approximately 1-2D from the near target. This steady state was maintained for 3-4 seconds while the near target was observed. Once the target was switched back to distance the accommodative response rapidly decreased before leveling off to a steady state once more. The usual fluctuation in the accommodative response (microfluctuations) and intermittent blinks are clear in each trace.

8.4.1 Latency

The mean latency between the onset of the near stimulus and the start of the accommodation response to the near stimulus (distance to near accommodation) was 568 ± 104 ms in the refractive surgery group and 378 ± 125 ms in the emmetropic group. One-way ANOVA showed this to be a significant difference (ANOVA, $F_{1, 18} = 13.418$, $p = 0.002$). The latency between the onset of the distance stimulus and the start of the disaccommodation response (near to distance accommodation) proved more difficult to measure. For the majority of subjects in both groups (70% of refractive surgery patients, 60% of emmetropes) the onset of the disaccommodation response occurred at the same point as the onset of the distance stimulus, rendering the latency effectively zero (see Figures 8.5a and 8.5b). The remaining subjects in both groups showed a slight latency for some of the responses which were typically well below 100ms. The data suggest that the disaccommodation response to a distant stimulus occurred very rapidly and was similar in both groups. Further analysis on such a small sample size is unlikely to accurately reflect any meaningful differences between the groups.

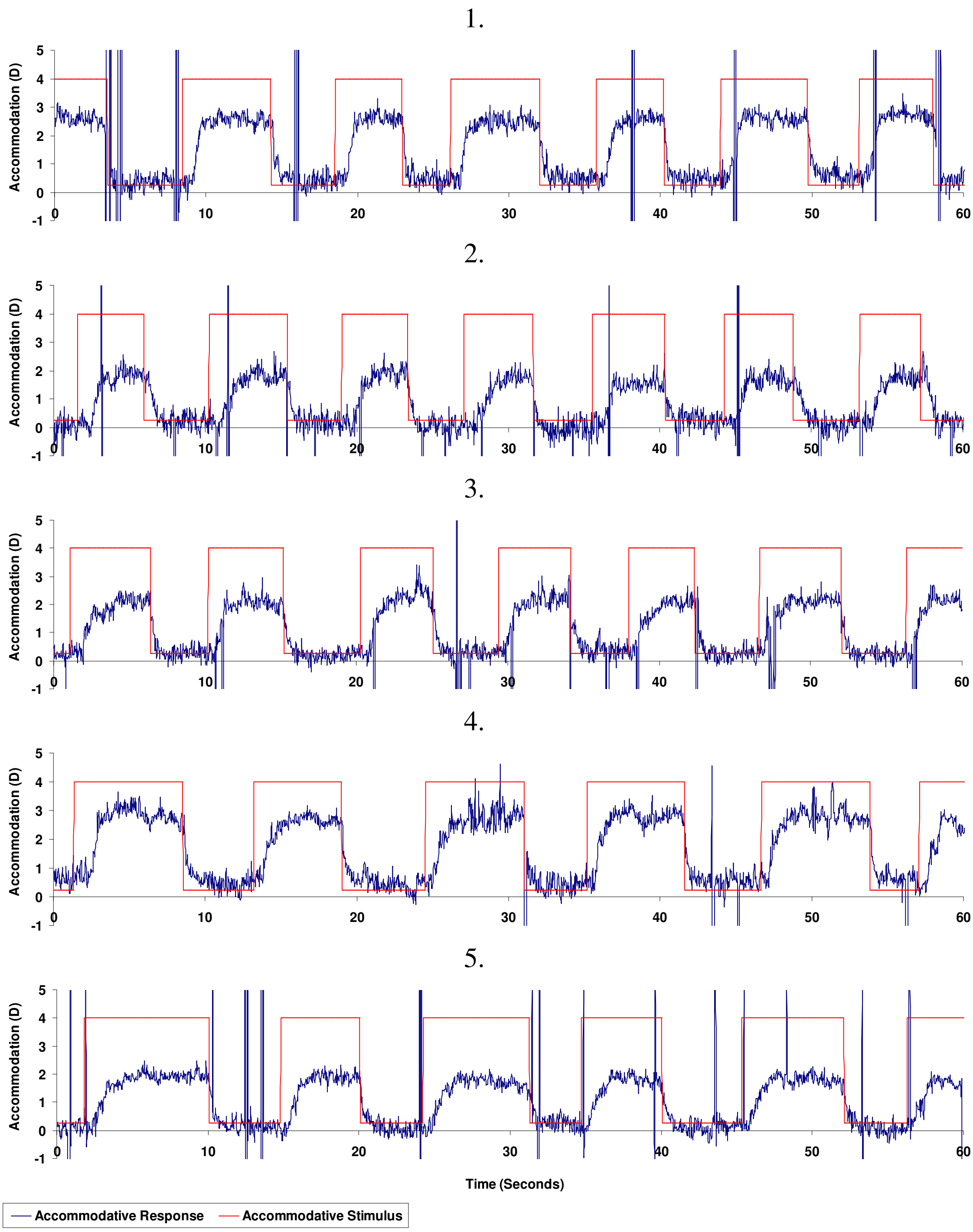


Figure 8.5a: Examples of typical dynamic stimulus/response plots obtained from five of the refractive surgery patients (prior to blink removal). Each graph (1-5) represents a different patient and shows data collected over a 1 minute period. The accommodation response trace (solid blue line) was measured at a temporal frequency of 30Hz. The corresponding accommodative stimulus (solid red line) alternated between 0.25D (distance target at 4m) and 4D (near target at 0.25m). Extreme high and low values within the accommodation response trace represent blinks.

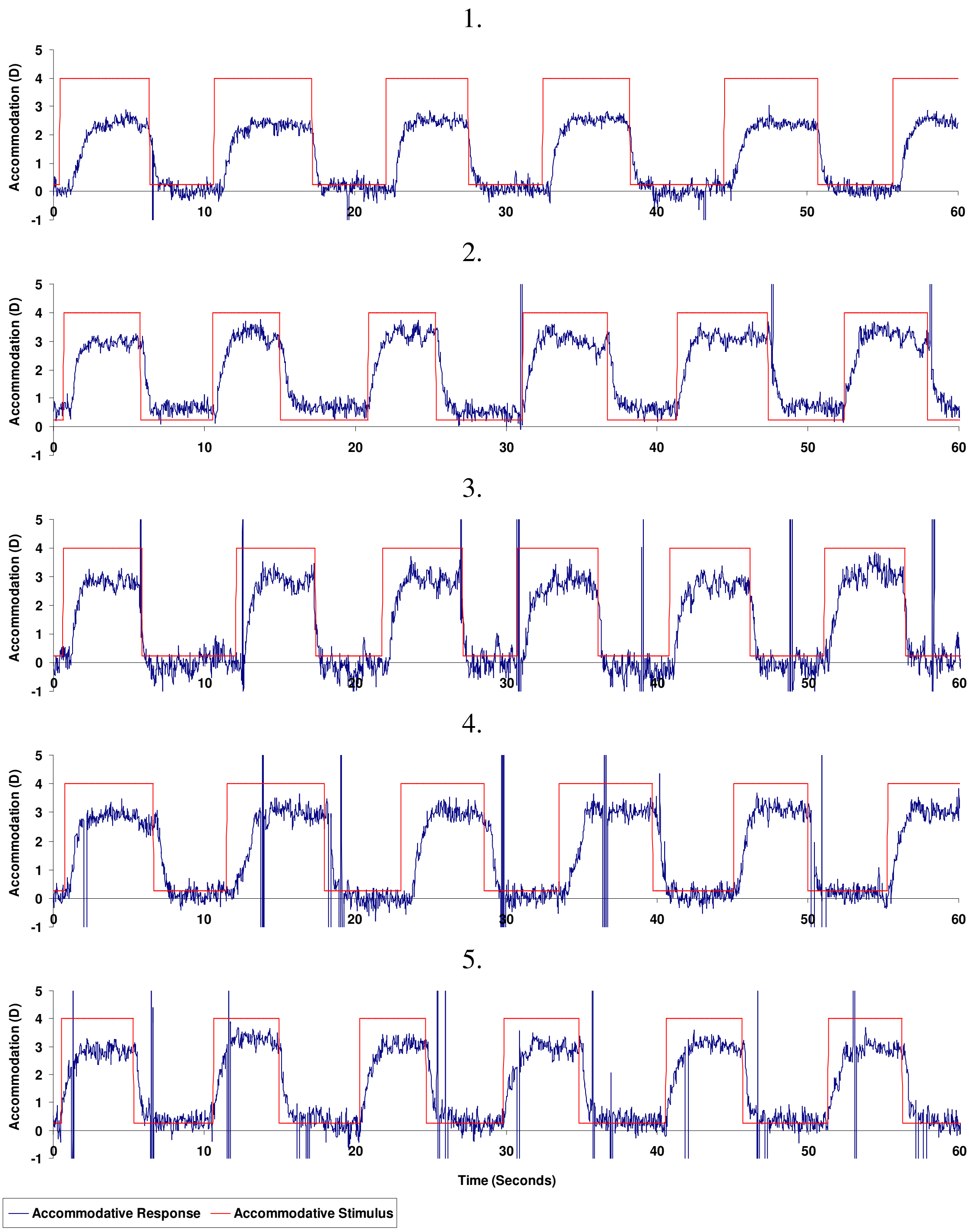


Figure 8.5b: Examples of typical dynamic stimulus/response plots obtained from five of the emmetropic control subjects (prior to blink removal). Each graph (1-5) represents a different subject and shows data collected over a 1 minute period. The accommodation response trace (solid blue line) was measured at a temporal frequency of 30Hz. The corresponding accommodative stimulus (solid red line) alternated between 0.25D (distance target at 4m) and 4D (near target at 0.25m). Extreme high and low values within the accommodation response trace represent blinks.

8.4.2 Exponential functions

Examples of the typical exponential fits to the individual accommodation and disaccommodation responses are shown in Figure 8.6. Results are shown for two refractive surgery patients (Figures 8.6a and b) and two emmetropic subjects (Figures 8.6c and d). The exponential equations provided excellent models for the data for the refractive surgery patients and the emmetropes for both accommodation and disaccommodation responses.

8.4.3 Amplitude

The amplitudes of the accommodation and disaccommodation responses (**a**) were calculated as the difference between the amplitude of accommodation at the start of the response ($\mathbf{y_0}$) and the final accommodation amplitude once the response had stabilized. No significant differences were found between the mean accommodative amplitudes and the mean disaccommodative amplitudes in either the refractive surgery group (ANOVA, $F_{1, 18}=0.135$, $p=0.717$) or the emmetropic group (ANOVA, $F_{1, 18}=0.302$, $p=0.589$). This indicates that the accommodative response returned to the same resting state after each period of near target viewing. The mean amplitude of response was 2.07 ± 0.33D in the refractive surgery group and 2.83 ± 0.26D in the emmetropic group. This was found to be a significant difference (ANOVA, $F_{1, 18}=31.745$, $p<0.001$).

8.4.4 Time Constants

For the refractive surgery patients the mean time constants were 0.4276 ± 0.0972 seconds and 0.2477 ± 0.0367 seconds for accommodation and disaccommodation respectively. For the emmetropic group the mean time constants were 0.3923 ± 0.0520 seconds and 0.2454 ± 0.0493 seconds for accommodation and disaccommodation respectively. The mean time constants for accommodation and disaccommodation were significantly different for both the refractive surgery group (ANOVA, $F_{1, 18} = 29.956$, $p < 0.001$) and the emmetropic group (ANOVA, $F_{1, 18} = 42.053$, $p < 0.001$), suggesting that the disaccommodation response was more rapid than the accommodation response in both groups. When comparing groups however, no significant difference was found between the refractive surgery group and the emmetropic group for either the accommodation time constants (ANOVA, $F_{1, 18} = 1.020$, $p = 0.326$) or the disaccommodation time constants (ANOVA, $F_{1, 18} = 0.014$, $p = 0.908$).

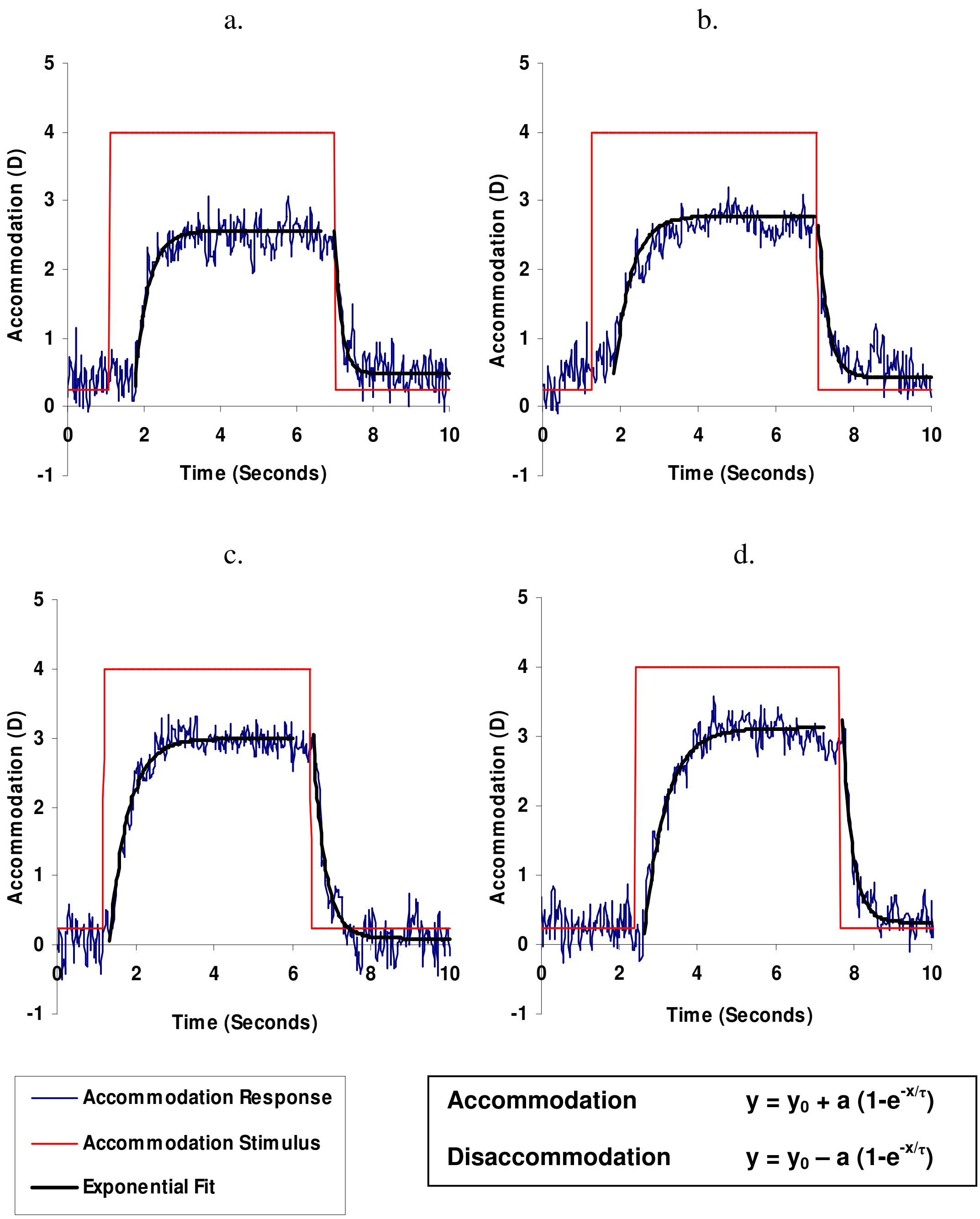


Figure 8.6: Individual dynamic accommodation plots for four participants over a continuous 10 second period. Data are from two refractive surgery patients (graphs a and b) and two emmetropic subjects (graphs c and d). The accommodation response trace (thin blue line) was measured at a temporal frequency of 30Hz and blinks (if any) have been removed. The corresponding accommodative stimulus (thin red line) alternated between 0.25D (distant target at 4m) and 4D (near target at 0.25m). The onset/offset time of the stimulus change varied between subjects due to the random nature of its presentation. Exponential functions (thick black lines) are fit to the accommodative and disaccommodative responses in each case. The equations used to fit the exponential functions are given below graph d.

8.4.5 Peak velocity

For the refractive surgery group the mean peak velocities were 5.16 ± 1.20 D/s and 8.61 ± 1.90 D/s for accommodation and disaccommodation respectively. For the emmetropic group the mean peak velocities were 7.41 ± 1.32 D/s and 12.08 ± 2.65 D/s for accommodation and disaccommodation respectively. The mean peak velocities for accommodation and disaccommodation were significantly different for both the refractive surgery group (ANOVA, $F_{1, 18} = 23.490$, $p < 0.001$) and the emmetropic group (ANOVA, $F_{1, 18} = 24.855$, $p < 0.001$). When comparing groups, significant differences were found between the refractive surgery group and the emmetropic group for both accommodative peak velocity (ANOVA, $F_{1, 18} = 15.953$, $p = 0.001$) and disaccommodative peak velocity (ANOVA, $F_{1, 18} = 11.309$, $p = 0.003$).

Figures 8.7-8.10 investigate the correlation between the various parameters of the dynamic accommodation responses (latency, amplitude of response, time constant and peak velocity) and the higher order distance resting aberrations (spherical aberration and total higher order RMS) for a 5.00mm natural pupil diameter. Correlations were investigated using Pearson product-moment correlation coefficient (r) for the parameters associated with both accommodative and disaccommodative responses (where applicable).

a. Spherical aberration b. Total higher order RMS (3^{rd}-5^{th} order)

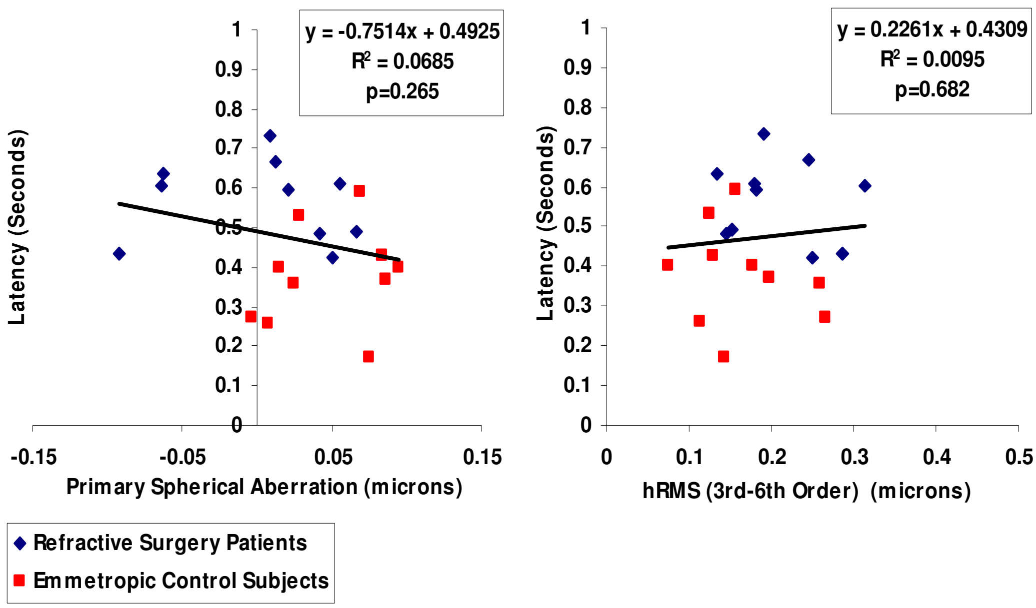


Figure 8.7: Latency of accommodation response (seconds) plotted against spherical aberration (µm, graph a) and total higher order aberration (RMS 3^{rd}-5^{th} order, µm, graph b). All the aberration measurements represent distance resting aberrations for a 5.00mm natural pupil diameter. Both graphs show results for the refractive surgery patients (blue diamonds, n=10) and the emmetropic subjects (red squares, n=10). Results are shown with linear best fit lines, equation, R^2 and p-value for all 20 participants.

Figure 8.7 shows the correlation between the latency of the accommodative response and spherical aberration (Figure 8.7a) and total higher order aberration (Figure 8.7b). There was a weak negative correlation between the latency and spherical aberration although this was not statistically significant (r = -0.262, n=20, p=0.265). There was a weak positive correlation between latency and total higher order aberration which was also not statistically significant (r = 0.098, n=20, p=0.682).

a. Spherical aberration b. Total higher order RMS (3^{rd}-5^{th} order)

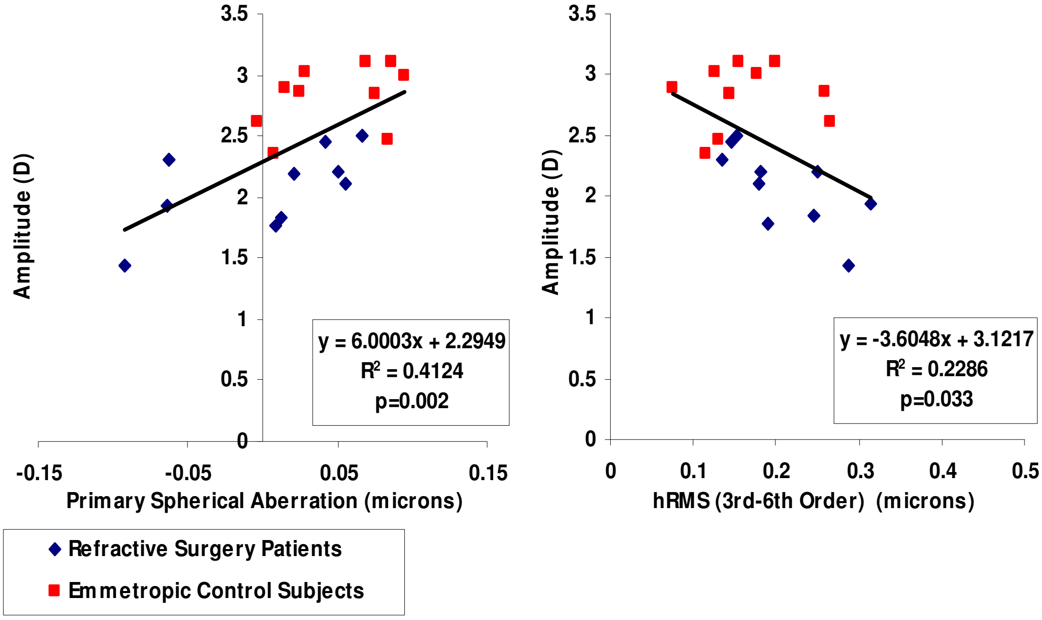


Figure 8.8: Amplitude of accommodation response (D) plotted against spherical aberration (µm, graph a) and total higher order aberration (RMS 3^{rd}-5^{th} order, µm, graph b). All the aberration measurements represent distance resting aberrations for a 5.00mm natural pupil diameter. Both graphs show results for the refractive surgery patients (blue diamonds, n=10) and the emmetropic subjects (red squares, n=10). Results are shown with linear best fit lines, equation and R^2 and p-value for all 20 participants.

Figure 8.8 shows the correlation between the amplitude of the accommodation response and spherical aberration (Figure 8.8a) and total higher order RMS aberration (Figure 8.8b). There was a significant positive correlation between the amplitude of response and spherical aberration (r = 0.642, n=20, p=0.002), with increasing levels of amplitude of response associated with increasing levels of positive spherical aberration. There was a significant negative correlation between the amplitude of response and total higher order RMS aberration (r = -0.478, n=20, p=0.033), with lower amplitudes associated with increasing levels of total higher order RMS aberration.

Figure 8.9a-d shows the correlation between time constant and distance resting spherical aberration and total higher order RMS aberration for both accommodation and disaccommodation. There was a significant positive correlation between time constant of accommodation and spherical aberration (r = 0.469, n=20, p=0.037), with higher time constants associated with increasing levels of positive spherical aberration. There was a weak negative correlation between time constant of accommodation and total higher order RMS aberration although this was not statistically significant (r = -0.202, n=20, p=0.394). The time constant of disaccommodation showed a very weak positive correlation with spherical aberration (r = 0.015, n=20, p=0.949) and total higher order RMS aberration (r = 0.087, n=20, p=0.714) although neither of these relationships were statistically significant.

Figure 8.10a-d shows the correlation between the peak velocity and distance resting spherical aberration and total higher order RMS aberration for both accommodation and disaccommodation. Peak velocity showed a weak positive correlation with spherical aberration for both accommodation (r = 0.155, n=20, p=0.513) and disaccommodation (r = 0.375, n=20, p=0.103) although neither of these relationships reached statistical significance. Peak velocity showed a weak negative correlation with total higher order RMS aberration for both accommodation (r = -0.213, n=20, p=0.366) and disaccommodation (r = -0.314, n=20, p=0.177) although neither of these relationships was found to be statistically significant.

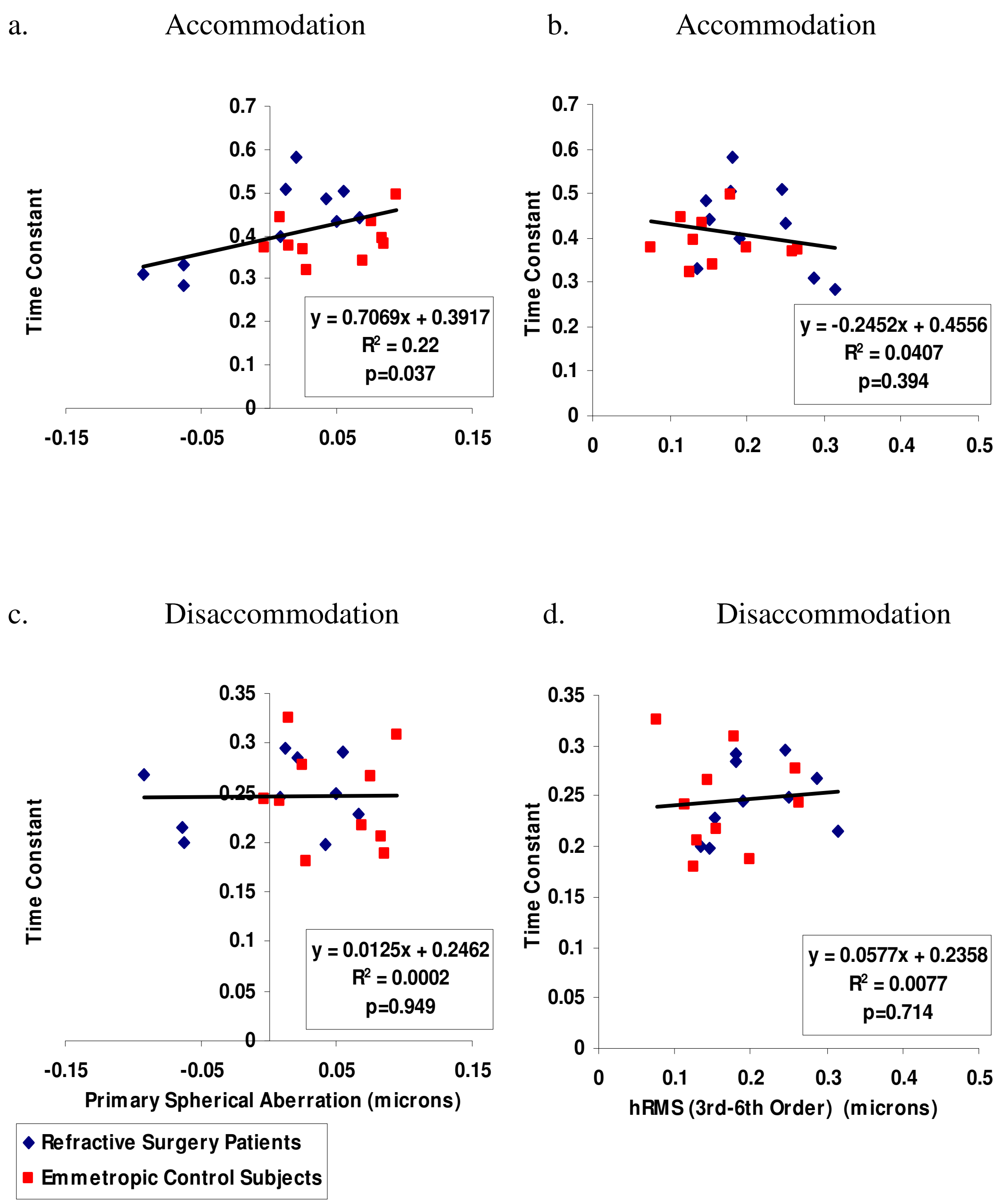


Figure 8.9: Time constant of accommodation (Seconds, graphs a and b) and disaccommodation (Seconds, graphs c and d) plotted against spherical aberration (µm, graphs a and c) and total higher order aberration (RMS 3rd-5th order, µm, graphs b and d). All measurements represent distance resting aberrations for a natural 5.00mm pupil diameter. Each graph shows the results for the refractive surgery patients (blue diamonds, n=10) and the emmetropic subjects (red squares, n=10). Results are shown with linear best fit line, equation and R^2 and p-value for all 20 participants.

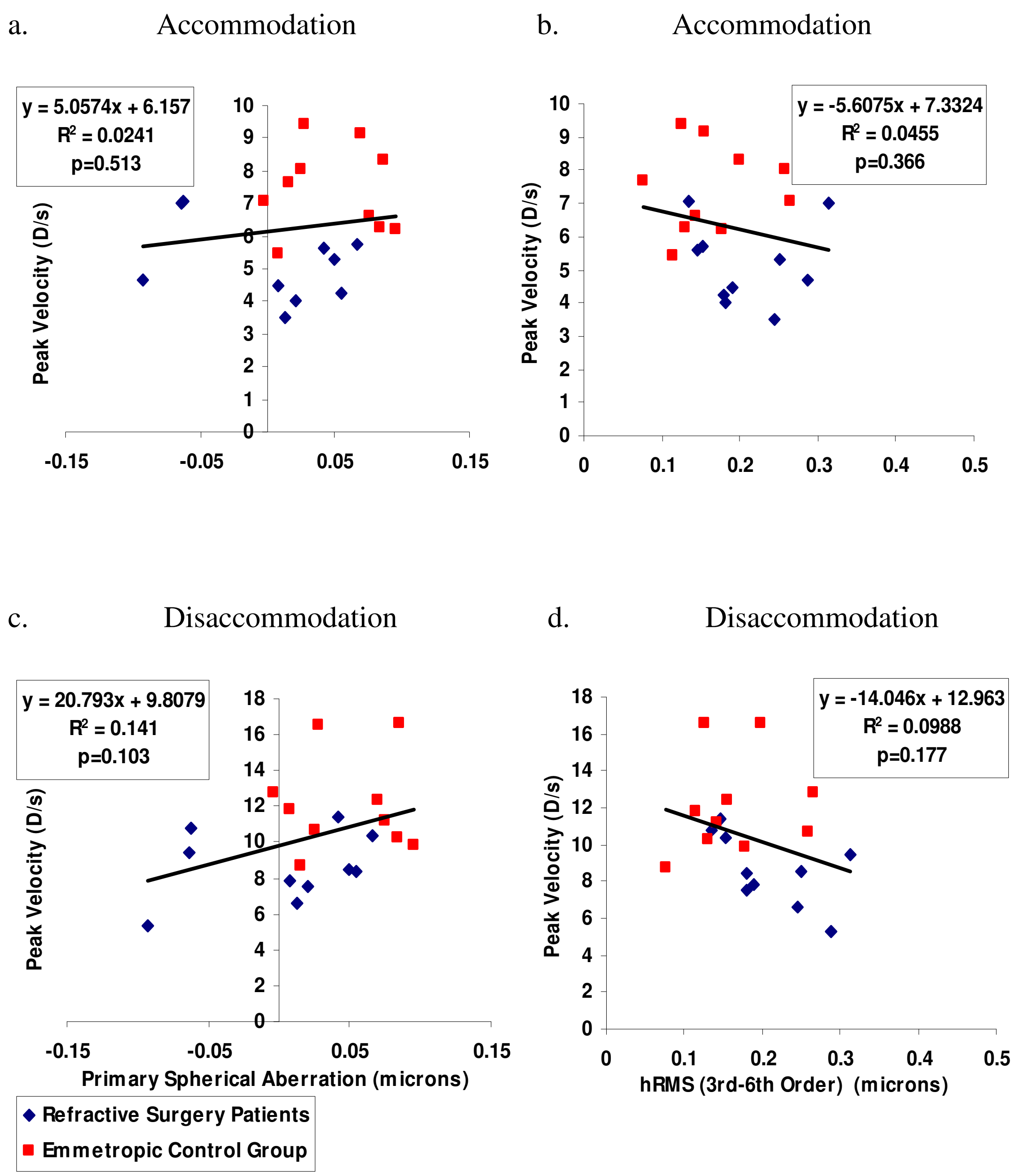


Figure 8.10: Peak velocity of accommodation (graphs a and b) and disaccommodation (graphs c and d) plotted against spherical aberration (µm, graphs a and c) and total higher order aberration (RMS 3rd-5th order, µm, graphs b and d). All measurements represent distance resting aberrations for a natural 5.00mm pupil diameter. Each graph shows the results for the refractive surgery patients (blue diamonds, n=10) and the emmetropic subjects (red squares, n=10). Results are shown with linear best fit line, equation and R^2 and p-value for all 20 participants.

8.5 Discussion

Good dynamic traces were obtained for all 20 subjects, consistent with the general form of responses found in previous studies (Kasthurirangan *et al.*, 2003; Mordi and Ciuffreda, 2004; Kasthurirangan and Glasser, 2005; 2006). The dynamic traces could be well modeled using exponential functions (Figure 8.6) which enabled accurate parameters to be calculated for amplitude, time constant and peak velocity. The results of this study suggest that there are differences in the dynamic responses between those that have undergone refractive surgery and emmetropic controls. The responses of the refractive surgery patients exhibited increased accommodative latency, decreased amplitude of response, and decreased accommodative and disaccommodative peak velocity in comparison to emmetropes.

Mean (± SD) accommodative latency was 378 ± 125 ms and 568 ± 104 ms in the emmetropic and refractive surgery groups respectively. This difference was found to be statistically significant. The accommodative latency values show broad agreement with previously published literature which has found that accommodative latency times generally fall in the range 200-500 ms (Campbell and Westheimer, 1960; Heron *et al.*, 2001; Mordi and Ciuffreda, 2004), although can be as high as 500-700 ms for some individuals, depending on the particular experimental conditions (Tucker and Charman, 1979).

Mean (± SD) amplitude of response to the 4D stimulus used in the experiment was 2.07 ± 0.33D and 2.83 ± 0.26D for the refractive surgery and the emmetropic group respectively. This was found to be a significant difference. These accommodative response amplitude values translate in to accommodative lag values of approximately

1.75D to 2.00D (refractive surgery patients) and 1.00D to 1.25D (emmetropes) to a target placed at 0.25m (4D stimulus). These lag values are broadly consistent with the expected lags of accommodation frequently found when people observe near targets (see e.g. Gwaizda *et al*., 1993; Abbott *et al*., 1998).

Mean (± SD) accommodative peak velocities were 5.16 ± 1.20 D/s and 7.41 ± 1.32 D/s, and mean (± SD) disaccommodative peak velocities were 8.61 ± 1.90 D/s and 12.08 ± 2.65 D/s for the refractive surgery patients and emmetropic controls respectively. Both groups showed higher time constants and lower peak velocities during the accommodative response in comparison to the disaccommodation response, indicating that the disaccommodation response occurred more rapidly than the accommodation response in both groups. The time constant and peak velocity results found here are comparable to those found by Kasthurirangan and Glasser, (2005). Kasthurirangan *et al*. (2003) have shown that the peak velocity is proportional to the accommodative response amplitude, with higher velocities being associated with higher response amplitudes. This relationship may help explain the difference found in peak velocity between the two groups as it would be expected that the lower amplitude of response found in the refractive surgery group would be accompanied by a lower peak velocity.

Previous studies have shown that changing higher order aberrations may adversely affect components of the accommodative response (Fernandez and Artal, 2005; Chin *et al*., 2009; Theagarayan *et al*., 2009). It is therefore tempting to suggest that the differences in dynamic accommodation responses found in the current study were due to differences in higher order aberrations between the two groups. It is possible that altered levels of higher order aberrations after refractive surgery combine with defocus in a way that produces an inappropriate cue for accommodation which consequently disrupts elements of the dynamic response.

Attempts were made to investigate whether the levels of ocular higher order aberration present could help explain any of the differences found in the accommodation responses between the two groups. In each group the latency of accommodation and the peak velocity of accommodation and disaccommodation showed no significant correlation with the levels of aberration present in the eye. Similarly, the time constants of disaccommodation showed no correlation with the levels of spherical or total higher order RMS aberration. The time constant of accommodation showed a positive correlation with spherical aberration, but not with the levels of total higher order RMS aberration. There is evidence that some individuals may rely more heavily on higher order aberrations as an accommodative cue than others (Chen *et al.*, 2006). This could be a possible reason for the lack of correlation between several of the accommodative response components and the levels of higher order aberration. It may be that the actual magnitude of aberrations is not the important factor. Of more importance may be the emphasis that the individual places on higher order aberrations as an accommodative cue. For example a small change in aberrations may be sufficient to disrupt accommodative functions in one individual, where as a large change in aberrations may have relatively little affect on accommodation in another individual that relies more heavily on other accommodative cues.

The amplitude of response appeared to show the most significant correlation with the level of aberrations. The amplitude of response showed a positive correlation with levels of spherical aberration and a negative correlation with the levels of total higher order RMS aberration. It is important to mention here the possibility that there were differences in the dynamic accommodation responses between the refractive surgery group (all myopes) and the emmetropic group related to refractive error. This may be particularly true for the amplitude of response. Previous studies have shown myopes tend to exhibit higher accommodative lags than emmetropes (McBrien and Millodot, 1986b; Gwaizda *et al.*, 1993). There is also some evidence that myopes can show reduced velocity of accommodation (O'Leary and Allen, 2001; Radhakrishnan *et al.*, 2007). It is therefore possible that refractive error group contributed to (or indeed caused) some of the differences in accommodation responses found in this study. In contrast, some previous studies have shown no significant differences in the dynamic accommodation responses of emmetropes and myopes (Kasthurirangan *et al.*, 2003; Kasthurirangan and Glasser, 2005). Measuring the same patient group pre-operatively and post-operatively (as in Chapters 5, 6 and 7) would have allowed control of these refractive group effects. However, this was not possible in the present study. Prior to surgery, correction of the myopia was required with either spectacles or contact lenses to allow visualization of the targets. During initial trials with the equipment prior to surgery, the Shin-Nippon auto-refractor was unable to acquire precise bar separation images through spectacle or trial lenses due to lens movement and reflections. This can be solved by fitting the patient with contact lenses. However, the pre-operative study measurements were typically taken on the day of refractive surgery, which prevented insertion of contact lenses for the measurements. Hence it was not possible to obtain accurate pre-operative data for comparison with post-operative results.

The results obtained for amplitude of response as a function of spherical aberration in Figure 8.8a appear counter-intuitive. It is thought that accommodative lag and ocular aberrations interact to optimize retinal image quality during close work (Plainis *et al*., 2005; Buehren and Collins, 2006; Collins *et al*., 2006) and has been suggested that increasing levels of negative spherical aberration could decrease accommodative lag by shifting the optimum focus in a myopic direction (Radhakrishnan *et al*., 2004; Collins *et al*., 2006). Indeed, this is supported by recent experimental work that altered spherical aberration using contact lenses (Allen *et al*., 2009; Theagarayan *et al*., 2009) and adaptive optics (Gambra *et al*., 2009). The refractive error effects may help explain the amplitude results found in Figure 8.8. Closer inspection of Figure 8.8 (graph a) shows that the emmetropes typically had low levels of positive spherical aberration as expected in a normal population (Porter *et al*., 2001), and high amplitudes of response (i.e. lower lags) relative to the refractive surgery patients (myopes). The refractive surgery group had a greater spread of aberration levels, which may be expected following surgery, and lower response amplitudes (higher lags) relative to the emmetropes. Due to the possible effects of refractive error, the amplitude results were re-analyzed for each group individually (see appendix 8a). When analyzed individually neither group showed a significant correlation between amplitude and level of spherical aberration. The emmetropes also showed no significant correlation between amplitude of response and total higher order RMS.

However, significant correlation was found between the amplitude of response and levels of total higher order RMS for the refractive surgery group. He *et al*. (2005) investigated the relationship between ocular aberrations and the accuracy of the accommodative response in emmetropic and myopic eyes. They found that myopes with reduced retinal image quality showed higher lags of accommodation, however this relationship did not hold for the emmetropes. The amplitude results of the current study are consistent with the results of He *et al*. (2005) showing that progressively higher lags are found with increasing levels of total higher order RMS aberration in those undergoing refractive surgery (pre-operatively myopes). It may be that the higher levels of aberration adversely affect image quality which in turn makes accurate accommodation more difficult.

Due to logistical reasons during the dynamic study, the distance aberrations had to be measured using different aberrometers for each group. It is therefore important to acknowledge that any differences between the measuring techniques may have introduced an additional source of error to the experiment. However, during additional experimental work (presented in Chapter 10) aberration measurements became available for a small group of patients on both aberrometers (n=7 patients). In an attempt to gauge the level of agreement between instruments, aberration measurements were compared between the two aberrometers (see appendix 8b). Statistical testing (paired two-tailed t-test) showed no significant differences between the measurements taken with the two aberrometers for total higher order RMS, RMS 3rd order, RMS 4th order, or spherical aberration ($p>0.05$). In addition, an established statistical analysis method for the comparison of clinical measurements described by

Bland and Altman (1986) was performed (see appendix 8c). The measurements obtained by the two aberrometers differed by less than 0.065µm in 95% of cases. Although these comparisons involve a different group of patients than those involved in the current study on accommodative dynamics, the comparisons suggest a reasonable level of agreement between the two aberrometers.

In conclusion, significant differences were found between the dynamic accommodative responses of patients that had undergone refractive surgery in comparison to an emmetropic control group. It is possible that altered levels of ocular aberrations following refractive surgery contributed to these differences, however it is also possible that the differences may be explained by differences in refractive error between the surgically corrected myopes and the emmetropic control group.

CHAPTER 9
CHANGES IN ASTIGMATISM AND HIGHER ORDER ABERRATIONS DURING ACCOMMODATION

9.1 Introduction

As the eye accommodates it undergoes a change in refractive power. In addition, the accommodative process is thought to alter ocular aberrations which in turn are likely to affect the quality of the image formed on the retina. A number of studies have reported changes in astigmatism (Ukai and Ichihashi, 1991; Mutti *et al*., 2001; Cheng *et al*., 2004; Radhakrishnan and Charman, 2007b), spherical aberration (Ivanoff, 1956; Koomen *et al*., 1956; Van Den Brink, 1962; Jenkins, 1963), and other higher order aberrations (He *et al*., 2000; Ninomiya *et al*., 2002; Plainis *et al*., 2005; Radhakrishnan and Charman, 2007a) during accommodation.

The principal source of these changes in aberrations is thought to be the crystalline lens. Whole-eye wavefront aberrations are expected to alter during accommodation due to the changes that occur in the shape, position and refractive index gradient of the crystalline lens (Garner and Smith, 1997; Garner and Yap, 1997). It has been suggested that changes in astigmatism during accommodation could result from inhomogeneous changes in lens or ciliary muscle contraction during accommodation (Brzezinski, 1982), or from a tilting of the lens during accommodation caused by the combined effects of slacker zonule and gravity (Radhakrishnan and Charman, 2007b). While the main source of changes in aberrations during accommodation is thought to be the crystalline lens, another potential source is the cornea. Numerous studies have investigated whether or not the cornea changes during accommodation, with conflicting results. Therefore, the occurrence of corneal changes during accommodation remains a matter of debate. Pierscionek *et al*. (2001) investigated changes in central corneal curvature during accommodation of up to 9D in 14 normal subjects using a keratometer. The results showed that 11 of the 14 subjects showed a change in corneal curvature of approximately 0.4D in at least one principal meridian between distance and near fixation. A similar study by Yasuda *et al*. (2003) measured corneal topography before accommodation (unaccommodated state) and at maximum amplitude of accommodation (fully accommodated state) in 14 normal subjects. The results showed that the cornea steepened by approximately 0.6D over the full range of accommodation. He *et al*. (2003) measured corneal shape and wavefront aberration change during accommodation between a distance target (0.25D) and a near target (5D) in 12 normal subjects. Their results suggest a flattening of the central cornea, and a significant alteration in spherical aberration and coma with increasing accommodation. Some subjects also showed variations in corneal total higher order RMS aberration during accommodation. In contrast, other studies have suggested that the corneal shape remains relatively stable during accommodation (Fairmaid, 1959; Lopping and Weale, 1965; Mandell and Helen, 1968; Buehren *et al*., 2003).

A number of potential mechanisms by which the cornea could alter during accommodation have been suggested including, the effect of contraction of the extra-ocular muscles on the cornea (Brzezinski, 1982) (i.e. when the effects of convergence are also considered), the effect of contraction of the ciliary muscle on the cornea (Piersionek *et al*., 2001), and the possible effects of increased intra-ocular pressure during accommodation (due to the lens shape changes) which may act on the cornea to alter its shape (He *et al.*, 2003).

The aim of this study was to investigate the changes in aberrations (astigmatism and higher order aberrations) during accommodation in eyes that have undergone refractive surgery for myopia. Aberrations were measured pre-operatively and post-operatively in a group of patients undergoing refractive surgery. The assumption was that changes in aberrations originating from the crystalline lens would remain the same relative to pre-operative measurements, but that the thinner post-operative cornea may be less resistant to the forces exerted on it during accommodation. It may be that that the post-operative cornea is therefore more likely to alter shape during accommodation and hence introduce greater levels of aberration during close work. As the cornea is the principal refractive component of the eye, changes to its shape during accommodation may be particularly important in relation to the optics of the eye.

9.2 Subjects

A total of 31 eyes of 31 healthy pre-presbyopic adults that had chosen to undergo refractive surgery for myopia and myopic astigmatism took part in the study of changes in astigmatism with accommodation. The patients taking part in this study were the same group that took part in the study described in Chapter 5 (see Table 5.1 for demographic characteristics). This study also examined the changes in higher order aberrations with accommodation in a subgroup of these 31 patients. The subgroup consisted of patients with a broad range of pre-operative refractive errors and ages that were able to travel to the University of Manchester prior to having refractive surgery performed. A total of seven subjects took part in the study on the changes in higher order aberrations during accommodation. All subjects were patients that had chosen to undergo refractive surgery at Manchester Royal Eye Hospital and were a subgroup of the cohort described in Chapter 4. The patients in the subgroup had a mean (± SD) age of 29.9 ± 5.9 years (range 23 to 42 years). In the tested eye the mean (± SD) pre-operative refractive error (mean sphere) was -5.05 ± 2.98D (range -1.75D to -9.12D) and the mean (± SD) preoperative BSCVA (LogMAR) was -0.09 ± 0.10 (range +0.10 to -0.18). All of the patients in the subgroup underwent LASEK surgery. Four of the procedures were wavefront-guided and the remaining three procedures were conventional (non-wavefront-guided) procedures. One month post-operatively the mean (± SD) refractive error (mean sphere) in the tested eye was -0.30 ± 0.25D. The mean (± SD) UCVA (LogMAR) was +0.08 ± 0.07 (range +0.20 to 0.00) and the mean (± SD) BSCVA was -0.02 ± 0.07 (range +0.10 to -0.10). Three months post-operatively the mean (± SD) refractive error (mean sphere) in the tested eye was +0.16 ± 0.30D. The mean (± SD) UCVA (LogMAR) was -0.05 ± 0.09 (range +0.10 to -0.18) and the mean (± SD) BSCVA was -0.11 ± 0.06 (range 0.00 to -0.18). All experimental procedures were explained and the subjects gave their informed consent prior to participation in the study.

9.3 Methods

9.3.1 Astigmatism during accommodation

Monocular accommodative responses were measured using a Shin-Nippon SRW-5000 auto-refractor to letter stimuli that were presented at a range of distances to create accommodative stimuli over a range of 0.25D to 4.0D (presentation distances used were: 4.0m, 1.0m, 0.5m, 0.33m and 0.25m). The method of how the data were collected has been described in Chapter 6 (see section 6.3). The data were then analyzed as described in section 9.3.3.1.

9.3.2 Higher order aberrations during accommodation

Changes in higher order aberrations during accommodation were measured pre-operatively and then at one month and three months following refractive surgery. Accommodation responses, ocular aberrations and pupil sizes were measured with a Shack-Hartmann aberrometer (IRX3, Imagine eyes, Paris) in the same clinical laboratory with the room lights switched off. All measurements were taken under monocular conditions with the non-tested eye occluded. All measurements were taken with a natural pupil, without the use of a mydriatic agent. Measurements commenced with the determination of the aberrometer target position corresponding to the far point, followed by the measurement of the ocular aberrations. The aberrometer incorporated an internal Badal system which allowed the vergence of the fixation target to be systematically altered in relation to the subject's far point. Using this system, the accommodative demand was increased between 0.00D and 4.00D in

0.50D steps and the accommodative response and whole-eye aberration profile was recorded during accommodation over the nominal 4.00D range. A 4.00D range was used to ensure that the tested range fell within the amplitude of accommodation for all patients. The accommodative response to any near stimulus was taken as the difference between the mean-sphere refractions measured with the near stimulus and that of the far point, with sign reversed to make the response positive. Each axial change in target position took 750ms. The target was then kept at a constant vergence for 1 second after which a measurement of the wave-front aberration was made, before continuing to the next stimulus level. The accommodative target viewed by the subjects during the measurements was incorporated in the aberrometer. The target was a black 6/12 Snellen optotype ("E") on an elliptical white background. The background subtended approximately 0.75 x 1.0 degrees of visual angle and had a luminance of 85cd/m^2. The subjects were instructed to keep the target as clear as possible at all times (employing both reflex and voluntary accommodation). No refractive corrections were worn, instead the correction of refractive error was provided by the aberrometer's internal lens system using the mean-sphere refraction obtained from the initial refractive error reading, and it was ensured that the target appeared clear to the patient before measurements commenced. At each study visit the measurements were repeated seven times, the first two runs were used as practice for the patient to become familiar with the task and the following five runs were the test runs from which the results were averaged.

9.3.3 Data Analysis

9.3.3.1 Astigmatism data

The cylindrical refractive errors obtained from the auto-refractor readings were converted to power vectors (Thibos *et al*., 1997; Atchison, 2004) using the equations:

$$\mathbf{J_{180} = -\frac{C}{2}(\cos 2\alpha)}$$

$$\mathbf{J_{45} = -\frac{C}{2}(\sin 2\alpha)}$$

Where:

C = Cylinder power (D)

α = Cylinder axis (Radians)

$\mathbf{J_{180}}$ and $\mathbf{J_{45}}$ = Power of two Jackson cross cylinder components

For each patient the mean of five readings was used for J_{180} and J_{45} at each stimulus level. Graphs were plotted for J_{180} and J_{45} as a function of accommodative response for each patient and linear regression lines were calculated for each graph. The gradient of each linear regression line was used to determine the change in J_{180} and J_{45} per dioptre of accommodation response for each patient.

9.3.3.2 Higher order aberration data

Within any study population it is likely that there will be a level of variation in natural distance resting pupil diameters. In addition, it is well known that pupil size varies with accommodation. The pupil typically shows a decrease in diameter with increasing accommodative response, although the level of pupil miosis during accommodation can vary widely between individuals (Radhakrishnan and Charman, 2007c). The values of Zernike coefficients used to quantify the levels of higher order aberration are dependant on pupil size. Because of the pupil size dependency of aberrations and the variation of pupil size with accommodation, it can be difficult to specify a single pupil size that provides a meaningful comparison across an entire study population. To solve this problem the measurements of higher order aberrations were converted to equivalent defocus values using the equation:

$$\mathbf{M = 4\sqrt{3}\ (C_n^f / r^2)}$$

(Thibos *et al.*, 2002b)

Where:

M = Equivalent defocus (D)

$\mathbf{C_n^f}$ = Zernike coefficient (µm)

r = Pupil radius (mm)

Equivalent defocus describes the amount of spherical defocus required to produce the same wavefront variance as that produced by the higher order aberration at the same pupil diameter (Thibos *et al.*, 2002b). Equivalent defocus values were calculated for spherical aberration, coma and total higher order RMS (3rd-6th order) for the natural pupil diameter at each accommodation response level. Coma and spherical aberration can also be expressed in an alternative dioptric form that enables comparison of results obtained for different pupil diameters (Radhakrishnan and Charman, 2007a). These values were calculated using the equations:

$$\textbf{Coma} = \frac{9\sqrt{8}}{r^3} \times \sqrt{\left((C_3^{-1})^2 + (C_3^{+1})^2 \right)}$$

Where:

Coma = Coma (D/mm)

C_3^{-1} = X-axis coma (μm)

C_3^{+1} = Y-axis coma (μm)

r = Pupil radius (mm)

$$\textbf{Spherical aberration} = \frac{24\sqrt{5}}{r^4} \times C_4^0$$

Where:

Spherical aberration = Spherical aberration (D/mm^2)

C_4^0 = Spherical aberration (μm)

r = Pupil radius (mm)

Graphs were plotted for the level of aberration against the level of accommodative response for each patient at each visit. Linear regression lines were fitted to these graphs and the gradients of the linear regression lines were used to determine the change in aberration per dioptre change in accommodation response.

9.4 Results

9.4.1 Astigmatism results

Figure 9.1 shows the change in J_{180} and J_{45} and as a function of accommodation response for all patients at each study visit. As expected, the overall levels of astigmatism appeared larger at the pre-operative visit than at the post-operative visits. No significant correlation was found between the levels of J_{180} or J_{45} and the accommodation response at any of the study visits. This suggests that the levels of astigmatism remained relatively constant during accommodation at each visit.

The gradient of the linear regression lines fitted to the data were used to determine the change in J_{180} and J_{45} per dioptre of accommodation response for each individual patient. Figure 9.2 shows the mean change in J_{180} and J_{45} for all patients at each study visit. The mean gradients for both J_{180} and J_{45} were between ± 0.04 DC/D at all visits. Repeated measures ANOVA showed no significant difference in the mean gradient between the different study visits for both J_{180} ($F_{2, 28}$ = 1.392, p=0.266) and J_{45} ($F_{2, 28}$ = 1.571, p=0.226).

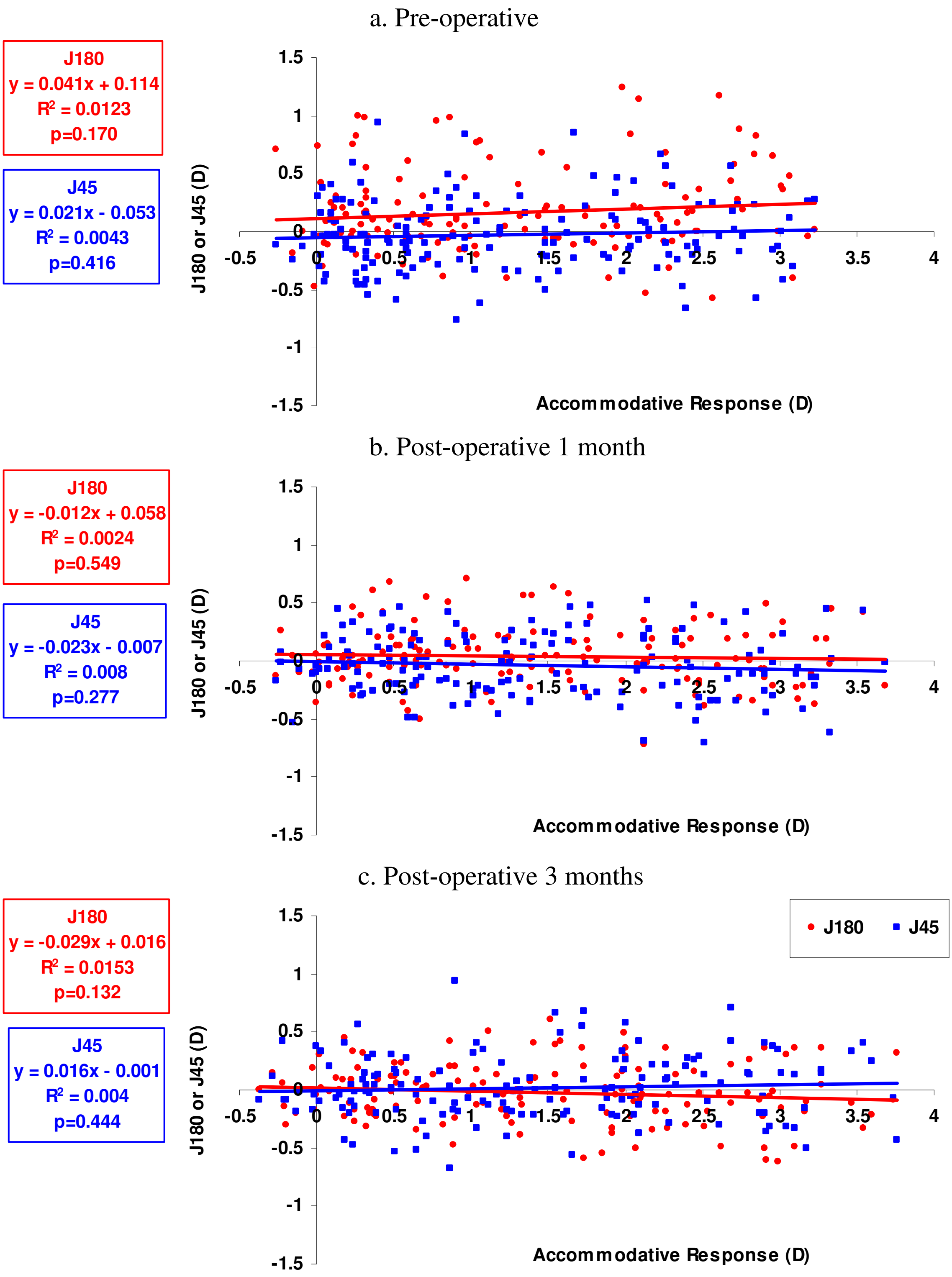


Figure 9.1: J_{180} and J_{45} as a function of accommodation response for patients undergoing refractive surgery. Results are shown pre-operatively (graph a, n=31 patients) and at one month (graph b, n=30 patients) and three months post-operatively (graph c, n=31 patients) along with the linear best fit lines, equation, R^2 value and p-value for correlation.

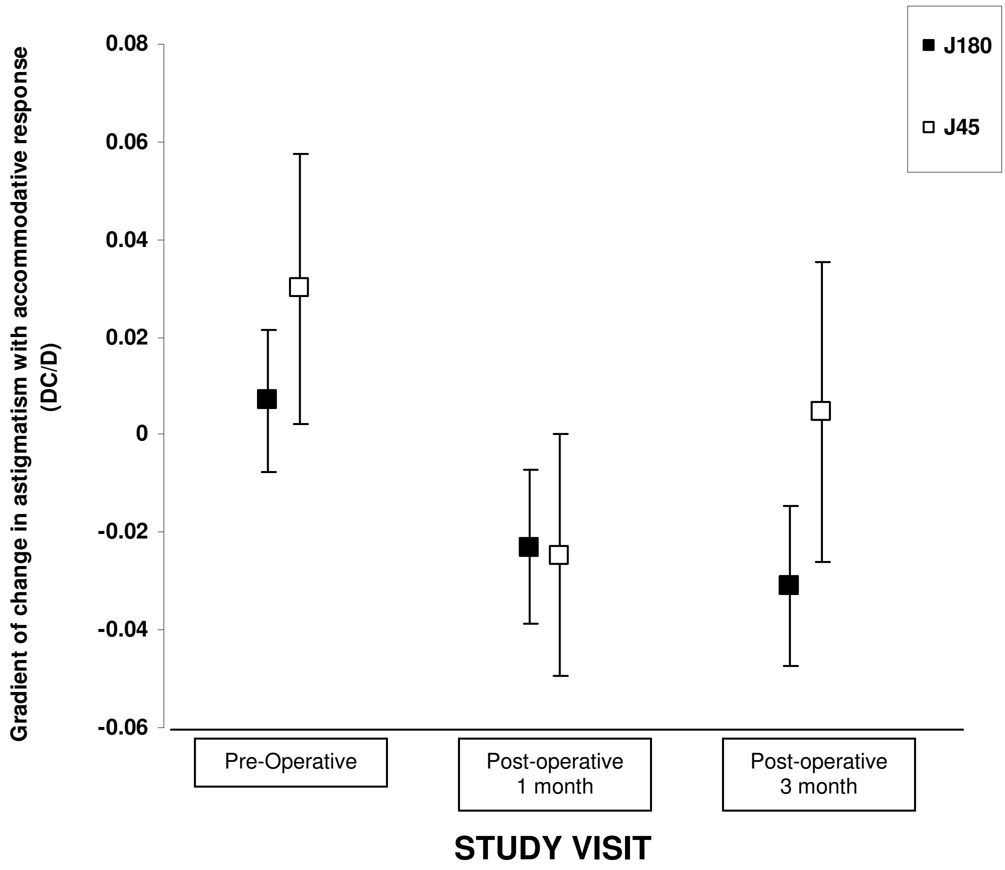


Figure 9.2: The overall mean (±SEM) change in J_{180} and J_{45} per dioptre of accommodation response across all patients. Results are shown prior to refractive surgery and then at one month and three months post-operatively.

9.4.2 Higher order aberrations

Figure 9.3 shows typical data for accommodative response and pupil diameter as a function of accommodative stimulus. Data shown in Figure 9.3 were obtained pre-operatively from two different patients. The accommodative stimulus-response functions followed the usual pattern with the response showing the classic lead of accommodation at low stimulus levels and a lag of accommodation with increasing stimulus levels. An initial non-linear region was observed at low stimulus levels (below 1D) for the majority of patients followed by a linear region at higher stimulus levels. This can be seen clearly in Figure 9.3b. The gradients for accommodative response/accommodative stimulus were therefore calculated over the nominal stimulus range 1-4D for each patient. All functions appeared linear over this region for all patients. All patients showed a decrease in pupil diameter with increasing accommodative response. This pupil miosis was relatively repeatable over the five readings for each individual (see Figure 9.3) but showed considerable variation between different patients.

It was assumed that miosis and accommodative response are more closely linked than miosis and accommodative stimulus. Therefore further graphs were plotted for pupil diameter as a function of the corresponding accommodative response for each patient at each visit. The gradients of these graphs were obtained to give the change in pupil diameter per dioptre of accommodative response. Across all study visits the change in pupil diameter per dioptre of accommodation for all patients ranged between -0.0199 mm/D and -0.9236 mm/D. Table 9.1 shows the results for the mean changes in pupil diameter with accommodation along with the mean stimulus-response function gradient for the group at each visit. There was a tendency for the pupil size to decrease more rapidly with accommodation after surgery, however, one-way repeated measures ANOVA showed no significant difference in change in pupil size with accommodation before and after refractive surgery ($F_{2,5} = 1.459$, p=0.317). In comparison to the pre-operative baseline, the stimulus-response function gradient showed a decrease following refractive surgery at both post-operative visits. This decrease did not reach statistical significance (one-way repeated measures ANOVA, $F_{2,5} = 1.043$, p=0.418).

a. Age 29, mean sphere -9.12D   b. Age 28, mean sphere -3.25D

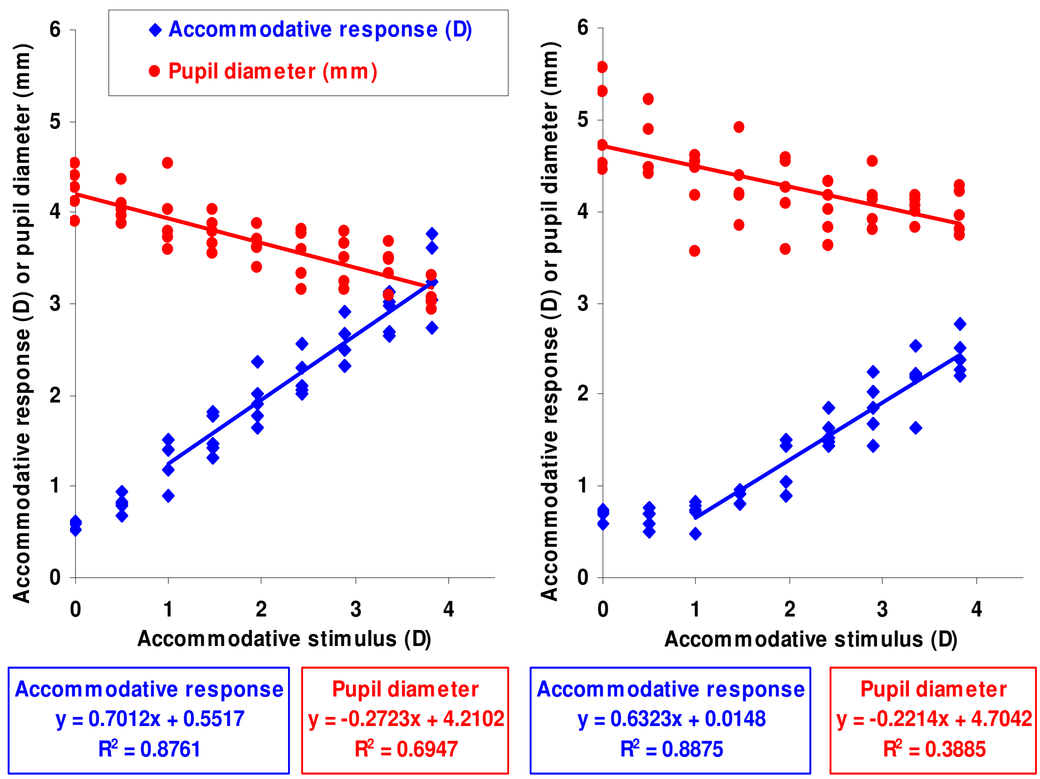


Figure 9.3: Examples of typical data for accommodation response (blue diamonds) and pupil diameter (red circles) as a function of accommodative stimulus. Results are shown pre-operatively for two different patients (a and b). Data from all five readings are shown at each stimulus level with linear regression lines, equation and R^2 values. The linear regression line was calculated over the whole stimulus range for the pupil size data and over the linear region (1-4D stimulus range) for the accommodation response data.

Visit	Change in pupil diameter per dioptre of accommodative response (mm/D)	Response function gradient
Pre-operative	-0.33 ± 0.22	0.70 ± 0.18
Post-op *1month*	-0.42 ± 0.27	0.58 ± 0.18
Post-op *3month*	-0.40 ± 0.36	0.61 ± 0.17

Table 9.1: Mean (± SD) change in pupil diameter per dioptre of accommodation response and accommodative stimulus-response function gradient for patients undergoing refractive surgery. Results are shown pre-operatively and at one month and three months post-operatively.

9.4.2.1 Natural pupil size data

Table 9.2 shows the results for the change in aberration levels with increasing accommodation response for all patients. Spherical aberration was found to increase in a negative direction with increasing accommodative response at each study visit. Coma and total higher order RMS aberration were found to increase with increasing accommodative response at each study visit. One-way repeated measures ANOVA showed that the mean change in aberration per dioptre change in accommodation response did not alter significantly over the three visits for any of the aberrations measured (see Table 9.2).

Aberration	Pre-operative	Post-operative *1month*	Post-operative *3 month*	p-value
Spherical (D)	-0.043 ± 0.041	-0.049 ± 0.033	-0.068 ± 0.033	0.198
Spherical (D/mm^2)	-0.022 ± 0.036	-0.055 ± 0.029	-0.071 ± 0.048	0.088
Coma (D)	0.016 ± 0.024	0.030 ± 0.051	0.025 ± 0.032	0.353
Coma (D/mm)	0.037 ± 0.030	0.058 ± 0.067	0.048 ± 0.045	0.660
Equivalent defocus RMS higher order (D)	0.020 ± 0.046	0.018 ± 0.037	0.020 ± 0.037	0.993

Table 9.2: Mean (±SD) change in aberration per dioptre change in accommodative response for patients undergoing refractive surgery. Results are shown pre-operatively and at one month and three months post-operatively with p-values representing the significance of changes between visits.

9.4.2.2 Fixed pupil size data

Natural distance resting pupil size generally fell between 4.0mm and 6.0mm and decreased to between 3.5mm and 5.5mm at maximum accommodation for all subjects. The wavefront data were therefore also analyzed for a fixed pupil diameter of 3.5mm at all accommodation levels. Graphs were drawn for each higher order aberration as a function of accommodative response for a 3.5mm natural pupil. Five experimental runs were recorded for each patient. Two runs from one patient at one visit, and one run from another patient at one visit were excluded due to poor accommodative responses (responses remained below 1D over the whole 4D stimulus range). Also, for one patient, two runs covered a 0-3D stimulus range only. This was because the pupil size fell below 3.5mm for stimulus levels of 3.5D and 4.0D. As an example of the type of changes found, Figure 9.4 shows the levels of spherical aberration (Figure 9.4a) and total higher order aberration RMS (Figure 9.4b) as a function of accommodation response for all measurements for all subjects. Spherical aberration was found to change in a negative direction with increasing accommodation at each study visit. The change in total higher order aberration with accommodation was less predicable. There was an increase in total higher order RMS with accommodative response pre-operatively, although this relationship did not hold at either of the post-operative visits. Table 9.3 shows the regression equations for different higher order aberrations as a function of accommodation response. Several higher order aberrations showed significant correlation with accommodation response at some of the study visits but the only higher order aberration to consistently show a significant correlation with accommodative response at all study visits was 4th order spherical aberration.

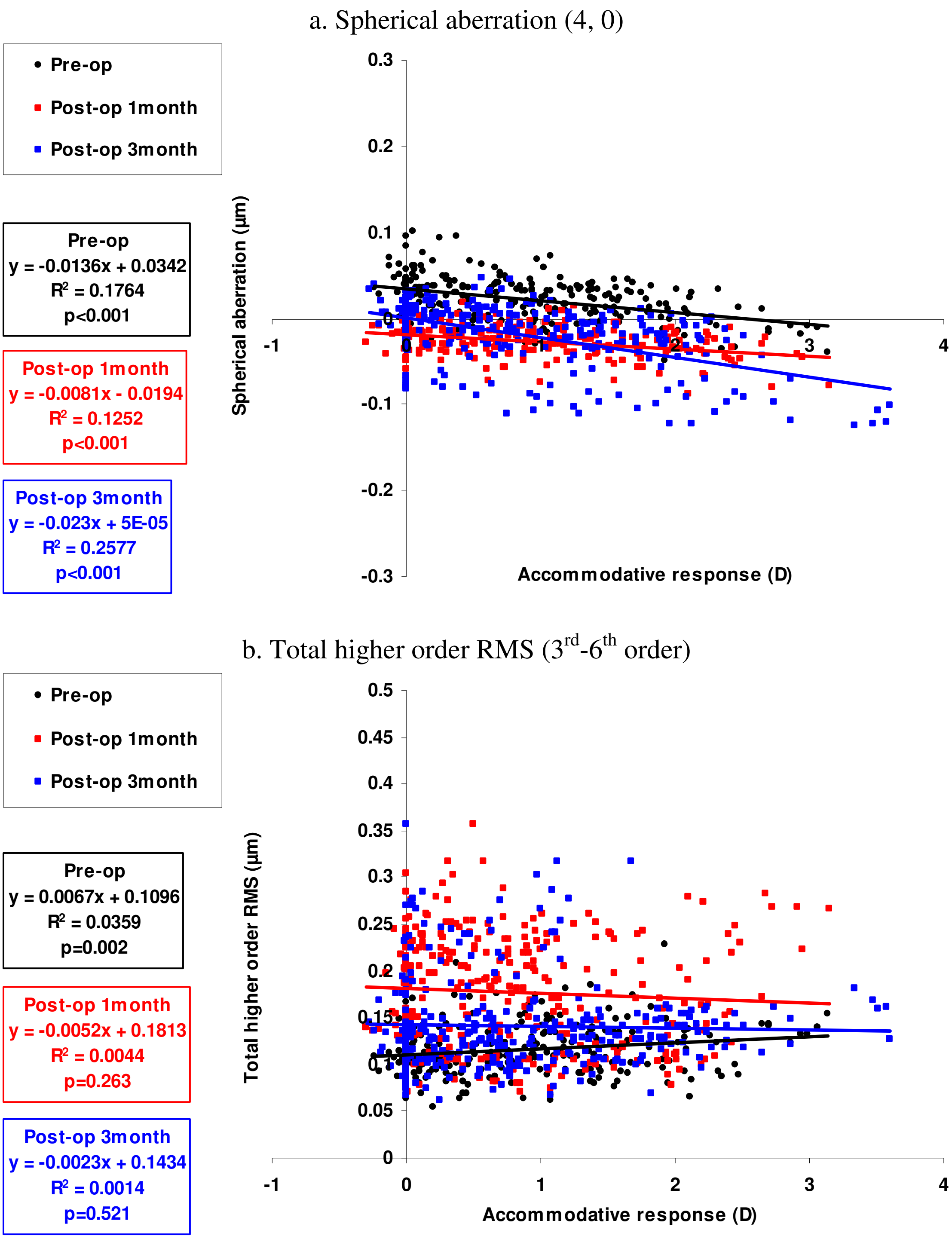


Figure 9.4: Spherical aberration (a) and total higher order aberration (b) over a 3.5mm natural pupil as a function of the accommodative response for patients undergoing refractive surgery. Results are shown pre-operatively (black circles) and at one month (red squares) and three months (blue squares) post-operatively. Data from all five readings are shown at each visit with linear regression lines, equation, R^2 value and p-value.

Aberration (Zernike order)	Visit	Regression Equation	R^2	p-value
Coma y-axis (3, 1)	Pre-operative	y = 0.022x – 0.025	0.079	<0.001
	Post-op *1month*	y = 0.009x – 0.002	0.012	0.0690
	Post-op *3month*	y = 0.006x + 0.007	0.010	0.0790
Coma x-axis (3, -1)	Pre-operative	y = -0.004x + 0.026	0.006	0.238
	Post-op *1month*	y = 0.031x – 0.027	0.052	<0.001
	Post-op *3month*	y = -0.007x + 0.042	0.004	0.292
Trefoil y-axis (3, -3)	Pre-operative	y = -0.014x + 0.001	0.068	<0.001
	Post-op *1month*	y = 4E-05x + 0.003	1E-07	0.996
	Post-op *3month*	y = -0.016x – 0.007	0.054	<0.001
Trefoil x-axis (3, -3)	Pre-operative	y = 0.007x – 0.042	0.027	0.008
	Post-op *1month*	y = 0.023x – 0.019	0.049	<0.001
	Post-op *3month*	y = 0.0003x – 0.016	7E-05	0.881
Spherical (4, 0)	Pre-operative	y = -0.014x + 0.034	0.176	<0.001
	Post-op *1month*	y = -0.008x – 0.019	0.125	<0.001
	Post-op *3month*	y = -0.023x + 5E-05	0.258	<0.001
Total higher order (3^{rd}-6^{th} order) RMS	Pre-operative	y = 0.007x + 0.110	0.036	0.002
	Post-op *1month*	y = -0.005x + 0.181	0.004	0.263
	Post-op *3month*	y = -0.002x + 0.143	0.001	0.521

Table 9.3: Regression equations for third order aberrations, fourth order spherical aberration and total higher order RMS aberration for a 3.5mm natural pupil diameter as a function of accommodative response at each study visit.

9.5 Discussion

The aim of this study was to investigate the changes in aberrations (astigmatism and higher order aberrations) during accommodation in a group of eyes that underwent refractive surgery for myopia. Figures 9.1 and 9.2 show the results for changes in astigmatism during accommodation. The results suggest that the levels of astigmatism remained stable during accommodation for both J_{180} and J_{45} and that the level of astigmatism during accommodation was not affected by refractive surgery.

Previous studies have reported changes in astigmatism with accommodation over a 0-4D range (Radhakrishnan and Charman, 2007b) a 0-6D range (Cheng *et al.*, 2004) and over the full range of accommodation of the tested subjects (Ukai and Ichihashi, 1991) in groups of normal subjects. These astigmatic changes have usually been found to be relatively small and vary widely between individuals. Differences in the ranges over which accommodation was measured in each of these previous studies may account for some of the differences in the results that they obtained. Radhakrishnan and Charman (2007b) found a weak but significant tendency for J_{180} to increase during accommodation across their whole subject group. However, changes in J_{180} were generally less than ±0.05 DC/D, and approximately half of their subjects showed no significant change in J_{180} with accommodation. Their results also showed that across the whole group, J_{45} showed no significant change with accommodation. Comparable results were found by Ukai and Ichihashi (1991) who found a variety of astigmatic changes with accommodation in a group of 20 normal subjects. Seven of their subjects showed an increase in astigmatism with accommodation in the order of 0.50D or less over the 5-10D accommodative range tested. Eight of their subjects showed no change in astigmatism during accommodation. The remaining five subjects showed other types of change, such as lower astigmatism at intermediate accommodation levels and increases at higher accommodative levels, or changes in astigmatism axis with increasing accommodation which were not necessarily accompanied by change in astigmatic power. Cheng *et al*. (2004) found that astigmatism changed for some individuals during accommodation, however, the magnitude and direction of change (positive or negative) varied widely between subjects. The mean change in astigmatism during accommodation in their group of 74 normal subjects was less than 0.1D over the 0-6D range of accommodation tested.

Changes in astigmatism during accommodation may be caused by inhomogeneous changes in lens or ciliary muscle contraction during accommodation (Brzezinski, 1982). It is possible that such changes would be essentially random in nature which may be a factor in the large variation between subjects found in previous studies (see e.g. Ukai and Ichihasi, 1991). It may also explain why no significant correlation was found when changes in astigmatism with accommodation were averaged across a group of patients in the present study. It has also been suggested that tilting of the lens during accommodation may contribute to astigmatic changes, particularly in the J_{180} component (Radhakrishnan and Charman, 2007b). There was no evidence for this in the present study. A possible reason for this is that the subjects viewed the accommodative targets along a horizontal meridian, where presumably the effects of lens tilt would be minimal.

Another potential source of changes in astigmatism during accommodation is the cornea. However, debate remains as to whether or not corneal changes take place during accommodation. Some studies have reported corneal changes during accommodation (Pierscionek *et al.*, 2001; Yasuda *et al.*, 2003) while others have found that the cornea remains stable during accommodation (Fairmaid, 1959; Lopping and Weale, 1965; Mandell and Helen, 1968; Buehren *et al.*, 2003). The results of the present study would favour the notion that the cornea remains stable during accommodation. In addition, the results suggest that the thinner post-operative cornea is no less resistant to any changes during accommodation.

Higher order aberrations (3^{rd}-6^{th} order) were also measured during accommodation on a subgroup of the patient cohort. The accommodative response functions showed that the patients accommodated reasonably well to the 4D stimulus created by the aberrometer. Accommodative stimulus-response function gradients were generally in the range 0.4 to 0.9 (Table 9.1). These were slightly lower than the gradients achieved for the whole group (in Chapter 6), probably due to the use of negative lenses to stimulate accommodation here (as opposed to altering target distance in Chapter 6). Post-operatively the stimulus-response function gradients were found to decrease by a similar magnitude to those found in Chapter 6. This decrease did not reach statistical significance, probably as a result of the limited sample size.

It is well known that pupil size tends to decrease with increasing accommodation. It was necessary to investigate these pupil size changes in this population to evaluate which pupil size to use when assessing the change aberrations during accommodation. As expected, pupil size was found to decrease during accommodation for all patients. Alterations in pupil diameter were typically in the order of -0.30mm and -0.40mm per dioptre of accommodation at each of the study visits (Table 9.1). This is comparable with previous studies that have found alterations in pupil size of -0.35mm/D (Gambra *et al.*, 2009), -0.18mm/D (Plainis *et al.*, 2005) and -0.45 mm/D (Alpern *et al.*, 1961). All patients showed a pupil size of at least 3.5mm during the accommodation measurements, which allowed the investigation of aberrations for a 3.5mm pupil diameter.

Table 9.3 shows that several of the higher order aberrations investigated showed significant correlation with accommodation response. However, the only higher order aberration to show a consistent correlation across all study visits was spherical aberration. Spherical aberration was found to always show a shift towards negative values with increasing accommodation. The changes in other aberrations were found to be less predicable: varying in magnitude and direction between individuals and study visits. These results are consistent with previous studies that have examined the change in higher order aberrations with accommodation (He *et al*., 2000; Ninomiya *et al*., 2002; Cheng *et al*., 2004; Plainis *et al*., 2005; Radhakrishnan and Charman, 2007a). The rate of change of aberrations during accommodation was not found to alter significantly over the three study visits for any of the aberrations calculated for a natural pupil size. This suggests that refractive surgery did not alter the rate of change in aberrations during accommodation.

In conclusion, the results of this study suggest that astigmatism remains stable during accommodation for both J_{180} and J_{45}, and that the levels of astigmatism during accommodation were not affected by refractive surgery. Changes in higher order aberrations during accommodation were found, which were consistent with those expected from previous studies. However, the results suggest that the rate of change of aberrations during accommodation is not affected by refractive surgery.

CHAPTER 10
TEAR FILM

10.1 Introduction

One of the principal functions of the tear film is to provide a smooth optical surface which contributes to production of a good quality retinal image and normal vision. The smooth surface of the anterior eye is maintained by the intermittent re-surfacing of the tear film by the blink reflex. However, between blinks the tear film does not remain stable. The tear film rapidly builds-up once the eye-lids are opened, it then stabilizes, reaching its most uniform state for a few seconds and then begins to thin, and eventually exhibit areas of localized disruption known as "tear break-up" (Benedetto *et al*., 1984; Wong *et al*., 1996; Nemeth *et al*., 2002).

The tear film has the greatest refractive power of any ocular surface due to the large change in refractive index that occurs at the transition between the air and the tear film. In the presence of a smooth tear film of uniform thickness, the combination of tear film and cornea has been shown to have the same optical power as the cornea alone (Albarran *et al*., 1997). However, during tear-break-up the localized areas of disruption will produce localized variations in thickness and curvature of the tear film which may introduce aberrations to the optical system of the eye (Tutt *et al*., 2000).

A number of studies have been carried out to investigate the changes in higher order optical aberrations that occur due to the tear film break-up between blinks (e.g. Koh *et al*., 2002; Montes-Mico *et al*., 2004a; b; c; 2005a; Lin *et al*., 2005). These studies have shown that aberrations tend to increase with increasing time following a blink and suggest that changes in the tear film are capable of introducing measurable changes in the optical quality of the eye. Differences between methodology and subject groups make direct comparison of studies difficult and evidently produces conflicting results in terms of the duration over which the deterioration in optical quality occurs and the within-subject and between-subject variability of the changes that can occur.

Corneal laser refractive surgery is known to cause a number of changes to the tear film, topography and ocular surface (Battat *et al*., 2001). Reported alterations include decreases in tear secretion (Benitez-del-Castillo *et al*., 2001), tear volume (Albietz *et al*., 2002), tear stability (Yu *et al*., 2000), tear clearance (Battat *et al*., 2001) and increases in tear osmolarity (Lee *et al*., 2000). Given the possible array of changes following refractive surgery, one would expect these alterations to have consequences for the optical quality of the eye.

A dynamic relationship exists between TBUT and blink rate. As the TBUT is typically greater than the inter-blink interval, the tears frequently never break up between blinks. However, the increase prevalence of dry eye and possible decrease in blink rate after refractive surgery (Yu *et al*., 2000; Toda *et al*., 2001; Albietz *et al*., 2002) may alter the dynamic relationship between TBUT and blink rate: making the tear film more likely to break-up between blinks in those that have undergone refractive surgery. Despite this, there has been relatively little published on the effects of tear film changes on the optical quality of the eye following refractive surgery.

The main aim of the present study was to explore the contribution of the tear film to higher order aberrations in eyes that have undergone refractive surgery. A secondary aim was to explore how the changes in ocular aberrations alter in the early and later post-operative periods by assessing participants during the first three months after surgery and another group who had refractive surgery in the past. The assumption was that changes contributing to the cause of dry eye especially in the early post-operative phase would cause the tear film to break up more rapidly creating a more unstable and irregular tear film layer. By collecting data with and without the use of anesthetic agents, the tear film could be observed in both its natural condition as well as over longer time intervals between blinks. The assumption was that aberrations would be higher after the instillation of anesthetics due to the reduction in basal tear production and associated reduction in TBUT (Norn, 1969; Lemp and Hamill 1973; Jordan and Baum, 1980). In addition, using both experimental conditions would enable comparison with previous studies that used anesthetics as well as those that did not.

10.2 Subjects

A total of 19 subjects took part in this study. These 19 subjects were sub-divided into three separate groups. All subjects were instructed to leave any contact lenses out and not to use any tear supplements on the day of the study visits.

The first group consisted of six healthy adults recruited from the staff and students at the University of Manchester, UK. None of these participants had undergone refractive surgery. The subjects had a mean age of 28.5 years (range 24 to 34 years), and a mean refractive error (mean sphere) of -1.21D (range 0.00D to -2.00D). All subjects were free from ocular disease, had a corrected visual acuity of 6/6 (Snellen) or better, normal anterior eye as assessed by slit-lamp bio-microscopy examination, no history of dry eye, and normal tear characteristics with TBUT of over 15 seconds.

The second group of subjects consisted of six healthy adults that had undergone refractive surgery for myopia at least six months previously (LASIK n=5, LASEK n=1). These subjects were recruited from the public access Optometry clinics at the University of Manchester, UK. The time elapsed since refractive surgery procedures ranged from 9 months to 5 years among subjects. Subjects had a mean age of 31.5 years (range 20 to 45 years), were free from ocular disease and had no significant ocular history other than having had refractive surgery. All subjects had unaided vision of 6/9 (Snellen) or better in the tested eye, correctable to 6/6 or better. Refractive errors were ±0.50D sphere with up to 1.00D of astigmatism. Anterior segment examination with slit-lamp bio-microscopy was normal and TBUT was over 10 seconds for all subjects. No specific details from the surgery were available although mean pre-operative refractive error was estimated to be -6.33D (range -3.00D to -9.00D) as reported by the subjects.

The third group consisted of seven healthy adult subjects that had elected to undergo refractive surgery at Manchester Royal Eye Hospital. This group was the same seven patients that took part in the study on the changes in higher order aberration with accommodation (see Chapter 9, section 9.2 for refractive details). Screening of the anterior eye with a slit-lamp bio-microscope was normal and no subjects had been diagnosed with dry eye or anterior surface disorders. Schirmer's I test (without anesthetic) showed 10mm of wetting or more in 1 minute or less for all subjects except one subject who showed 10mm of wetting in 2½ minutes. TBUT was over 10 seconds for all subjects. The Schirmer's test and TBUT measurements were conducted on a different day to the aberration measurements. The project protocol was approved by the Senate Committee on the Ethics of Research on Human Beings of the University of Manchester (information sheet and consent forms are included in appendices 10a and 10b respectively). Written informed consent was obtained from all subjects after the nature and possible consequences of the study had been explained.

10.3 Methods

Ocular aberrations were measured using a Shack-Hartmann aberrometer (IRX3, Imagine eyes, Paris). All measurements were taken in the same clinical examination room with the lights turned off. The room had relatively constant humidity and temperature and measurements were taken in the absence of obvious ventilation currents. One eye was used for aberration measurements, with the other eye occluded. Initially the aberrometer target position corresponding to the far point was determined. The subject was then instructed to blink several times and fixate on a distant target created by the aberrometer while keeping their eyes open for as long as possible without blinking or manually holding their lids open. During this period of non-blinking, a measurement of ocular aberrations was obtained dynamically at the rate of 1Hz, starting immediately after the last blink and continuing for a 15 second period. These measurements of aberrations for 15 seconds following a blink were repeated five times. Measures of the mean and variability were then calculated from these readings. No refractive correction was worn, instead the correction of refractive error (if any) was provided by the aberrometer's internal lens system using the mean sphere obtained from the initial refractive error reading, and it was ensured that the target appeared clear to the subject before measurements commenced.

The 12 participants that were recruited from the University of Manchester attended for a single study visit and measurements were obtained both before and after the instillation of a topical anesthetic. For the anesthetic condition, a single drop of Oxybuprocaine Hydrochloride (BNX) 0.4% (Minims, Chauvin, UK) was instilled into the lower fornix of each eye. The topical anesthetic was instilled in both eyes to avoid the possibility of unilateral stimulation causing bilateral lacrimation. After a period of 10 minutes the aberration measurements were repeated. The eyes were examined using slit-lamp bio-microscopy at the end of the experiment for signs of an adverse reaction or corneal staining.

The seven refractive surgery patients recruited from Manchester Royal Eye Hospital attended for three visits. Baseline measurements were obtained at the first visit (pre-operatively). Two further visits were at one month and three months post-operatively. No anesthetics were used on the day of the aberration measurements for this group of patients.

10.3.1 Data analysis

The manufacturer's software was used to calculate the Zernike wave-front aberration coefficients from the Shack-Hartmann images for the full natural pupil diameter (coefficients up to the 6^{th} order). Coefficients were then determined for a 4.0mm pupil for all eyes. Coma-like aberrations were calculated as the square root of the sum of squares of the 3^{rd} and 5^{th} order aberrations, spherical-like aberrations were calculated as the square root of the sum of squares of the 4^{th} and 6^{th} order aberrations, and root-mean-square (RMS) aberrations were calculated as the square root of the sum of squares of the 3^{rd} to 6^{th} order aberrations. Data were plotted for each subject showing the alteration in each aberration over the 15 second post-blink period both before and after the instillation of the anesthetic.

10.4 Results

Figure 10.1 shows typical results for a control subject that did not have refractive surgery. The results show the level of higher order aberrations as a function of time following a blink for all five measurement runs, before and after the installation of anesthetic. Prior to the instillation of anesthetic (Figure 10.1a) the total higher order aberrations tended to remain relatively stable during the 15 second post-blink period (see measurements 1, 2 and 5). However, for some experimental runs (measurement 4, and possibly measurement 3) the level of total higher order aberrations was found to increase during the 15 seconds post-blink period. The results suggest that this increase was primarily caused by an increase in coma-like aberrations, and to a lesser extent, increases in spherical-like aberrations (see Figures 10.1c and 10.1e). Topical anesthesia (Figure 10.1b) did not appear to make a large difference to the aberration levels. The results following topical anesthesia were similar to those found prior to anesthesia. The measurement runs typically showed stable aberration levels during the 15 second post-blink period although some measurement runs did show a modest increase in aberrations with increasing time following a blink. A general observation was that levels of coma-like aberrations tended to be more variable than the levels of spherical-like aberration. This was most obvious during the first 10 seconds following a blink, during which the spherical-like aberrations altered very little.

Figure 10.2 show the typical results from a subject that had undergone refractive surgery in the past. The results show the level of higher order aberrations as a function of time following a blink for all five measurement runs, before and after the instillation of anesthetic. Prior to the installation of anesthetic (Figure 10.2a) the levels of aberration remained relatively stable throughout the 15 second post-blink period. Topical anesthesia (Figure 10.2b) appeared to make a difference to the levels of aberration present. The majority of measurement runs following topical anesthesia showed a tendency for the total level of aberrations to increase with increasing time after a blink. The results suggest that this increase was caused by an increase in the coma-like aberrations, with spherical-like aberrations remaining stable during the 15 second post-blink period.

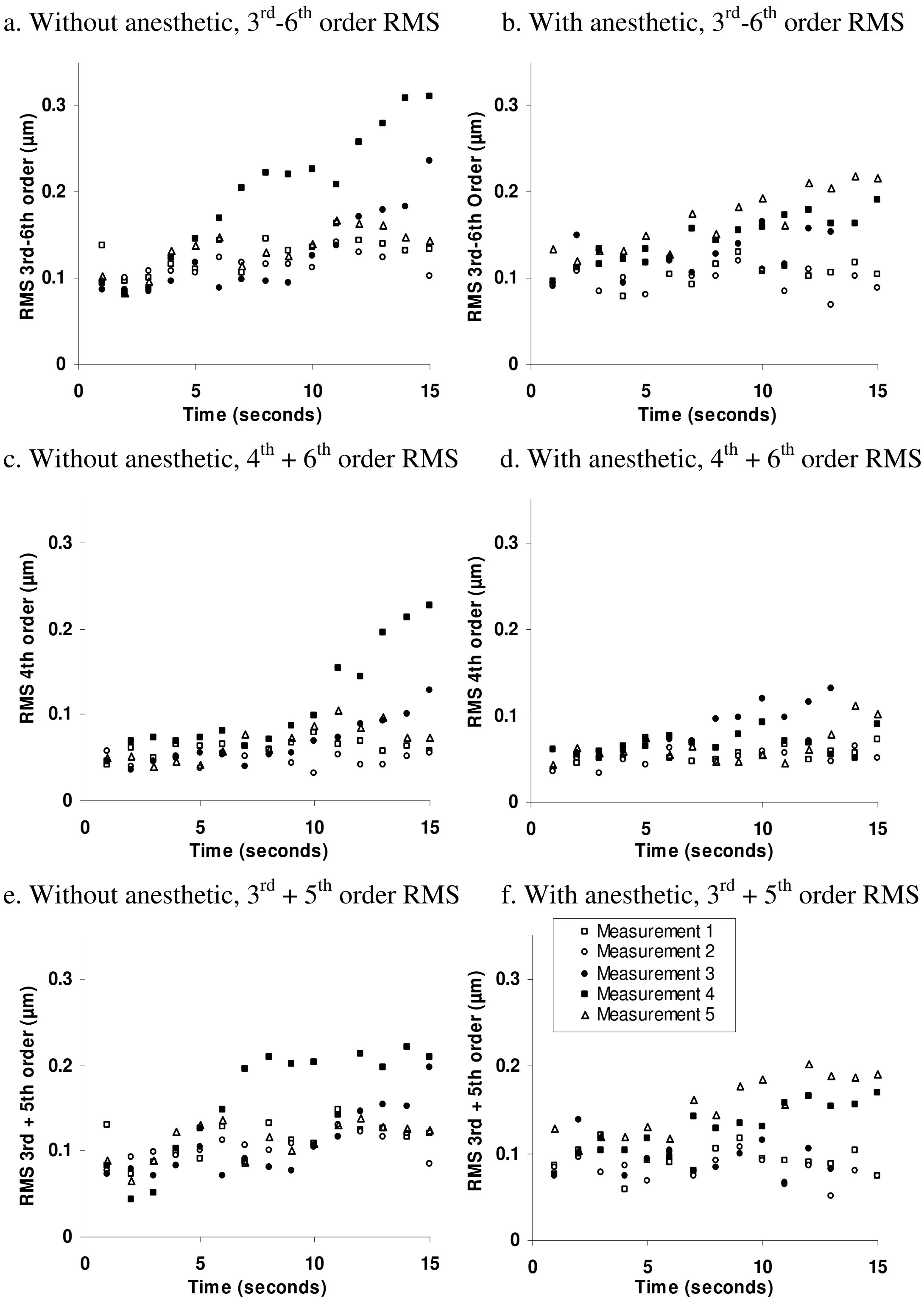


Figure 10.1: Aberration levels as a function of time following a complete blink for one subject from the group that did not have refractive surgery. Results are shown for all five measurement runs prior to (left graphs) and after (right graphs) instillation of Oxybuprocaine Hydrochloride 0.4%. Aberrations are shown for a 4.0mm natural pupil for total higher order RMS (graphs a and b), 4^{th} + 6^{th} order RMS (graphs c and d) and 3^{rd} + 5^{th} order RMS (graphs e and f).

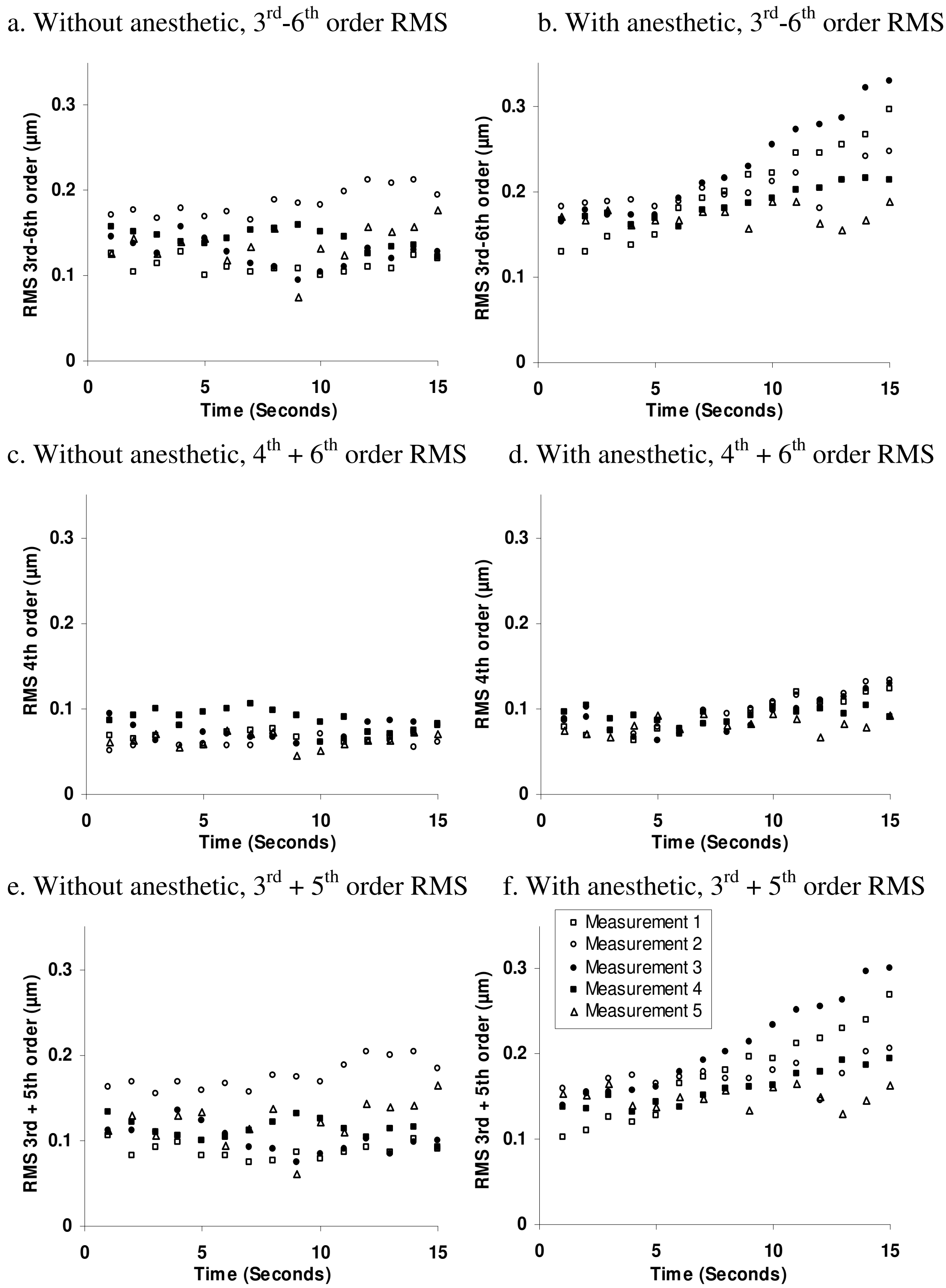


Figure 10.2: Aberration levels as a function of time following a complete blink for one subject from the group that had undergone refractive surgery in the past. Results are shown for all five measurement runs prior to (left graphs) and after (right graphs) instillation of Oxybuprocaine Hydrochloride 0.4%. Aberrations are shown for a 4.0mm natural pupil for total higher order RMS (graphs a and b), 4th + 6th order RMS (graphs c and d) and 3rd + 5th order RMS (graphs e and f).

Figure 10.3 shows the total higher order aberration levels with and without anesthesia, as a function of time following a blink for the non-surgical (control) group and those having undergone refractive surgery in the past. The non-surgical group showed a mean total higher order aberration of approximately 0.10µm for a 4.0mm pupil diameter. This appeared to remain stable during the 15 second post-blink period and was not affected by topical anesthesia. The subjects that had undergone refractive surgery showed consistently higher levels of total higher order RMS with a mean typically in the range 0.15µm-0.25µm for a 4.0mm pupil diameter during the 15 second post-blink interval. Prior to topical anesthesia the mean aberration level remained stable at approximately 0.15µm. Following topical anesthesia the aberrations tended to remain stable for the first 10 seconds following a blink and then increase and become more variable beyond 10 seconds.

Figure 10.4 shows typical results for a patient that was recruited prior to undergoing refractive surgery. The results show the level of higher order aberrations (mean of five measurement runs) as a function of time following a blink at each of the three study visits. Pre-operatively the mean higher order aberration level was approximately 0.10µm for a 4.0mm pupil diameter. This increased to between 0.25µm-0.30µm at one month post-operatively, before falling to between 0.15µm-0.20µm at three months post-operatively. At each visit the mean aberration levels remained stable throughout the 15 second post-blink period with no repeatable systematic increase in aberrations during the 15 second period.

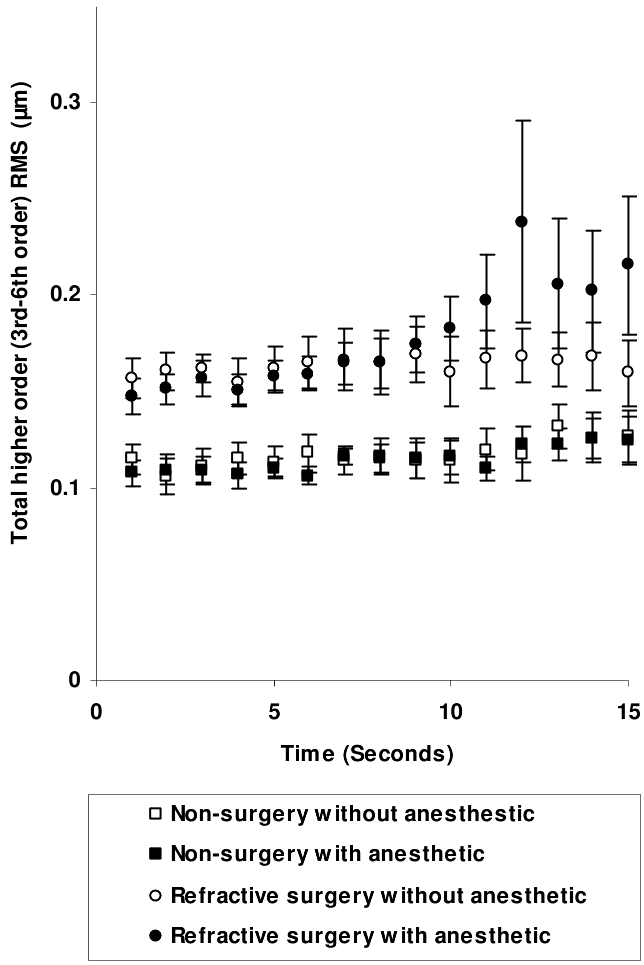


Figure 10.3: Mean (± SEM) total higher order aberration data (3^{rd}-6^{th} order) as a function of time following a complete blink. The graphs show results for patients having undergone refractive surgery (circles, n=6) and the group that did not undergo refractive surgery (squares, n=6), before the instillation of Oxybuprocaine Hydrochloride 0.4% (open symbols) and after the instillation of Oxybuprocaine Hydrochloride 0.4% (closed symbols). Results are for a 4.0mm natural pupil diameter.

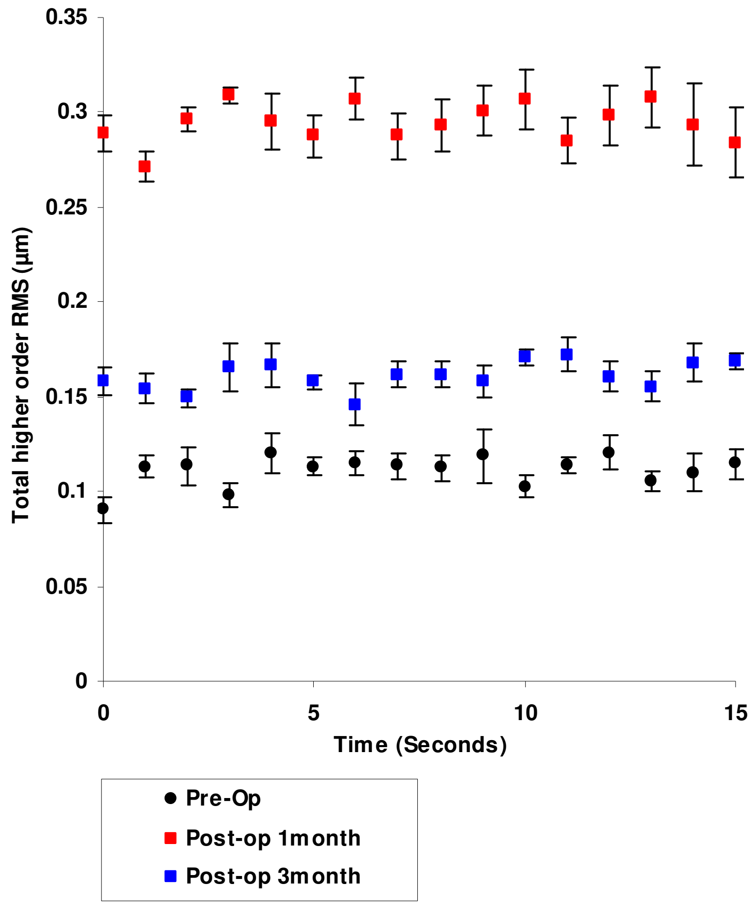


Figure 10.4: Typical aberration data obtained for one subject undergoing refractive surgery. The graph shows the mean (± SEM) mean total higher order aberration (3^{rd}-6^{th} order RMS) as a function of time following a complete blink. Results are shown pre-operatively (black circles) and at one month (red squares) and three months (blue squares) post-operatively. Aberrations were measured for a 4.0mm diameter natural pupil diameter.

Figure 10.5 shows the mean higher order aberration levels as a function of time following a blink at each study visit for the whole group undergoing refractive surgery. Pre-operatively the mean higher order aberration level was approximately 0.15µm for a 4.0mm pupil diameter. This increased to between 0.20µm-0.25µm at one month post-operatively before falling to between 0.15µm-0.20µm at three months post-operatively. On average there was no repeatable systematic increase in aberrations during the 15 second post-blink period.

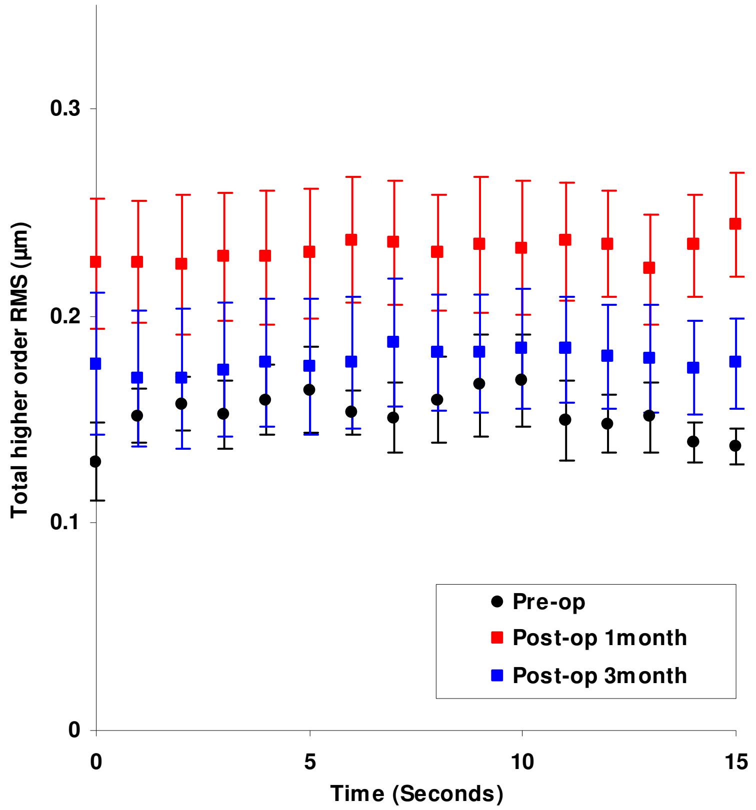


Figure 10.5: Mean (± SEM) total higher order aberration data (3rd-6th order) as a function of time following a complete blink for patients undergoing refractive surgery. Results are shown pre-operatively (black circles) and one month (red squares) and three months (blue squares) post-operatively. Aberrations were measured over a 4.0mm natural pupil diameter.

10.5 Discussion

Corneal damage during LASIK and LASEK results in the severing of corneal nerves to a varying degree and a subsequent reduction in corneal sensitivity (Benitez-del-Castillo *et al*., 2001; Battat *et al*., 2001). This in turn compromises the blink rate, reduces tear secretion and increases tear osmolarity (Lee *et al*., 2000; Yu *et al*., 2000; Battat *et al*., 2001; Benitez-del-Castillo *et al*., 2001; Albietz *et al*., 2002). As a result of these changes to the anterior eye, dry eye is a frequent occurrence during the first six months following refractive surgery (Yu *et al*., 2000; Albietz *et al*., 2002). Confocal microscopy has been used to monitor the apparent recovery of corneal nerve structural morphology which tends to parallel the return of corneal sensitivity to levels approaching those seen pre-operatively by 6-9 months after surgery (Linna *et al*., 1998; 2000a; Benitez-del-Castillo *et al*., 2001; Perez-Gomez and Efron, 2003). This recovery is associated with a gradual reduction in the severity and prevalence of dry eye symptoms over a similar period (Donnenfeld *et al*., 2004). However for a significant number of people, dry eye symptoms persist and can become a chronic complication.

When measuring aberrations of the eye, the tear film represents the most anterior ocular surface and tear film disruption can influence the measurements obtained (Tutt *et al*., 2000; Koh *et al*., 2002; Montes-Mico *et al*., 2004a; b; 2005a). As a result, ocular aberration measurements have been used successfully in the investigation of dry eye conditions (Montes-Mico *et al*., 2004c; 2005a). The present study attempted to improve our understanding of the contribution of the tear film to higher order aberrations following refractive surgery.

In general, the present study measurements from the control participants suggested that the total higher order aberrations tended to remain relatively stable during a 15 second post-blink period. However, on examining the data from individual subjects there was considerable variability in that the level of total higher order aberrations was found to increase post-blink during some measurement runs. The results obtained in these participants during topical anesthesia were similar, with the aberration measurements typically remaining stable during the post-blink period and some measurements showing an increase in aberrations with time. A general observation was that levels of coma-like aberrations tended to be more variable than the levels of spherical-like aberration. This was most obvious during the first 10 seconds following a blink, during which the spherical-like aberrations altered very little. The increased variability of coma-like aberrations could perhaps be expected due to the directional effects of lid movement, gravitational effects, and uneven local rates of evaporation associated with the shape of the palpebral aperture (Buehren *et al.*, 2001; Montes-Mico *et al.*, 2004b). However, other studies have also found changes in spherical aberration, which could be caused by a tendency for the tear film to thin at different rates at the centre of the palpebral aperture in comparison to the periphery (Koh *et al.*, 2002; Montes-Mico *et al.*, 2004a), possibly as a result of temperature differences across the ocular surface (Morgan *et al.*, 1993).

The findings of an increase in the level and variability of aberrations over time in some runs is in agreement with published literature (Montes-Mico *et al.*, 2004a; 2005a; Mihashi *et al.*, 2006). However, this trend was not evident in all control subjects in the present study. This is perhaps due to the variations between subjects in the initial stability of the tear film and variations in the effect that the topical anesthetic had in their tear film stability. For example, one subject had a reduction in mean TBUT from 19.8 seconds to 5.8 seconds following anesthesia, whereas in other subjects the effect of the anesthetic on TBUT was minimal. The TBUT and location of tear break-up are known to be inherently variable, exhibiting considerable within-subject and between-subject variability (Norn, 1969; Rengstorff, 1974). Since the structural dynamics of the tear film are known to vary between subjects, it is perhaps unsurprising that the optical dynamics appear to display similar diversity.

In the group that had previously had refractive surgery (i.e. the late post-operative period), the levels of aberrations again remained relatively stable throughout the post-blink period. However, following instillation of the topical anesthetic there was a tendency for the total level of aberrations to increase with time after a blink. The results suggest that this increase was caused by an increase in the coma-like aberrations, with spherical-like aberrations remaining more stable. The finding that the instillation of an anesthetic agent changes some of the optical characteristics of the tear film was expected. However this change was only evident in the refractive surgery group, not in the controls. Although the temporal characteristics were affected in some subjects, the actual levels of the initial aberrations were similar before and after the instillation of anesthetic. The effect of the anesthetic would be expected to decrease tear film secretion (Norn, 1969; Lemp and Hamill, 1973; Jordan and Baum, 1980) and hence mimic the effects of aqueous deficiency. Therefore changes to aberrations may be expected to occur sooner after a blink as observed in dry eye patients (Montes-Mico *et al.*, 2005a). However, in 'true' dry eye it is likely that other aspects of the tear film will also be affected, increasing the level of irregularity and affecting the ocular aberrations to a much greater extent than simple thinning of the tear film. Although the length of time that had elapsed since surgery indicates that the corneal nerve structure and function would have largely recovered, topographic alterations may somehow continue to inhibit tear stability when the eye is challenged for example by pharmacologically-induced corneal anesthesia.

For the group of participants undergoing corneal laser refractive surgery, pre-operatively the mean higher order aberration level was approximately 0.15μm for a 4.0mm pupil diameter. This increased (to between 0.20μm-0.25μm) at one month post-operatively before falling to 0.15μm-0.20μm at three months. On average, there was no repeatable systematic increase in mean aberrations over time during the post-blink measurement period at any of the study appointments. Previous studies in normal subjects (not having undergone refractive surgery) have suggested that there is an initial reduction in aberrations following a blink (see e.g. Montes-Mico *et al*., 2004b) due to the initial stabilization of the tear film (Benedetto *et al*., 1984). Therefore the apparent stability of the tear film over time post-operatively in the patients undergoing surgery was somewhat surprising. It should be acknowledged that with the IRX3 aberrometer it can be difficult to time the onset of the aberration measurements to coincide precisely with the immediate post-blink time frame, and that it is possible that a delay of 1 or 2 seconds was introduced in some subjects during some measurement runs. This could explain why the initial decrease in aberrations in the early post-blink phase was not as evident in this study compared to other studies (Montes-Mico *et al*., 2004b). It was hoped that taking the mean of several measurements would help reduce any possible impact of these difficulties. However by averaging, subtle differences between runs may have been missed.

It should be noted that some previous studies have measured ocular aberrations of the anterior surface (Montes-Mico *et al.*, 2004a; 2005a) whereas the present study measured whole-eye aberrations. However, Montes-Mico *et al.* (2004b) measured changes to both corneal aberrations and whole-eye aberrations during tear break-up, and found very similar results with both techniques. The findings of this study are therefore also likely to be comparable to those that have measured only anterior surface aberrations.

In conclusion, the results of this study, like those of an earlier study (Lin *et al.*, 2005), suggest that pattern of aberrations induced by post-blink tear changes may differ in subjects following refractive surgery, particularly in the early recovery period. However, topographic corneal changes and tear film changes that endure may leave refractive surgery patients vulnerable to tear-related increased levels of aberration for years to come. Further studies that improve our understanding of the magnitude and visual implications of these alterations are warranted.

FINAL SUMMARY, LIMITATIONS AND PROPOSALS FOR FUTURE WORK

The core theme of this experimental work has been the investigation of the impact that alterations to ocular aberrations following refractive surgery have on the accommodative mechanism. Patients recruited for the accommodation studies underwent successful refractive surgery. Surgical results showed good efficacy, safety and stability which were consistent with results expected from previously published studies that have investigated surgical outcome. A novel finding during the investigation of surgical outcome was that QIRC scores varied with time post-operatively. This suggests that, when measuring the impact of refractive surgery on quality of life, the timing of the post-operative administration of the questionnaire is important and should be well defined. It would be interesting to conduct future studies to further investigate the temporal changes in quality of life scores following refractive surgery. Short time periods (days/weeks) could be used to establish the point at which the improvements in quality of life scores become apparent. Longer time periods (months/years) could be used to investigate the point at which the quality of life scores stabilize.

Following surgery, significant alterations to a number of accommodative functions were discovered. Ocular amplitude of accommodation was found to increase (by approximately 0.50D) following refractive surgery, suggesting a potential benefit to those approaching presbyopia. However, the results also suggest that this increase may be masked by a greater (apparent) decrease in spectacle amplitude of accommodation that occurs due to the effects of lens effectivity. These findings suggest that while a contact lens corrected myope may experience a modest delay in presbyopic symptoms following refractive surgery, a spectacle corrected myope may experience the symptoms of presbyopia slightly earlier than they otherwise would have done had they not undergone refractive surgery. Mean stimulus-response function gradient was found to decrease following refractive surgery and this decrease was found to be linked to the changes in spherical aberration following surgery. Distance facility rate was found to increase by approximately 2-3 cycles/minute following refractive surgery. Taken collectively, the results of the accommodation studies suggest that refractive surgery can have an impact on elements of the accommodative response, and that in part, alterations to higher order aberrations may contribute to these alterations in accommodation. This work provides further insight into the potential effects of refractive surgery on ocular physiology and also provides further evidence that higher order aberrations are involved with the control of accommodation.

Significant differences were also found in the parameters of accommodative dynamics between those undergoing refractive surgery and emmetropic controls. These findings warrant further investigation to establish whether these differences can be attributed to the effects of refractive surgery, or whether these were pre-existing differences due to refractive error group. Future improvements to the image acquisition abilities of the Shin-Nippon machine during dynamic measurements may allow more accurate readings to be taken through spectacle lenses. This would allow measurements to be compared on the same group of patients prior to and following refractive surgery. Alternatively, comparison of the results with a group of contact lens wearing myopes would help establish whether these differences were attributable to the impact of refractive surgery or refractive error group.

All of the refractive surgery patients recruited to the study underwent surgery for stable myopia. This was due to the fact that the overwhelming majority of patients attending the clinics (in the age range tested) were seeking surgery to correct myopia. It should be acknowledged that the results are therefore only likely to be applicable to those undergoing surgery for myopia. Future studies could examine the impact of refractive surgery for hyperopia on the accommodative mechanism.

Understanding the role of higher order aberrations in accommodative control is important because inaccurate accommodation responses may expose the eye to chronic defocus which has been implicated in myopia development and progression. To date, a variety of experimental approaches have been used to investigate the role of aberrations in accommodative control. These have included manipulating aberrations using adaptive optics systems, inducing aberrations using contact lenses, and conducting psychophysical experiments. The experimental work presented here shows that investigation of the impact of refractive surgery on accommodation may provide an alternative approach to gain insight into the role of higher order aberrations in the process of accommodative control.

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APPENDIX

CHAPTER 4

4a: Participant information sheet for the study conducted at Manchester Royal Eye Hospital.

4b: Consent form for the study conducted at Manchester Royal Eye Hospital.

4c: QIRC questionnaire.

4d: Figure 4.1 re-drawn over greater scale to show complete data set.

CHAPTER 5

5a: Example of critical amplitude chart.

CHAPTER 8

8a: Figure 8.7 re-analyzed for correlation within each refractive group.

8b: Comparison of data from the Shack-Hartmann aberrometer and the Allegretto Wave Analyzer.

8c: Bland-Altman plot for the level of agreement between the Allegretto Wave Analyzer and the Shack-Hartman aberration measurements.

CHAPTER 10

10a: Participant information sheet for tear film study.

10b: Consent form for tear film study.

Appendix 4a: Participant information sheet for the study conducted at Manchester Royal Eye Hospital.

MANCHESTER 1824

The University of Manchester

Central Manchester and Manchester Children's University Hospitals NHS Trust NHS

PARTICIPANT INFORMATION SHEET
(Version 1.2, 30/01/08)

Study Title: Refractive Eye Surgery and Focusing Ability
(Version 1.1)

Researchers: Mr. J. Taylor, Dr. H. Radhakrishnan, Dr. C. O'Donnell, Mr. A. Brahma

We would like to invite you to take part in a research study. Before you volunteer to take part it is important that you understand why the research is being done and what it will involve. Please take time to read the following information and talk to others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?
This study is being carried out as part of a PhD project funded by the University of Manchester. We aim to investigate how refractive eye surgery impacts on the ability of the eye to focus to near objects.

Why have I been approached?
You have been approached as you are undergoing refractive eye surgery. We will be recruiting 50 people to take part in the study.

What will happen to me if I take part?
You will have a series of measurements taken on the front of your eyes. We will measure the thickness and shape of the front of your eye and find out how the optics of your eyes are performing using a number of instruments to photograph the light being reflected by your eye. We will then take a series of measurements that allow us to accurately determine how well your eye can focus. During these measurements you will be required to focus on letter targets presented at different distances in front of you. You will also be asked to fill in 2 short questionnaires. The first one of these is designed to find out how refractive eye surgery alters your quality of life. The second asks specific questions about your focusing ability and near vision.
To enable us to assess the effects of surgery on your eyes, it will be necessary for the researchers to have access to your medical records relevant to your eye surgery. This will be for the purposes of research for this study only. All your information will be handled in strict confidence.

How long will it take?
You will be required to attend for 3 visits in total. The first visit will be before your eye surgery to obtain baseline information. The other 2 visits will then be at 1 month and 3 months after surgery. The measurements taken at these visits will allow us to see if the surgery has affected your ability to focus. Where possible, these visits will take place on the same day as your eye surgery check-up appointments. The individual visits can be quite time consuming, as the measurements have to be repeated several times in order for the data to be reliable. Each visit is expected to take 1 hour, in addition to the normal

Participant Information sheet (1.2): Refractive Eye Surgery and Focusing Ability (1.1)
Page 1 of 1

appointment time. The measurements will be taken in a clinical laboratory at Manchester Royal Eye Hospital.
We do have some machines at the University of Manchester that enable us to take more detailed measurements for some of the aspects of focusing that we are interested in. You may be asked to attend for additional measurements at the University, although this again is voluntary. The University visits would be on the same days as the hospital visits and last about 30 minutes. They would involve similar non-invasive measurements on your eyes and require you to look at letter targets. If you cannot attend the University appointments, you can still join the study and attend the hospital appointments only.

What are the risks involved in taking part?
All of the tests are non-invasive and therefore there are no adverse effects associated with taking part. Participation in this study is additional to the usual appointments and procedures involved in your eye surgery and does not replace or interfere with any aspects of the normal care you receive.
All research in the NHS is looked at by an independent group of people called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and approved by a local NHS Research Ethics Committee on behalf of the Central Manchester and Manchester Children's University Hospitals NHS trust (REC reference number 08/H1014/1). This research is covered by insurance policies held by the University of Manchester. Specific details of these policies are available from the Research Practice and Governance Co-ordinator whose contact details are overleaf.

What are the benefits in taking part?
The results of this study may lead to a better understanding of any problems with focusing that people experience after refractive eye surgery. If we identify any individuals with focusing problems after the surgery, the researchers may be able to provide advice on options that are available to limit the impact of the problem. We cannot promise that the study will help you but the information we get from this study may help improve the treatment of people undergoing refractive eye surgery.

Will my taking part be confidential?
Yes. Your personal details will be held on a computer and will not be made available to any third party. Any results published will be anonymous. A copy of the data held on computer about you is available on request in accordance with the Data Protection Act. Your eye surgeon will be informed that you are taking part in the study.

Do I have to take part?
It is up to you to decide. We will describe the study and go through this information sheet, which we will then give to you. We will then ask you to sign a consent form to show that you agree to take part. Your participation in the study is voluntary. You are free to withdraw at any time without penalty and without giving a reason. This would not affect the standard of care that you receive. If you withdraw from the study we may use your data collected prior to withdrawal for the purposes of this study only.

Expenses and payments
You will not be paid for taking part in this study, but reasonable travel expenses will be offered to all participants.

Complaints procedures
If you have a concern about any aspect of this study, initially you should ask to speak to the researchers who will do their best to answer your questions (contact details below). However, if you are not satisfied with the outcome or wish to make a complaint to someone independent of the research you can do so to:

The Research Practice and Governance Co-ordinator
Research Office
Christie Building
University of Manchester
Oxford Road
Manchester
M13 9PL

Email: Research-Governance@manchester.ac.uk

Telephone: 0161 275 8093 / 7583

Please note: The position of Research Practice and Governance Co-ordinator is a job-share position and is covered by Mrs April Lockyer (Monday - Wednesday) and Dr Karen Schafheutle (Wednesday - Friday).

Contact details
If you decide to take part you can ask questions at any time. If you have any questions about this research contact:

Mr. J. Taylor (Optometrist, PhD Student)
Faculty of Life Sciences, Moffat Building, Sackville St, The University of Manchester.
E-mail: John.Taylor@postgrad.manchester.ac.uk

OR

Dr. H. Radhakrishnan (Optometrist, University Lecturer, PhD Supervisor)
Faculty of Life Sciences, Moffat Building, Sackville St, The University of Manchester.
E-mail: hema.radhakrishnan@manchester.ac.uk
Tel: 0161 306 8763.

Appendix 4b: Consent form for the study conducted at Manchester Royal Eye Hospital.

MANCHESTER 1824

The University of Manchester

Central Manchester and Manchester Children's University Hospitals NHS Trust NHS

CONSENT FORM FOR PARTICIPANTS

Title: Refractive Eye Surgery and Focusing Ability (Version 1.1)

Researchers: Mr. J. Taylor, Dr. H. Radhakrishnan, Dr. C. O'Donnell, Mr. A. Brahma

Participant name:____________________________________

PLEASE INITIAL BOX:

1. I confirm that I have read and understand the participant information sheet (version 1.2, 30/01/08) for the above study. ☐
2. The purpose and nature of the study has been explained to me. I have had the opportunity to consider the information, ask any questions and have had these answered satisfactorily. ☐
3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without prejudice. ☐
4. I understand that relevant sections of my medical records and data collected during the study may be looked at by individuals within the research team, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
5. I agree to my eye surgeon being informed of my participation in the study. ☐
6. I understand that the project is for the purpose of research only, and not for the treatment or detection of any visual condition that I may have. ☐
7. I have been provided with a copy of this informed consent form, and the information for participants ☐
8. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of person Taking consent	Date	Signature

When completed, 1 for patient, 1 for researcher file, (original) to be kept in medical notes.

Consent Form (1.1): Refractive Eye Surgery and Focusing Ability (1.1).
Page 1 of 1

Appendix 4c: QIRC questionnaire.

If you have had REFRACTIVE SURGERY (LASIK, PRK etc.), please answer the questions on this page and read the instructions on how to complete the rest of the questionnaire.

If you have not had refractive surgery, please turn to page 2 now.

- How long is it since you had refractive surgery? ________________

Please determine which of the following two groups you belong to see how to answer the questions on pages 4-7.

a) If you do not wear spectacles or contact lenses SINCE your refractive surgery (LASIK, PRK etc.), please tick the appropriate box for the questions on pages 4-7 as the example below.

Example: How much difficulty do you have reading very small print?

Not applicable	None at all	A little bit	A moderate amount	A lot	So much that I can't do this activity
		✓			

TURN TO PAGE 4

b) If you occasionally still wear spectacles and/or contact lenses SINCE your refractive surgery, please estimate how many hours per day you wear them on average. Ordinary sunglasses DO NOT count as spectacles.

Spectacles	Hours/day
Contact lenses	Hours/day

How old are your current contact lenses? ________________

How old are your current spectacles? ________________

Please answer the questions on pages 4-7 depending on whether you were wearing the correction or not, as in the example below:

S: as your answer for when wearing spectacles.
C: as your answer for when wearing contact lenses.
N: as your answer when not wearing contact lenses or spectacles.

Example: How much difficulty do you have reading for long periods?

Not applicable	None at all	A little bit	A moderate amount	A lot	So much that I can't do this activity
	S		*N*		

TURN TO PAGE 4

If you wear SPECTACLES AND/OR CONTACT LENSES during all your waking hours, please complete this page to see how to complete the questions on pages 4-7

If you only wear spectacles and/or contact lenses for part of the day, turn to page 3 now.

a) **Tick / complete the appropriate boxes regarding your current optical correction.** Ordinary sunglasses DO NOT count as spectacles.

i) Spectacles only. Worn full-time.	

How old are your current spectacles ___________? Go to example 1 below

ii) Contact lenses only. Worn full time	

How old are your current contact lenses ___________? Go to example 1 below

iii) Both spectacles and contact lenses.	Spectacles	Hours/day
	Contact lenses	Hours/day

How old are your current contact lenses? ______________

How old are your current spectacles? ______________ Go to example 2 below

Example 1: How much difficulty do you have reading very small print?

Not applicable	None at all	A little bit	A moderate amount	A lot	So much that I can't do this activity
		✓			

Example 2: How much difficulty do you have reading for long periods?

Not applicable	None at all	A little bit	A moderate amount	A lot	So much that I can't do this activity
	C	*S*			

TURN TO PAGE 4

If you wear SPECTACLES AND/OR CONTACT LENSES on a part-time basis, please complete this page.

a) **Tick and/or complete the appropriate boxes regarding your current optical correction**. Ordinary sunglasses DO NOT count as spectacles.

i) Spectacles only. Worn part-time.		How many hours do you wear them?	Hours/day

i) Contact lenses only. Worn part-time.		How many hours do you wear them?	Hours/day

iii) Both spectacles and contact lenses.	Spectacles	Hours/day
	Contact lenses	Hours/day

b)

How old are your current contact lenses? ________________ Answer N/A if this

How old are your current spectacles? ________________ does not apply to you

Instructions on how to complete this questionnaire.

If you wear spectacles and/ or contact lenses on a part-time basis, use:	**S:** as your answer for when wearing spectacles **C:** as your answer for when wearing contact lenses. **N:** as your answer for when not wearing spectacles or contact lenses.

Example for a part-time spectacle wearer:

How much difficulty do you have reading for long periods?

Not applicable	None at all	A little bit	A moderate amount	A lot	So much that I can't do this activity
		S		***N***	

Example for a part-time contact lens wearer:

How much difficulty do you have reading for long periods?

Not applicable	None at all	A little bit	A moderate amount	A lot	So much that I can't do this activity
		C		***N***	

QIRC

Please fill out all the questions below regarding your current spectacles or contact lenses. Patients who have had refractive surgery should respond for how they are NOW, not how they were before surgery.

1. How much difficulty do you have driving in glare conditions?

Don't drive for reasons other than my vision	None at all	A little bit	A moderate amount	A lot	So much that I can't do this activity

2. During the past month, how often have you experienced your eyes feeling tired or strained?

Don't know / Not applicable	Never	Occasionally	Fairly often	Very often	Always

3. How much trouble is not being able to use off-the-shelf (non prescription) sunglasses?

Don't know / Not applicable	None	A little bit	A moderate amount	Quite a lot	Extreme

4. How much trouble is having to think about your spectacles or contact lenses or your eyes after refractive surgery before doing things; e.g. travelling, sport, going swimming?

Don't know / Not applicable	None	A little bit	A moderate amount	Quite a lot	Extreme

5. How much trouble is not being able to see when you wake up; e.g. to go to the bathroom, look after a baby, see alarm clock?

Don't know / Not applicable	None	A little bit	A moderate amount	Quite a lot	Extreme

6. How much trouble is not being able to see when you are on the beach or swimming in the sea or pool, because you do these activities without spectacles or contact lenses?

Don't know / Not applicable	None	A little bit	A moderate amount	Quite a lot	Extreme

7. How much trouble is your spectacles or contact lenses when you wear them when using a gym / doing keep-fit classes / circuit training etc?

Don't know / Not applicable	None	A little bit	A moderate amount	Quite a lot	Extreme

---

8. How concerned are you about the initial and ongoing cost to buy your current spectacles/ contact lenses/ refractive surgery?

Don't know / Not applicable	Not at all	A little bit	A moderate amount	Quite a lot	Extremely

9. How concerned are you about the cost of unscheduled maintenance of your spectacles/ contact lenses/ refractive surgery; e.g. breakage, loss, new eye problems?

Don't know / Not applicable	Not at all	A little bit	A moderate amount	Quite a lot	Extremely

10. How concerned are you about having to increasingly rely on your spectacles or contact lenses since you started to wear them?

Don't know / Not applicable	Not at all	A little bit	A moderate amount	Quite a lot	Extremely

11. How concerned are you about your vision not being as good as it could be?

Don't know / Not applicable	Not at all	A little bit	A moderate amount	Quite a lot	Extremely

12. How concerned are you about medical complications from your choice of optical correction (spectacles, contact lenses and/or refractive surgery)?

Don't know / Not applicable	Not at all	A little bit	A moderate amount	Quite a lot	Extremely

13. How concerned are you about eye protection from ultraviolet (UV) radiation?

Don't know / Not applicable	Not at all	A little bit	A moderate amount	Quite a lot	Extremely

---

We are now interested in the effect that your optical correction (spectacles, contact lenses or refractive surgery) have had on the way you have been feeling. The effect on your feelings may be obvious (e.g., you may feel that you look better in your new spectacles) or it may be indirect (e.g., you may feel more confident since wearing contact lenses or having refractive surgery because you feel that you look better).

14. During the past month, how much of the time have you felt that you have looked your best?

Don't know / Not applicable	Never	Occasionally	Fairly often	Very often	Always

15. During the past month, how much of the time have you felt that you think others see you the way you would like them to (e.g. intelligent, sophisticated, successful, cool, etc)?

Don't know / Not applicable	Never	Occasionally	Fairly often	Very often	Always

16. During the past month, how much of the time have you felt complimented / flattered?

Don't know / Not applicable	Never	Occasionally	Fairly often	Very often	Always

17. During the past month, how much of the time have you felt confident?

Don't know / Not applicable	Never	Occasionally	Fairly often	Very often	Always

18. During the past month, how much of the time have you felt happy?

Don't know / Not applicable

Never	Occasionally	Fairly often	Very often	Always

19. During the past month, how much of the time have you felt able to do the things you want to do?

Don't know / Not applicable

Never	Occasionally	Fairly often	Very often	Always

20. During the past month, how much of the time have you felt eager to try new things?

Don't know / Not applicable

Never	Occasionally	Fairly often	Very often	Always

Are there any other important issues related to your spectacles / contact lenses / refractive surgery that we have not asked about? Please briefly indicate any such issues...............

This is the end of the questionnaire

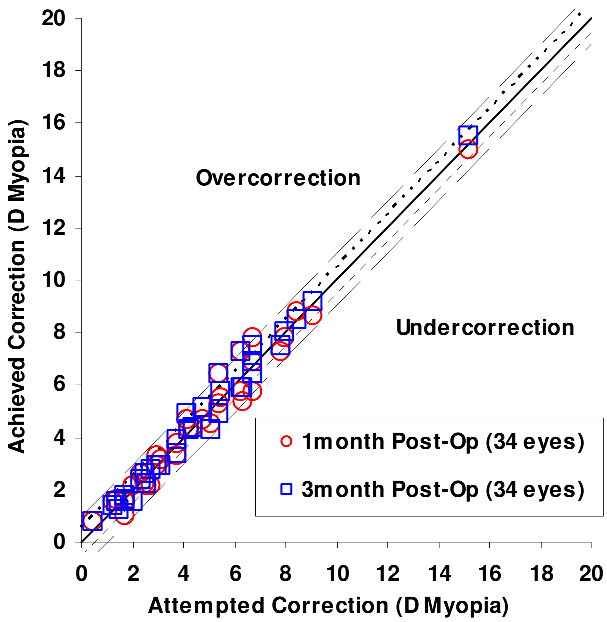
Thank you for completing it!

Please hand it back to the person that gave you it or one of their colleagues.

....

Appendix 4d: Figure 4.1 re-drawn over greater scale to show complete data set.

a. Right eye data



b. Left eye data

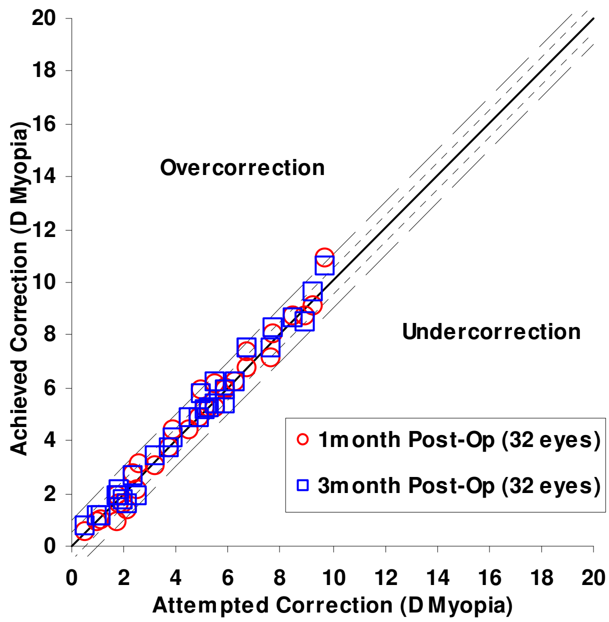


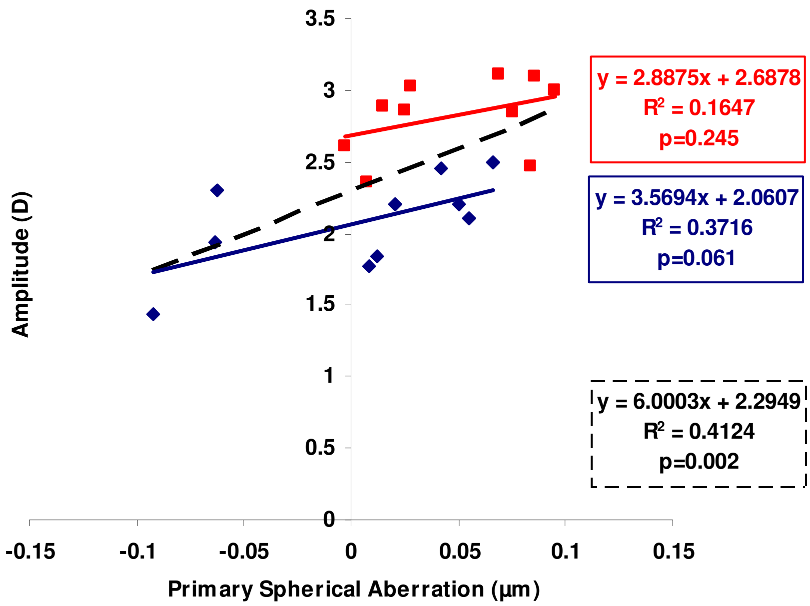
Figure 4.1: Achieved refractive correction (mean sphere) for right and left eyes as a function of attempted correction.

Appendix 5a: Example of critical amplitude chart (shown at approximately double its printed size used in the experiments).

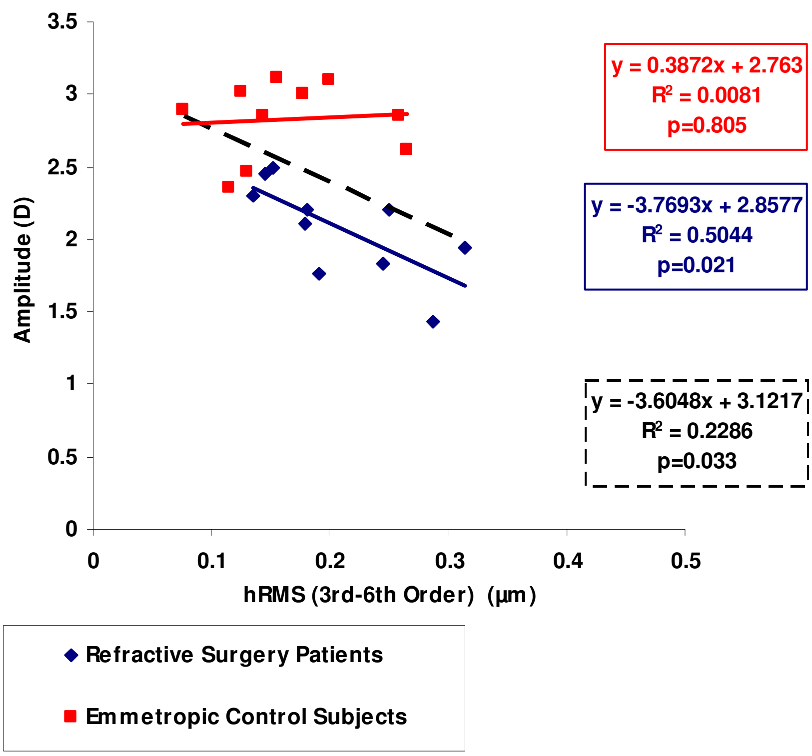
determined vine extreme
have shallow naturalize envy veteran
structures exactly make urgency reassemble jabs
smattering long factory disrupt legislates fire
harness membership land glisten government fold
queasiness yelp objects reciprocal twig verdict
flourished degrade sale beautiful city colour
faculty urns candidates ball haggard parachutes
welcome counsellor skin accelerate oblongs nest
flavouring dine tragedy sand neglect judgements
engrave similarity chin binoculars pier cabinet
bark foundation library over withdrawal romance
kingdom acid mannerism lantern youngsters into
determined vine extreme made attempt quarantine

Appendix 8a: Figure 8.8 re-analyzed for correlation within each refractive group.

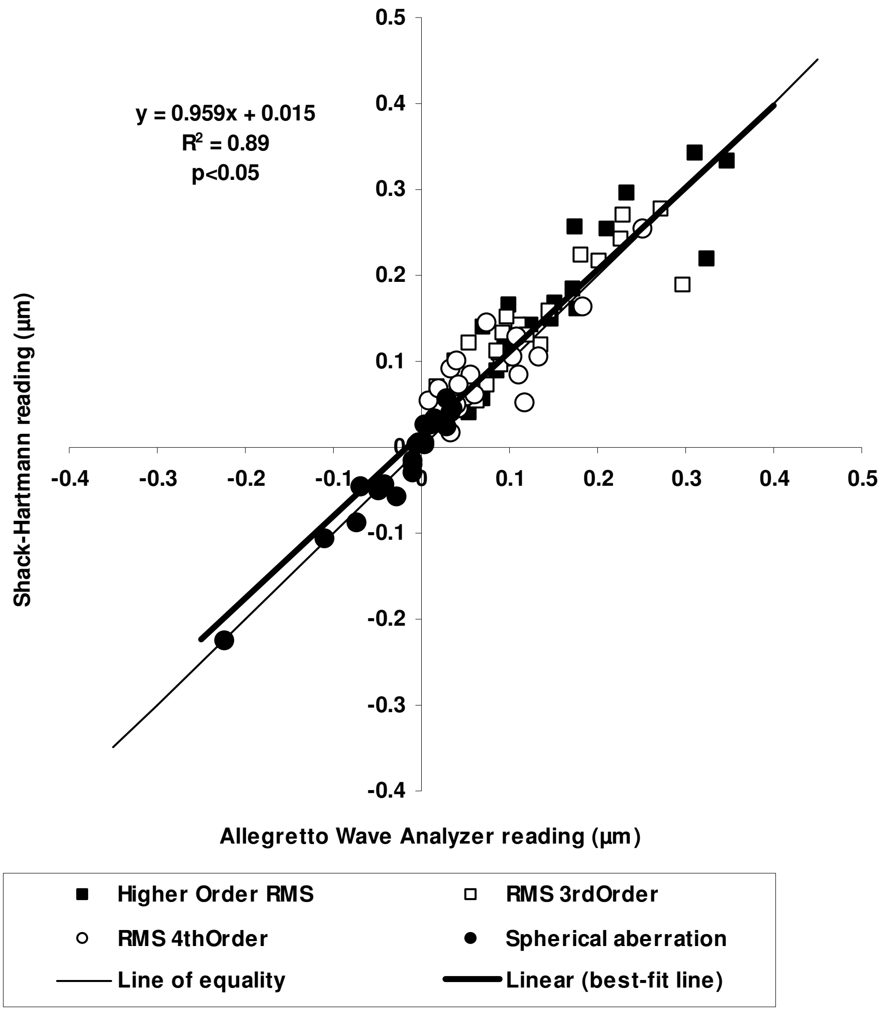
a. Amplitude of response plotted against spherical aberration



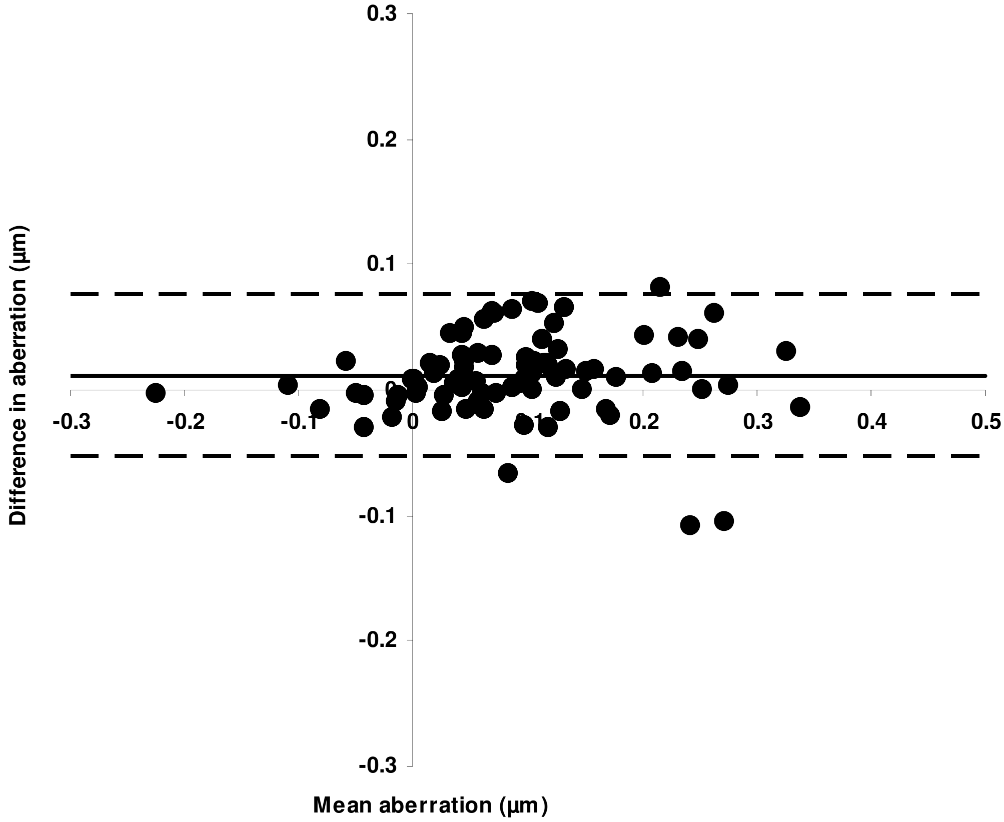
b. Amplitude of response plotted against total higher order aberration



Appendix 8b: Comparison of data from the Shack-Hartmann aberrometer and the Allegretto Wave Analyzer. Data are shown for a group of patients (n=7) undergoing refractive surgery for myopia. The graph shows all measurements taken over three visits (pre-operatively, one month post-operatively and three months post-operatively). Each reading is the mean of five measurements for a 4.0mm pupil diameter.



Appendix 8c: Bland-Altman plot for the level of agreement between the Allegretto Wave Analyzer and the Shack-Hartman aberration measurements. Graph shows the difference in aberration measurement between the two aberrometers against the mean aberration level measured with the two techniques. The mean difference is represented by the solid line and the 95% confidence limits by the dashed lines. Data are shown for a group of patients (n=7) undergoing refractive surgery for myopia. Mean aberration measurements for total higher order RMS, RMS 3rd order, RMS 4th order and spherical aberration are presented across three study visits (pre-operatively, one month post-operatively and three months post-operatively) for a 4.0mm pupil diameter.



Appendix 10a: Participant information sheet for tear film study.

INFORMATION FOR PARTICIPATING SUBJECTS

Title: The contributions of corneal topography and pre-corneal tear film to ocular surface monochromatic aberrations

Researchers: Mr J. Taylor, Dr H. Radhakrishnan, Dr C. O'Donnell.

You are being invited to take part in a research study that is being carried out as part of a PhD project. Before you agree to take part it is important that you understand why the research is being done and what it will involve. Please take time to read the following information and talk to others if you wish.

What is the purpose of the study?

This study aims to investigate some of the potential visual side effects of refractive surgery. We will measure structural aspects of the pre-corneal tear film and cornea to evaluate how these may affect visual performance. In the long term it is hoped that this will provide explanations for visual disturbance caused as a result of surgery, however our experiments may not be of any direct benefit to you.

Why have I been chosen?

You have been chosen as you either have normal eyesight or you have undergone refractive surgery, or orthokeratology.

What will happen to me if I take part?

You will have a series of measurements taken on the front of your eyes. We will measure the thickness and shape of the front of your eye and find out how the optics of your eyes are performing using a number of instruments to photograph the light being reflected by your eye. This can be quite time consuming, as the measurements have to be repeated several times in order for the data to be reliable. We will then use eye drops to temporarily alter the sensitivity of the eye and the tear film and repeat the measurements.

What are the risks involved in taking part?

This study involves the use of eye drops that temporarily alter the sensitivity of the eye. For this reason participants should avoid the risk of foreign body injury to the eye (ie rubbing eyes, dusty environments) for the period the drops are effective (approx. 30mins). There may also be mild watering of the eyes and irritation when the drops are put in, this should only last a few seconds. There is also a possibility of an allergic reaction to the drops occurring. Although this is very rare the signs could include watery and red eyes. The front of your eyes will therefore be checked for these signs prior to you leaving the clinic.

How long will it take?

The entire procedure is expected to take approx. 45mins, and no longer than an hour.

Will my taking part be confidential?

Your personal details will be held on a computer and will not be made available to any third party. Any results published will be anonymous. A copy of the data held on computer about you is available on request in accordance with the Data Protection Act.

Contact details

Your participation in the study is voluntary and you are free to withdraw from the study at anytime without penalty. If you decide to take part you can ask questions at any time. If you have any questions about this research contact:

Mr J. Taylor, Faculty of Life Sciences, Moffat Building, Sackville St, The University of Manchester. E-mail: John.Taylor@postgrad.manchester.ac.uk, OR

Dr H. Radhakrishnan, Faculty of Life Sciences, Moffat Building, Sackville St, The University of Manchester. Tel: 0161 306 8763, E-mail: hema.radhakrishnan@manchester.ac.uk.

Appendix 10b: Consent form for tear film study.

CONSENT FORM FOR PARTICIPATING SUBJECTS

Title: The contributions of corneal topography and pre-corneal tear film to ocular surface monochromatic aberrations.

Name of Researchers: Mr J. Taylor, Dr H. Radhakrishnan, Dr C. O'Donnell.

Subject name:__________________________________

PLEASE INITIAL BOX:

1. I consent to participate in the above project, the purpose and nature of which has been explained to me. I have read the information for participating subjects accompanying this form. ☐
2. I authorize the investigators to conduct with me the tests and procedures necessary for this study. ☐
3. I acknowledge that:

3.1 I have been informed that I am free to withdraw from the project at any time, for any reason and without prejudice. ☐

3.2 The project is for the purpose of research only, and not for the treatment or detection of any visual condition that I may have. ☐

3.3 The confidentiality of the information I provide will be safeguarded. ☐

3.4 I am free to ask questions at any time before or during the study. ☐

3.5 The drugs being used in this study do have some side effects and risks, which have been explained to me. ☐

3.6 I have been made aware of where to seek help should I have any subsequent concerns about side effects from the drugs used in this study. ☐

3.7 I have been provided with a copy of this informed consent form, and the information for participating subjects. ☐

3.8 I agree that during my participation I will observe all relevant safety precautions which have been explained to me and are referred to in the volunteer information sheet. ☐

If you have any questions regarding any aspect of this study please contact:
Dr H.Radhakrishnan at Hema.Radhakrishnan@manchester.ac.uk OR
Mr. J.Taylor at John.Taylor@postgrad.manchester.ac.uk

Signed:__________________________________ Date:____/____/______

Witness:__________________________________ Date:____/____/______

****

If you wish to withdraw from the project, complete the form below and return it to Mr. Taylor or Dr. Radhakrishnan, or Dr. O'Donnell.
I wish to withdraw from the above study.

Signed:__________________________________ Date:____/____/______

SUPPORTING PUBLICATION

The following pages include a copy of a research paper published in *Journal of Vision* based on the work presented in Chapter 3.

Refereed article:

Taylor J, Charman WN, O'Donnell C, Radhakrishnan H. (2009). Effect of target spatial frequency on accommodative response in myopes and emmetropes. *J. Vision.* **9(1):16**, 1-14.

Effect of target spatial frequency on accommodative response in myopes and emmetropes

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Hema Radhakrishnan Faculty of Life Sciences, Moffat Building, University of Manchester, Manchester, UK

This study investigates whether systematic differences exist between the accommodation response/stimulus curves of emmetropes and myopes when the targets are sinusoidal gratings, in particular whether myopic accommodation is relatively less effective when presented with targets of high spatial frequency due to increased tolerance to defocus blur. Ten emmetropes (overall mean sphere +0.19 D, range −0.37 to +1.37 D) and 10 myopes (overall mean sphere −2.89 D, range −1.13 to −6.63 D) viewed Gabor targets with dominant frequencies 1, 4, 8 and 16 c/deg. Maximal grating contrast was 80% and the full, green, stimulus field was 6 deg. Subjects were aged between 18 and 37 years. A further high-contrast 6/30 optotype target was included for comparison purposes. Viewing was monocular, the other eye being occluded. Stimulus demand was varied with trial lenses over the nominal range 0 to 6.0 D and the corresponding accommodation responses were recorded with an open-view, Shin-Nippon SRW-5000 auto-refractor. The resulting accommodation response/stimulus curves were characterized by their slopes over the stimulus range 1.5 to 6.0 D and by an "error index" indicating the extent to which the responses differed from the ideal 1:1 response/stimulus line. No significant differences were found between the mean accommodative behavior of the two refractive groups for any target. There were, however, substantial inter-subject differences. Some subjects in both groups showed more accurate responses with the higher spatial-frequency targets, while others showed optimal response at intermediate frequencies. Although it has been reported in the literature that, in comparison to emmetropes, myopes have reduced sensitivity to blur and response/stimulus curves of lower slope, the present study failed to demonstrate any reduction in their responses to gratings of relatively high spatial frequency. For each target the two refractive groups showed similar accommodative behavior.

Keywords: accommodation, myopia, spatial frequency, response–stimulus curves, auto-refractor

Citation: Taylor, J., Charman, W. N., O'Donnell, C., & Radhakrishnan, H. (2009). Effect of target spatial frequency on accommodative response in myopes and emmetropes. *Journal of Vision, 9*(1):16, 1–14, http://journalofvision.org/9/1/16/, doi:10.1167/9.1.16.

Introduction

Recent decades have seen a rising incidence of myopia, most notably in far eastern countries. Genetic factors undoubtedly play an important role in myopia development, as may nutrition. However, it has long been speculated (e.g. Cohn, 1886; Curtin, 1985; Donders, 1864; Landolt, 1886; Ware, 1813) that environmental factors, particularly near-work, also have a strong influence. As a result, many have suggested that today's high levels of myopia may be at least partly associated with the increased volumes of educational and occupational near-work that form part of current patterns of life (see, e.g. Goldschmidt, 2003; Mutti, Zadnik, & Adams, 1996; Zadnik & Mutti, 1998 for reviews). If this is true, then a clearer understanding of the mechanisms by which near-work precipitates myopia development in genetically susceptible individuals might allow earlier refractive or other intervention, to minimize any subsequent adverse changes in refractive development.

Several candidate mechanisms have been suggested, including the hypothesis that the potentially myopic eye suffers from unusually large levels of higher-order monochromatic aberration. These in turn lead to a less accurate accommodation response, so that the near image suffers from high levels of both aberration and accommodation lag (e.g. Collins, Buehren, & Iskander, 2006; Gwiazda, Bauer, Thorn, & Held, 1995; Gwiazda, Thorn, Bauer, & Held, 1993; He, Gwiazda, Thorn, Held, & Vera-Diaz,

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2005). Myopia is then precipitated through a combination of axial form deprivation and hyperopic defocus, both of which stimulate excessive increase in axial length, as demonstrated in animal experiments (see, e.g. Norton, 1999; Smith, 1998; Wildsoet, 1997 for reviews). Alternatively, the aberration of the myopic eye may be normal but some other factor causes large lags in accommodation and this hyperopic defocus leads to axial elongation and myopia.

Current evidence does not favor the concept that the myopic eye has systematically higher levels of aberration (Charman, 2005) but several studies have suggested that myopes have a lower monocular accommodative stimulus–response gradient than emmetropes (e.g. Abbott, Schmid, & Strang, 1998; Gwiazda et al., 1993; McBrien & Millodot, 1986). The largest differences were found for higher accommodative demands (McBrien & Millodot, 1986) and when accommodation was stimulated with negative lenses (Abbott et al., 1998; Drobe & de Saint-André, 1995; Gwiazda et al., 1993, 1995). In contrast, however, no differences in the slope for different refractive groups were found by Ramsdale (1985) when accommodation was stimulated by varying target distance under binocular conditions, by Seidel, Gray, and Heron (2003) for Badal stimuli up to 4.50 D under monocular conditions, or by Seidel, Gray, and Heron (2005) under binocular free-space conditions. In a longitudinal study under free-space binocular conditions, Rosenfield, Desai, and Portello (2002) found slightly lower slopes for stable myopes as compared to stable emmetropes or progressing myopes.

Why might myopes have lower response/stimulus slopes? It has been speculated that larger accommodative lags might be tolerated by myopes, as compared to emmetropes, because of their reduced sensitivity to defocus blur (Collins et al., 2006; Jiang, 1997; Rosenfield & Abraham-Cohen, 1999; Vasudevan, Ciuffreda, & Wang, 2006). This reduced sensitivity is associated with a reduced effect of defocus on visual performance (Thorn, Cameron, Arnel, & Thorn, 1998). Moreover, there is strong evidence for blur adaptation in uncorrected myopes (Rosenfield, Hong, & George, 2004). On the other hand, Schmid, Iskander, Li, Edwards, and Lew (2002) failed to find a statistical difference in the blur detection abilities of myopic and non-myopic children, although myopic children showed greater individual variation. Longitudinal studies comparing the magnitude of initial accommodative near lag with the subsequent myopia progression appear to yield conflicting results (Allen & O'Leary, 2006; Weizhong, Zhikuan, Wen, Xiang, & Jian, 2008).

McBrien and Millodot (1987) found that late-onset myopes had significantly lower levels of tonic accommodation (around 0.5 D) than early-onset myopes or emmetropes (around 0.9 D) (see also, Maddock, Millodot, Leat, & Johnson, 1981; Rosenfield & Gilmartin, 1987). Some studies suggest that, unlike emmetropes, myopes have significantly different sensitivities to positive and negative defocus (Radhakrishnan, Pardhan, Calver, & O'Leary, 2004a, 2004b).

When grating objects are observed, the degrading effect of any given level of defocus blur on the contrast of the retinal image increases with the spatial frequency of the grating, although the exact contrast changes vary with such factors as the pupil diameter, wavelength and ocular aberration (e.g. Atchison, Woods, & Bradley, 1998; Charman, 1979; Charman & Jennings, 1976; Green & Campbell, 1965; Legge, Mullen, Woo, & Campbell, 1987; Marcos, Moreno, & Navarro, 1999). If, then, myopes have a reduced sensitivity to defocus blur and less accurate accommodation responses to targets of broad spatial bandwidth than those of emmetropes, this may be because they place a greater importance on the lower spatial frequency components of the retinal image than on those of higher spatial frequency. If this is true, it might be expected that myopes would have greater problems than emmetropes when asked to accommodate to targets containing mainly high spatial frequencies.

We have therefore studied the form of the monocular response/stimulus curve to grating targets of different spatial frequencies and to a letter target of wider spatial bandwidth in groups of emmetropic and myopic subjects of similar age, to determine whether they show obvious differences in the form of their response curves. The hypothesis was that myopes would show a lower slope than emmetropes when the target was a grating of higher spatial frequency. Accommodation was stimulated monocularly using negative lenses, since earlier studies suggest that these conditions might yield the greatest differences between refractive groups. Under these circumstances, of the components of accommodation identified by Heath (1956a), proximal accommodation is absent (or counter-productive) and there is no convergence-accommodation. Although these monocular, restricted conditions for accommodation do not match the free-space, binocular viewing conditions of real life, where numerous accommodative cues are available, it was hoped that they would optimize the chances of revealing any systematic deficits of the accommodative abilities of myopes as compared to emmetropes.

Methods

The study followed the tenets of the Declaration of Helsinki and written informed consent was obtained from all participants after the nature 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. Twenty adult subjects (14 female, 6 male) between the ages of 18 and 37 were recruited from among the staff and students at the University of Manchester, UK. All subjects were free from ocular disease and myopic retinal degeneration. They had a visual acuity of 6/6 or better in the tested eye and no known accommodative anomalies or significant ocular history. Only one subject was an experienced observer for accommodation and psychophysical studies. Subjects with astigmatism of over 1.25 D were excluded from the study, and the right eye was used for all measurements. Ten of the subjects were emmetropic (overall mean sphere +0.19 D, range −0.37 D to +1.37 D), and 10 were myopic (overall mean sphere −2.89 D, range −1.13 D to −6.63 D). The mean age was 25.1 years (range 19 to 37) for the emmetropes and 26.4 years (range 20 to 36) for the myopes. The myopic group included 7 early-onset myopes (myopia onset at age 14 years or before) and 3 late-onset myopes (myopia onset at 15 years of age or older). In the early-onset myopes, 3 were progressing myopes (defined as an increase of 0.5 D or more in the previous 2 years as reported by the subject) and 4 were stable. In the late-onset myopes 1 was progressing, while 2 were stable. All subjects underwent a full subjective refraction on the right eye (based on least-negative prescription with maximum achievable visual acuity). Myopic refractive error was corrected for distance viewing with thin disposable soft contact lenses to within ±0.25 D (best sphere), which was confirmed with over-refraction and visual acuity measurements. Any residual refractive error was then corrected with trial lenses. Contact lenses were worn by 8 of the 10 myopes, who were all habitual contact lens wearers. The other 2 myopes had refractive errors −1.00/−0.25 × 5, and −1.00/−0.25 × 175, and did not wear contact lenses for the experiment. Instead a −1.00 D lens was added in the trial frame in addition to the lenses used to alter target vergence.

The grating targets, which were placed at a distance of 1 m from the eye, consisted of vertical, sine-wave Gabor targets (Gabor, 1946). Gabor targets were used rather than true gratings to minimize any edge effects which might affect the subjects' accommodation. The target luminance was described by a function of the form:

$$L = L_{mean}(1 + C \sin\{2\pi Fx\} \ . \ \exp[-(x^2 + y^2)/2\sigma^2]), \quad (1)$$

where L_{mean} was the mean luminance (45 cd/m^2), x and y were angular Cartesian coordinates on the screen, measured from the peak of the Gaussian envelope, C was the grating contrast (0.8 or 80%), F the target's dominant spatial frequency and σ the standard deviation of the Gaussian envelope (constant at 1.2 degrees). All targets subtended a total of 6 deg of visual angle. There were 4 grating targets (spatial frequencies, F = 1, 4, 8, and 16 cycles/degree) and one 80% contrast optotype "E" target. Note that, because the Gaussian envelope was the same for all the Gabor targets, their relative bandwidth decreased with the nominal center frequency F. The octave bandwidths were 0.453 (1 c/deg), 0.112 (4 c/deg), 0.056 (8 c/deg) and 0.028 (16 c/deg): there was negligible content at higher harmonics of the fundamental frequencies.

The optotype was a letter "E". This subtended a visual angle of 25 minutes of arc (equating to a 6/30 letter), with the horizontal bars crudely approximating to a 6 c/deg square-wave grating. The letter was sufficiently large to be recognizable with large errors of focus, so that any subject who habitually minimized their accommodative effort could recognize the letter in the presence of substantial accommodative lag. In contrast, to produce accurate retinal focus subjects ideally needed to accommodate to produce maximal edge sharpness rather than to simply ensure letter recognition.

All the targets were included in a PowerPoint presentation, alternately interleaved with blank screens, and 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, UK).

Stimulus–response functions were measured by altering the target vergence with lenses. The subjects viewed the targets presented on the monitor at a fixed 1 m distance (vergence −1.00 D) with a natural pupil through an open-view Shin-Nippon SRW-5000 auto-refractor (Ajinomoto Trading Inc, Tokyo, Japan, see Mallen, Wolffsohn, Gilmartin, & Tsujimura, 2001). The auto-refractor incorporated a circular aperture that allowed a 6 deg field at 1 m: this served to black out the surround and remove other possible accommodative stimuli. As the aperture was positioned at 19 cm (vergence −5.26 D) from the eye, it represented a much higher and more peripheral stimulus than the main targets and was not expected to have any effect on the responses. The left eye was occluded and the targets were observed monocularly through the aperture using the right eye, with the room lights off. The subjects wore a trial frame, at a vertex distance of 12 mm, into which lenses (+1.00, −0.50, −2.00, −3.50, −5.00 D) were placed to alter the vergence of the targets and create accommodative stimuli covering the range 0–6 D in 1.5 D steps (nominally +0 D, 1.5 D, 3 D, 4.5 D and 6 D). The size and spatial frequency of each set of targets was adjusted to compensate for magnification produced by the different trial lenses used and target vergences were corrected for the vertex distance of the trial lenses. Note that both the target and the field aperture were seen through the lenses, so that the vergence of the latter always remained about −5 D greater than that of the target. The grating targets were presented in random order to each subject, followed by the optotype.

Subjects were told to view the targets "keeping them as clear as possible at all times." Although the subjects were familiarized with the requirements of their task, no attempt was made to systematically train them through practice or feedback to produce maximal responses, since it was hoped that they would produce "natural" responses which reflected their accommodative performance in normal life. When the subject reported that each stimulus was clear, 3 readings were taken with the auto-refractor. Each target was interleaved with a blank screen and the target was presented for the minimum duration (i.e. just long enough for the subject to be able to report the target to be clear and to take the readings), to avoid grating adaptation effects. Accommodation responses, expressed in vector form (Thibos, Wheeler, & Horner, 1997), were calculated from the means of each triplet of auto-refractor readings, with appropriate allowance for the power and vertex distance of the trial lenses worn. An increase in power of the eye, corresponding to a more negative refraction, was taken as a positive accommodation response. Estimated responses for the vertical grating targets were based on measurements of refraction in the horizontal meridian of the eye: those for the optotype were based on best-sphere refractions.

Data analysis

Two single-figure indices were used to characterize each response/stimulus curve: its slope and the accommodative error index. The error index was used because slope values alone do not demonstrate whether the responses succeed in yielding precisely focused retinal images. A curve with a slope of unity does not necessarily coincide with the "ideal" 1:1 or Donders' response/stimulus line and substantial lags or leads may still be present. The accommodative error index (Chauhan & Charman, 1995) takes account of both the extent to which responses deviate from Donder's line over the chosen stimulus interval and the goodness of fit of the data points to the regression line. The index essentially involves determining the mean magnitude of the response error between the ideal line and the regression line over the stimulus interval and dividing it by the value of r^2 for the regression line (r is the product moment correlation coefficient). If the regression line fit is

$$y = mx + c, \tag{2}$$

where y is the response, x the stimulus, m the slope and c the intercept, and the regression line does not cross the Donder's line, the accommodative error index, I, is given by:

$$I = |(1 - m)[(x_2 + x_1)/2] - c|/r^2, \tag{3}$$

where x_1 and x_2 are the stimulus levels defining the range over which the regression fit applies. If the two lines intersect within the chosen stimulus interval, a slightly more elaborate expression must be used (Chauhan & Charman, 1995).

Results

Stimulus–response functions for each target type were plotted for each subject. The accommodative response curves generally showed the usual form of an initial non-linear region followed by a quasi-linear region (Ciuffreda, 1991, 1998). There were, however, considerable inter-subject variations in the form of the curves for different targets. Figure 1 shows some typical data. Note that emmetrope 3 (−0.25/−0.25 × 175) has reasonably consistent responses but emmetrope 4 (+0.25/−0.25 × 135), who has generally more scattered responses, has difficulty in accommodating to the gratings at zero vergence. Myope 4 (−1.00/−0.25 × 5) has reasonably accurate responses which vary little with the target except for the highest stimuli, whereas myope 9 (−6.50/−0.25 × 20) produces erratic and inaccurate responses to almost all the stimuli.

As a further indication of the differences between individual subjects, Figure 2 shows the full set of response/stimulus curves for the optotype target. Note that one emmetrope found it difficult to relax accommodation to view the optically more-distant stimuli, and that one of the myopes completely failed to accommodate systematically to the target.

In an initial attempt to quantify possible differences between the various response/stimulus curves, the accommodative response slope was calculated for the quasi-linear part of the accommodative response curve by determining the regression line fit for data obtained with 1.5 D stimulus onward. The results for individual subjects in the two refractive groups are shown in (Figures 3A and 3B).

The emmetropic group (Figure 3A) appears to be divided into two equal sub-subgroups, showing for the grating targets different patterns of change in slope with spatial frequency. In the first sub-group, slopes tend to increase with the spatial frequency of the target. In the second, slopes are maximal at around 4 c/deg and decrease at higher spatial frequencies. There appears to be no correlation between the pattern of behavior and the age of the subjects. With the exception of one 21 year-old, who has an unusually low slope, slopes for optotypes are generally similar to the maximal slopes for the grating targets.

Mixed performance for the grating targets is also observed among the myopic group, but it is more difficult to classify the differences involved (Figure 3B). There is no obvious relation between the pattern of slope change and the magnitude, onset or progression of the myopia. It is of interest that some myopes (−1.37 D, −2.25 D) had very poor response gradients for the optotype, while the −2.00 myope (stable) essentially failed to accommodate to all but the lowest frequency of grating and the optotype. In general a greater spread of accommodative behavior is observed in the myopic group than in the emmetropic group.

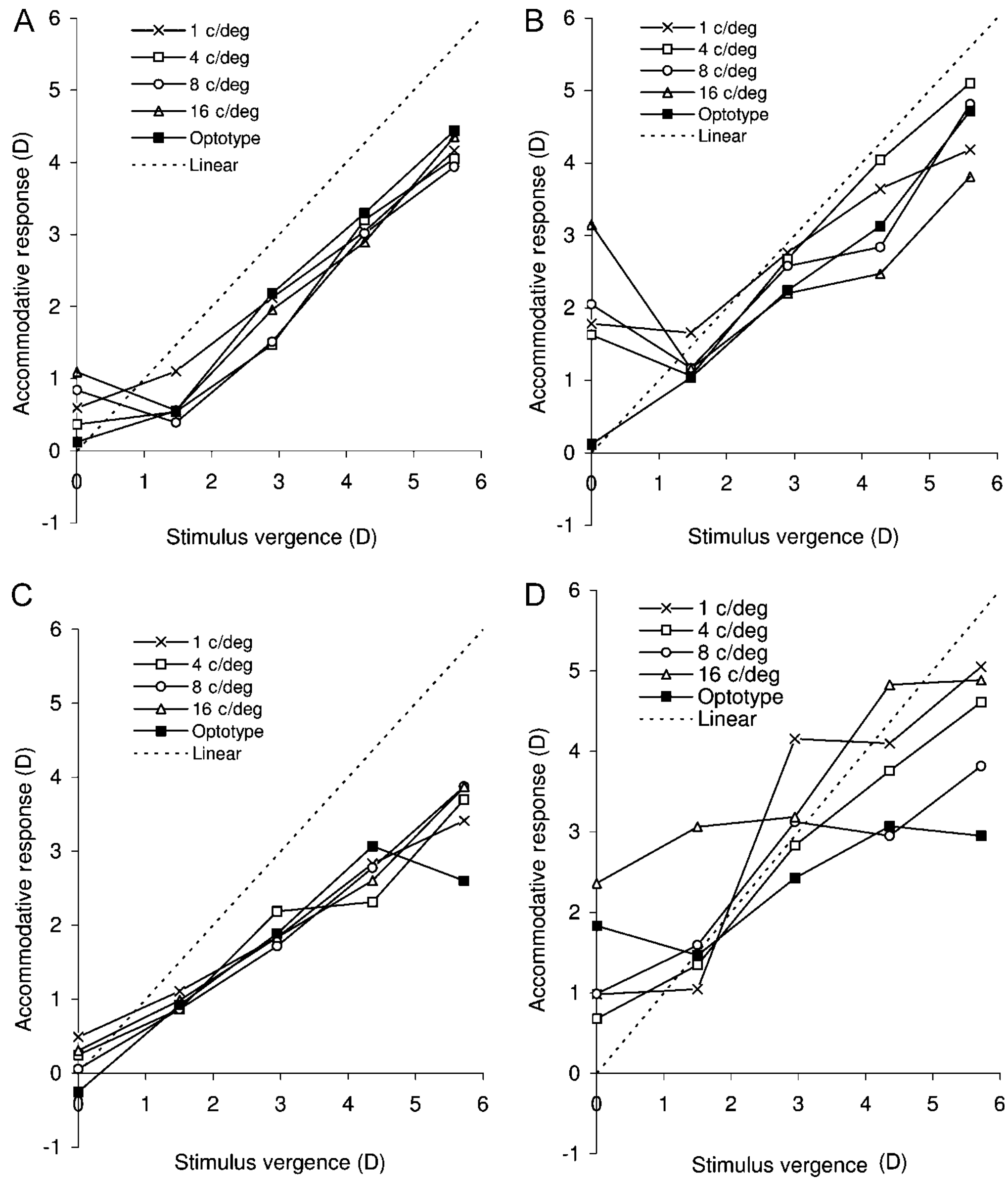

Figure 1. Examples of accommodation response/stimulus curves for the five targets: (A) emmetrope 3, age 25, (B) emmetrope 4, age 21, (C) myope 4, −1.12 D mean sphere, age 23, late-onset, stable, and (D) myope 9, −6.62 D mean sphere, age 23, early-onset, progressing.

The mean slopes of the subjects within the two groups are given in Table 1. Note that the standard deviations are larger for the myopic group. There are, however, no significant differences between the mean slopes of the two refractive groups (non-parametric Kruskal–Wallis ANOVA by ranks: $p = 0.95$) and the spatial frequency of the individual targets has no significant effect on the slope of the accommodative response curve (Kruskal–Wallis ANOVA by ranks: $p = 0.21$). It is evident from Table 1 (see also Figure 2) that the variability found in the accommodative response functions was greater in the myopic group for all targets.

While the slope values show how the response is changing with the stimulus, they give no indication of the magnitudes of the actual errors (lags or leads) of focus, which may be very high even though the slope is close to unity. Unfortunately, evaluation of such errors with infrared auto-refractors is not straightforward, since the results of all auto-refractors include corrections for the position of the reflecting layer within the retina and for longitudinal chromatic aberration between the infra-red and visible wavelengths. In addition, they include a further correction to bring their results into line with those of clinical subjective procedures. The latter are typically carried out at a testing distance of 6 m (vergence −0.17 D) and involve a "least negative, most positive correction." They thus leave the "emmetropic" eye slightly myopic, relying on depth-of-focus to give clear vision of the test chart. Overall, then, it is likely that an auto-refractor measurement of perfect "emmetropia"

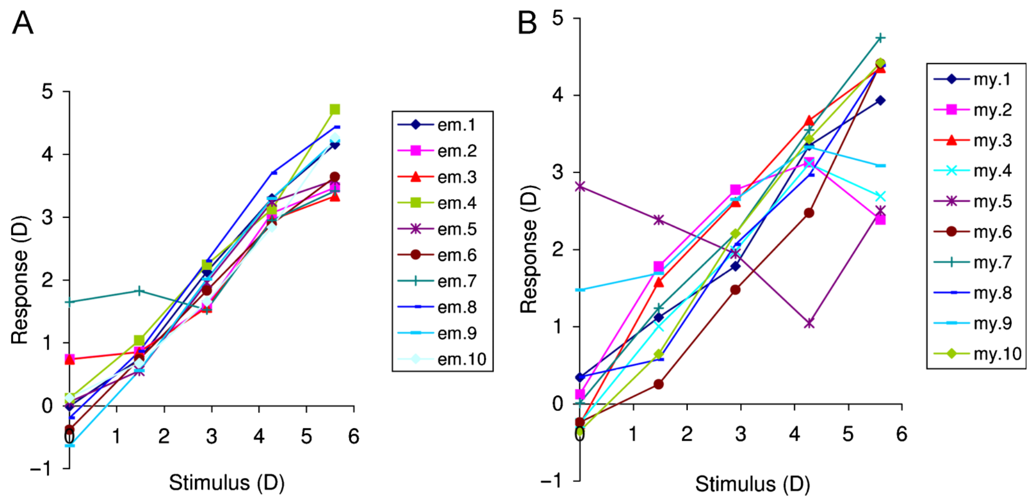

Figure 2. Response/stimulus curves for the high-contrast 6/30 optotype as measured with the auto-refractor for (A) emmetropes and (B) myopes.

implies an eye that, from the strictly optical point of view is, slightly myopic. As far as we are aware, no one has established the difference between the true and outputted values of refractive error for the Shin-Nippon instrument. For the present purposes, we have assumed that our Shin-Nippon estimates of responses are 0.25 D too low. We have therefore amended the intercept values in our regression line fits by this amount when the fits are used to derive the error indices.

The accommodative error index values for the different subjects and targets for the nominal stimulus range 1.5 to 6.0 D are shown in Figure 4. Apart from one poorly

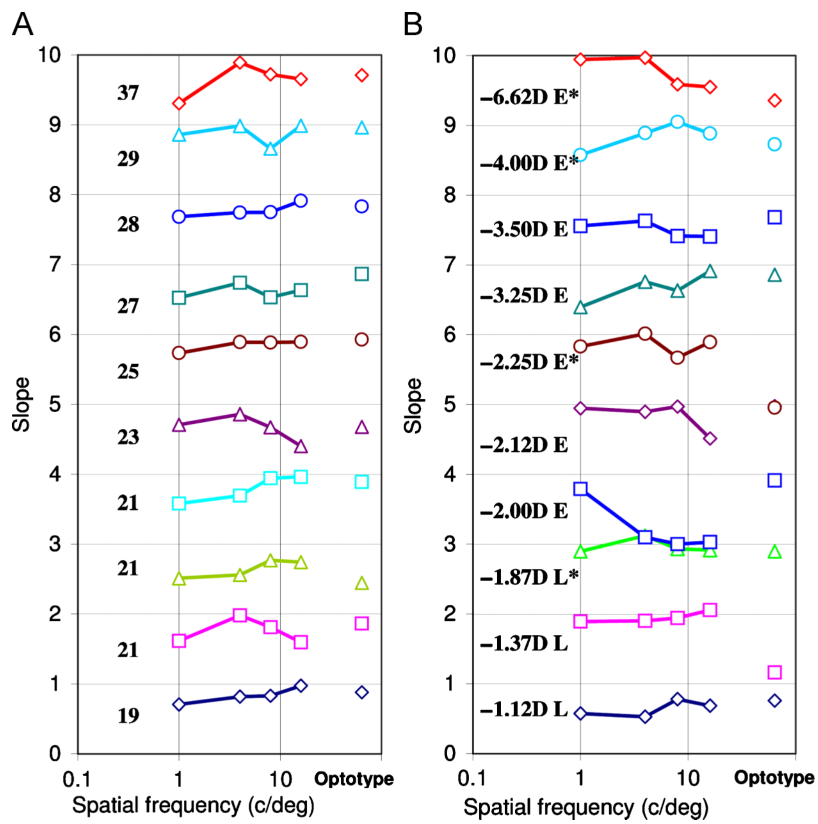

Figure 3. Slopes of regression-line fits to the response/stimulus data over the stimulus interval 1.5 to 6.0 D inclusive for individual subjects as a function of stimulus spatial frequency and for the optotype target. For clarity, results for each subject are successively displaced upward by one unit (A) emmetropic subjects arranged in order of ascending age (B) myopic subjects, arranged in order of increasing mean sphere error. E and L indicate early- or late-onset myopia and * indicates that the myopia is progressing.

Target	Emmetropes (N = 10)	Myopes (N = 10)
1 c/deg	0.62 ± 0.15	0.74 ± 0.20
4 c/deg	0.83 ± 0.13	0.78 ± 0.30
8 c/deg	0.76 ± 0.12	0.70 ± 0.32
16 c/deg	0.78 ± 0.20	0.68 ± 0.31
Optotype	0.81 ± 0.15	0.66 ± 0.32

Table 1. Mean slopes and standard deviations of the accommodation response/stimulus curves, over the stimulus interval 1.5 to 6.0 D inclusive, for the different targets for the emmetropic and myopic refractive groups.

Target	Mean AEI, emmetropes (D)	Mean AEI, myopes (D)
1 c/deg	0.84 ± 0.30	0.67 ± 0.34
4 c/deg	0.57 ± 0.29	0.77 ± 0.82
8 c/deg	0.85 ± 0.35	0.82 ± 0.78
16 c/deg	0.59 ± 0.22	1.04 ± 0.85
Optotype	0.87 ± 0.31	0.96 ± 0.76

Table 2. Mean accommodative error indices, in dioptres, and their standard deviations for the different targets for the emmetropic and myopic refractive groups.

accommodating myopic subject, who also had unusually low slope values, and particular combinations of individual subjects and targets, error indices are generally of the order of 1 D or less.

The mean values of the error index are given in Table 2. Note that in general the indices are quite high. Since r^2 values for the response/stimulus plots generally exceeded 0.9, this implies that mean errors of accommodation were quite large (typically between 0.5 and 1.0 D). However, in a few cases when slopes were very low r^2 values were also very low, giving unrealistically high values of error index: in these cases the index was assigned a value of 3, giving the ceiling effect observable in Figure 4B.

Kruskal-Wallis analysis of variance by ranks shows no significant difference in the mean accommodative error indices between myopes and emmetropes (p = 0.53) and between different spatial frequencies of the targets used in the study, including the optotypes (p = 0.25).

As noted earlier, several subjects had difficulty in accommodating to stimuli at zero vergence (i.e. at optical infinity). Table 3 shows the mean (±1 *SD*) accommodative errors (generally leads) with these stimuli for the individual subjects within each refractive group. The values presented like those of Figure 1 are directly based on the auto-refractor readings, with no further correction for possible zero error. The problems experienced by some subjects, who include both myopes and emmetropes, are obvious.

Discussion

The present study fails to demonstrate any systematic differences between the response/stimulus curves of emmetropic and myopic refractive groups and, in particular, fails to demonstrate that changing the spatial frequency of a grating target produces significantly different variations in the accommodation responses of the two groups. Thus we cannot confirm the hypothesis that myopes normally make less use of high spatial frequency information to guide their accommodation response.

However, under the conditions used, where only a limited subset of the components of accommodation may be active, the striking aspect of the results is that they are heavily dependent on the individuals involved. The

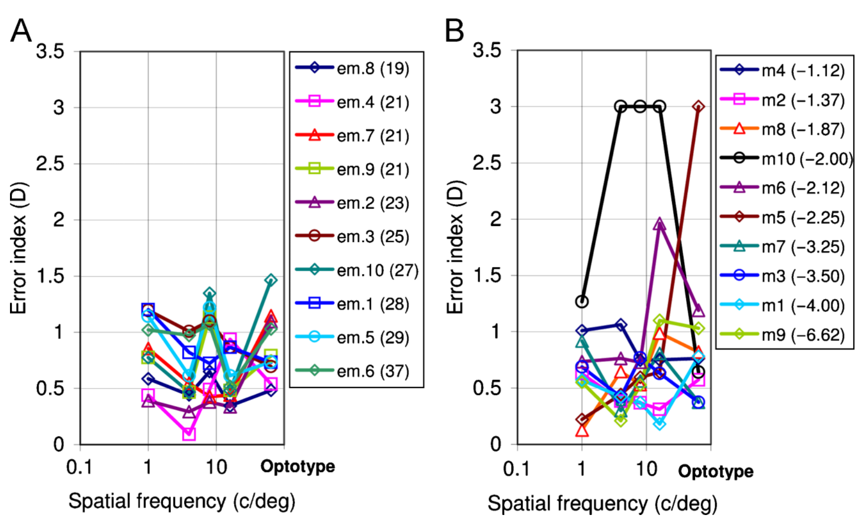

Figure 4. Changes in the error index, I, as a function of the spatial frequency of the grating target and for the optotype (A) emmetropes (B) myopes. Ages (years) are given for the emmetropes and refractive errors (D) for the myopes.

Target	Mean response, (emmetropes), D	Mean response (myopes), D
1 c/deg	0.60 ± 0.48	0.48 ± 0.78
4 c/deg	0.40 ± 0.91	0.40 ± 0.84
8 c/deg	0.62 ± 0.92	0.56 ± 1.30
16 c/deg	0.97 ± 1.33	1.45 ± 1.64
Optotype	0.16 ± 0.64	0.40 ± 1.00

Table 3. Mean responses (D) and their standard deviations to targets at optical infinity (zero vergence) based directly on the auto-refractor readings.

response/stimulus curves of individuals to any target differ in three important ways:

1. In the gradient of their linear portions.
2. In the magnitude of the errors of accommodation.
3. In the response to very low vergence targets.

Considering first the results obtained with relatively narrow-band grating targets, it is well known that image modulation falls away more rapidly with defocus as the spatial frequency of the target increases (Charman & Tucker, 1977, 1978). Thus if accommodation always acted to produce near-maximal image modulation, tolerances to focus error would be smaller at higher spatial frequencies. The effect is complicated by the presence of accommodation-dependent spherical aberration, which results in a spatial-frequency dependence in the optimal focus, that for low spatial frequencies being closer to the marginal focus and that for higher spatial frequencies closer to the paraxial focus (Charman, 1979; Charman, Jennings, & Whitefoot, 1978; Green & Campbell, 1965; Koomen, Skolnik, & Tousey, 1951). Further complication arises from accommodative miosis and the change in spherical aberration with accommodation (Plainis, Ginis, & Pallikaris, 2005). It would be expected that response and stimulus would be equal at a value approximating to the individual's tonic level of accommodation (typically around 1 D, Leibowitz & Owens, 1978; McBrien & Millodot, 1987), with leads at the lowest stimulus levels and lags at levels above the tonic value.

Many earlier authors have explored the accommodation response/stimulus curve for sinusoidal grating targets (e.g. Bour, 1981; Charman & Tucker, 1977, 1978; Owens, 1980; Phillips, 1974), although none of them appears to have systematically studied the effect on the results, if any, of the subject's refractive error. A common, and expected, finding in all studies is that accommodation to low spatial frequency sinusoidal gratings (1 c/deg or less) tends to produce low response gradients, since large errors of focus are required to substantially change image contrast at low spatial frequencies. Charman and Tucker (1977, 1978) found that the response/stimulus gradient tended to be maintained or increase at higher spatial frequencies whereas Bour (1981), Owens (1980), and Phillips (1974), found that response accuracy was optimal at spatial frequencies of 3–5 c/deg, around the peak of the photopic contrast sensitivity function, and that gradients decreased at higher and lower spatial frequencies. Some of these differences can reasonably be explained in terms of the different instructions given to the subjects, which in Charman and Tucker's case encouraged the maximal use of voluntary accommodation, whereas Owens' subjects were told to "view naturally, without straining the eye," thereby encouraging subjects to rely mainly on reflex accommodation (Ciuffreda & Hokoda, 1985; Francis, Jiang, Owens, & Tyrrell, 2003; Owens, 1980; Stark & Atchison, 1994). Further work using dynamic stimuli (Mathews, 1998; Mathews & Kruger, 1994; Stone, Mathews, & Kruger, 1993) supports the view that higher spatial frequencies play little role in reflex accommodation.

All of our subjects were given the instruction to "keep the targets clear." Examination of Figure 3 suggests that in practice half of the emmetropes had gradients that increased with spatial frequency while in the other half they peaked at around 4 c/deg or showed ambiguous changes. Thus the emmetropic group displayed mixed behavior similar to that found by Ciuffreda and Hokoda (1985). The myopes' behavior was broadly similar, with the exception that one subject showed little response to any grating except 1 c/deg. While there were minor differences in the mean slopes for each grating (Table 1) the differences between the refractive groups do not reach statistical significance. Thus the mean slope data fail to show that the effect of target grating frequency is markedly different in emmetropes and myopes. The same null result was found for the error indices. Although the present study did not show a statistically significant difference in the accommodative response functions between the two refractive groups, the variability of the accommodative response functions was found to be larger in the myopic group.

When the individual subjects are considered, however, substantial inter-subject differences in both slopes and error indices are found. We attribute these to variations in the reliance that individuals place on the different components of accommodation, allied to the nature of the defocus changes in the images of sinusoidal gratings.

For larger errors of focus, the grating images are subject to the phenomenon of spurious resolution (Smith, 1982). It is therefore possible that some subjects may accommodate to bring one of the secondary, supra-threshold spuriously resolved images onto the retina, rather than attempting to accommodate to the primary image (Charman & Tucker, 1977). The result is substantial accommodative error, usually a lag, since there is a tendency to minimize the accommodation exercised when the target vergence is high.

In the present case, accommodation to a spuriously resolved image is most likely to occur for the 16 c/deg grating, which has the narrowest relative spatial bandwidth. The exact effects depend on the pupil size and

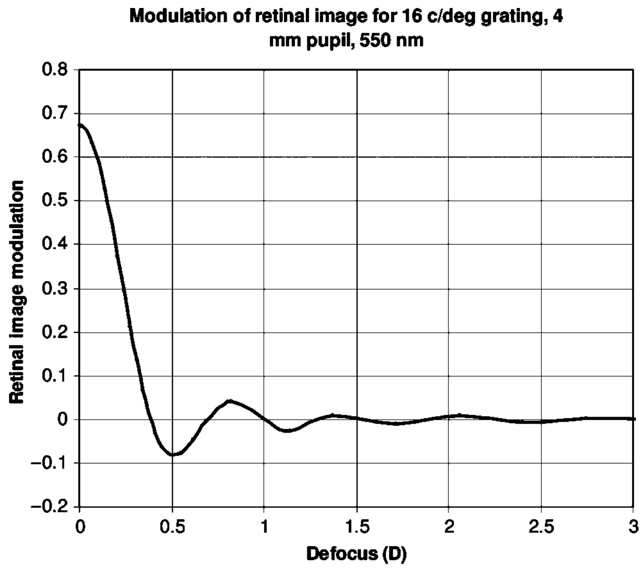

Figure 5. Changes in the modulation in the retinal image of a 16 c/deg grating for an aberration-free eye with a 4 mm pupil and light of wavelength 550 nm.

aberrations of the individual subject, Stiles-Crawford apodization, the frequency spectrum of the object, and the spectral composition of the illumination but, to qualitatively illustrate their nature, Figure 5 shows the through-focus changes in retinal image modulation for an 80% modulated 16 c/deg grating target (as used in the study) which might be expected for a diffraction-limited eye with a 4 mm pupil working at a wavelength of 550 nm. The retinal contrast threshold for this spatial frequency is less than 0.01, (Campbell & Green, 1965; Sekiguchi, Williams, & Brainard, 1993). Note that the modulation in the peaks of spurious resolution is substantially higher than this, so that the grating may be detected, not necessarily in the correct phase, at several positions of focus. Evidently, then, a subject may report that the image is "clear" when viewing a spuriously resolved image with a substantial accommodative lag.

The probability of an individual choosing to accommodate to a spuriously resolved image presumably depends upon the reliance placed on each of the components of accommodation. For accurate accommodation to the higher spatial frequency gratings, the subject must exercise enough accommodation to successfully locate the primary image of the grating, rather than one of the spuriously resolved images. Since, in the stimulus conditions used, convergence and proximity cues are lacking and blur cues may be ambiguous, if the target is not at a vergence corresponding to the tonic accommodation level of the individual, subjects may have to rely on voluntary accommodation to bring the grating target into approximately correct focus. Hence those subjects who habitually rely primarily on proximity and binocular cues are likely to accommodate poorly to the higher-frequency gratings. It appears that both the emmetropic and myopic groups contained such subjects, leading to a reduction in slope and an increase in error index (Figures 3 and 4). The precise nature of their accommodative errors will depend upon the position of their tonic levels in relation to the stimulus values.

The 6/30 letter "E" target represents a slightly different challenge to the accommodation system. It is a broad-band-frequency target which can be resolved with relatively large errors of focus (around 1.5 D, e.g. Rabbetts, 1998). More precise accommodation simply improves edge sharpness, as higher spatial frequency components come into better focus, and in principle it ought to be much easier to achieve an accurate focus than with sinusoidal grating targets (Ciuffreda, Dul, & Fisher, 1987; Heath, 1956b; Tucker & Charman, 1987). However, it is of interest that, although most subjects accommodated reasonably well to the optotype, except perhaps at the highest (5.72 D) stimulus level, their errors of focus and error indices (Figure 4) were quite substantial, suggesting that they were using a criterion which depended more on a tolerance to defocus based on a "troublesome" or "bothersome blur" criterion rather than on "just noticeable blur" (Atchison, Fisher, Pedersen, & Ridall, 2005; Ciuffreda et al., 2006). One of the myopes completely failed to accommodate systematically as the stimulus vergence varied, giving a gradient of effectively zero (Figure 2): others have also found that young, clinically normal, adult subjects may fail to accommodate when presented with static or dynamic stimuli (e.g. Chen, Kruger, Hofer, Singer, & Williams, 2006; Heron, Charman, & Grey, 1999). In general, for the optotype, variations between the response curves of subjects were larger within the myopic group. Another possible reason for the low accommodative responses found in some of the subjects could be the lack of chromatic cues in the targets used in the present study (Fincham, 1951; Kruger, Mathews, Katz, Aggarwala, & Nowbotsing, 1997). Since all the targets were presented using the green phosphor of the CRT monitor, the accommodative response of at least some of the subjects is likely to be lower than the response found under more natural polychromatic conditions.

It could be argued that responses of at least some subjects would have been both more accurate and more consistent had they been trained to the task. Our reasons for not doing this have been mentioned earlier: we felt that subjects should be asked to accommodate in a way that felt natural to them and which reflected their normal judgments of the clarity of the stimuli under the conditions of the study. Under conditions where some cues to accommodation have been removed it is usually found that subjects learn to make use of alternative cues to guide their responses. For example, Fincham (1951) found that 60% of subjects who accommodated normally in white light were initially unable to accommodate in monochromatic light but most soon learned to do so.

To determine whether the responses could be influenced by further encouragement and instruction, the measurements

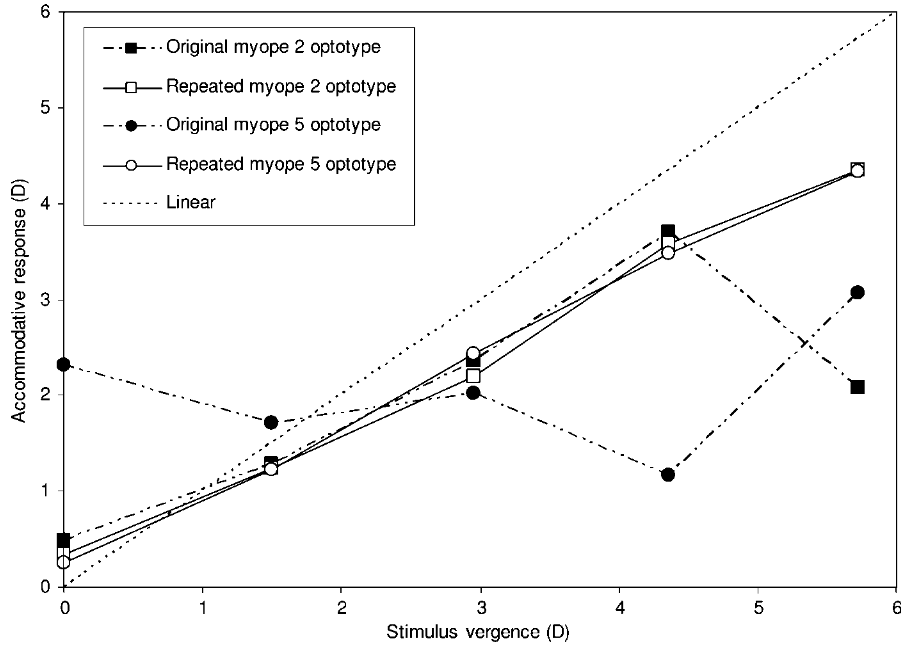

Figure 6. Response/stimulus curves for the optotype target for myopic subjects 2 and 5 in the original and repeat measurements.

for the optotype target were repeated for the two myopic subjects with the lowest gradients. Before the repeat session, it was emphasized to subjects that they should concentrate on achieving maximal perceived contrast and sharpness when accommodating. Figure 6 compares the initial and repeated data for the subjects. The accommodative response gradients for the optotype targets improved from 0.27 to 0.76 for myope 2 and from 0.23 to 0.74 for myope 5. The new values are comparable to the group mean for the emmetropes.

It is evident from Figure 6 that the original low gradient for myope 2 was caused by the subject's failure to accommodate adequately to the 5.72 D stimulus: all the other repeated measurements were very close to the original measurements. The repeated results for myope 5 showed far more typical responses in comparison to the irregular responses obtained for this subject originally. This emphasizes the problem of carrying out studies of this type. To what extent are we assessing voluntary aspects of accommodation rather than the limits of performance of the system?

All subjects had originally claimed that the target was "clear," even though for some it must have been markedly out of focus. Those subjects with reasonably accurate initial responses showed similar responses upon repetition. With training and encouragement, the initially under-accommodating subjects achieved more accurate responses, as shown above. However, while this result shows that these subjects have the potential to accommodate reasonably well, it appears that with monocular stimuli they initially do not normally bother to do so. As noted earlier, it may be that under normal binocular conditions, they habitually place a strong reliance on vergence accommodation to help the response to rise to an appropriate level and that monocular studies give little indication of their real-life accommodation abilities. As a result, under monocular conditions they must learn to use voluntary accommodation as a replacement for the missing convergence accommodation. As noted earlier, an alternative, or additional, factor that may pose initial problems for some individuals who place strong reliance on chromatic cues is the relatively narrow spectral bandwidth of the targets (Fincham, 1951; Kruger et al., 1997).

For all targets, it is of interest that many of the subjects experienced considerable difficulty in relaxing their accommodation to view the targets at zero vergence (optical infinity, see Table 3). In this case, subjects are required to reduce their accommodation below its tonic level in the face of significant opposing proximal cues, a task that proved particularly difficult for several subjects when the target was a 16 c/deg grating.

One further factor that deserves consideration when comparing the responses of individual subjects is the possible effect of their pupil size and aberrations on depth-of-focus and hence, possibly, on the accuracy of their responses. We did not measure individual depths-of-focus. Pupil diameters in the experiment were generally in the range of 4–6 mm, in which depth-of-focus varies only weakly with pupil diameter (e.g. Atchison & Smith, 2000). In related studies (Charman & Radhakrishnan, 2009) we found no systematic differences in the pupil diameters or accommodative miosis (mm/dioptre of accommodation response) between emmetropes and myopes. Some previous studies have shown that monochromatic aberrations can play an important role in driving accommodation (Chen et al., 2006; Fernández & Artal, 2005; Wilson, Decker, & Roorda, 2002). Monochromatic aberrations show a large degree of variability between individuals (Castejón-Mochón, López-Gil, Benito, & Artal, 2002; Paquin, Hamam, & Simonet, 2002; Porter, Guirao, Cox, & Williams, 2001) and also change as a function of accommodation (Cheng et al., 2004; Radhakrishnan & Charman, 2007). With this in mind, it is possible that differences in monochromatic aberrations between individuals may account for some of the variability observed in the present study.

Finally we note that a mixture of early, late, stationary and progressing myopes was included in our subject groups and it remains possible that significant differences from emmetropes might have been found had the myopic group been more homogeneous. However, examination of the data for individual subjects as shown in Figures 3B and 4B gives no obvious indication that this is likely to be the case.

Conclusion

The present study fails to establish the existence of any systematic difference in the responses of emmetropes and myopes to sinusoidal grating targets. The dominant feature of the data in both refractive groups is intersubject variation, which we attribute to variations in the reliance that different individuals place on particular accommodative components.

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